MANAGEMENT OF ENDOCRINE DISEASE

Thyroid and female infertility: more questions than answers?!

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Abstract

Severe thyroid dysfunction may lead to menstrual disorders and infertility via direct and indirect interactions with the hypothalamo–pituitary–ovarian axis and the reproductive organs. However, the exact prevalence of infertility in women with thyroid disorders remains unknown. Fertility problems may persist even after restoring normal thyroid function, and then surgery and/or an assisted reproductive technology (ART) may be necessary to obtain a pregnancy. The initial step in an ART treatment is the ovarian stimulation, putting strain on the thyroid gland, potentially leading to (permanent) hypothyroidism in women with thyroid autoimmunity (TAI) or when already treated with thyroid hormones (LT4). Moreover, women with ovarian and unexplained causes of infertility have a higher prevalence of TAI. In women treated with LT4, a serum TSH level <2.5 mIU/L should be targeted before ART. In women with TSH levels >4.0 mIU/L, fertilisation rates, embryo quality and live birth rates may be impaired but also improved with LT4 therapy. In euthyroid women with TAI, LT4 should not be given systematically, but on a case-by-case basis if serum TSH is >2.5 mIU/L. For all of the above reasons, women of infertile couples should be screened routinely for the presence of thyroid disorders. In this review, we will focus on the gaps in the current knowledge, the remaining questions on the associations between thyroid (disorders) and (assisted) reproduction and make proposals for future investigations that may lead to a better understanding and contribute to novel treatment options in the long term.

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Thyroid disorders and spontaneous conception failure

Introduction

The prevalence of thyroid disorders in women aged 20–45 years in Europe varies between 5 and 7% for subclinical hypothyroidism (SCH), 0.2–4.5% for overt hypothyroidism (OH), 0.3–1% for hyperthyroidism and 5–10% for thyroid autoimmunity (TAI) (1, 2, 3). Differences between countries can be present according to the iodine status, the ethnic backgrounds of the population and the cut-offs used to define SCH (4, 5).

Invited Author's profile

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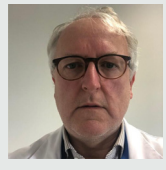

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Several interactions exist between thyroid hormones (TH) and the hypothalamic-pituitary-ovarian axis (6). One is the synergistic interaction between follicle-stimulating hormone (FSH) and T3 to exert direct stimulatory effects on granulosa cell functions, LH/hCG receptor formation and apoptosis suppression (7). TH may reduce granulosa cell aromatase activity, impair pre-antral follicle development, and regulate ovarian function, in part via its effects on nitric oxide synthase (8). Thyroid receptors (T3-r and TSH-r) are present on the developing and mature oocyte and T3, T4 and thyroid antibodies are present in the follicular fluid (9, 10, 11).

In addition to the changes occurring directly at the ovarian unit, a number of hormonal changes can affect the reproductive system indirectly. In the case of hypothyroidism, altered metabolic clearance, increased peripheral aromatisation and decreased sex hormone-binding globulin (SHBG) result in decreased total testosterone and oestradiol (E2) concentrations whilst their unbound fraction increases. Prolactin levels tend to increase too, which may impair pulsatile secretion of gonadotropin-releasing hormone (GnRH) (6).

Ovarian senescence is closely associated with the depletion of a woman's follicular pool during her reproductive lifespan. The women's oocyte supply is established during foetal development and cannot be replenished once her ovarian reserve is compromised due to injury or disease (including thyroid disorders) and therefore, fertility potential (12).

In the initial stage of pregnancy, implantation failure can be present but remain unaware and confused with normal menses. Thyroid disorders have also been associated with implantation failure, and in later pregnancy stages with (recurrent) clinical miscarriage. The association between thyroid disorders and (recurrent) miscarriage after spontaneous pregnancies has been discussed in previous review papers. (13, 14)

Discussion

Infertility in women with (subclinical) hypothyroidism

More severe forms of hypothyroidism may lead to ovulatory dysfunction and an insufficient corpus luteum development with low progesterone production. Indeed, menstrual aberrations are reported in 25–60% of the cases compared to 10% in euthyroid women. If treated with LT4, hormonal changes and the menstrual pattern may normalise and therefore, potentially improve fertility too (6). However, evidence proving that LT4 can lead to spontaneous pregnancy in women with (overt) hypothyroidism is rather anecdotic and probably only effective in case of ovarian dysfunction and not when male infertility, endometriosis or tubal obstruction are the cause of infertility (15). Recent guidelines on thyroid and infertility recommend starting LT4 treatment promptly in case of overt thyroid dysfunction and when TSH values are >4.0 mIU/L/the upper limit of the reference range (ULRR) (16).

Aspects to be investigated more in detail are the role of TH in the follicular fluid as well as the function(s) of TH – and TSH receptors present on the reproductive organs, from the earliest follicle stages over the oocytes and the endometrium.

In a study by Weghofer *et al.* in women of advanced reproductive age and TSH levels >3.0 mIU/L, significantly lower anti-Müllerian hormone (AMH) levels were measured, compared to women with TSH levels <3.0 mIU/L (17). A retrospective study in 2568 Chinese women initiating ART showed significantly lower AMH concentrations, antral follicle counts (AFC) and higher FSH levels in women aged ≥35 years with SCH (18). Though thyroid disease appears to affect ovarian reserve negatively in subsets of women with (unexplained) infertility and advanced reproductive age, a Belgian study in 4894 young women with and without fertility problems could not demonstrate an impact of TAI and hypothyroidism on AMH levels (19).

In one study, increasing AMH levels were shown in women with TAI and TSH levels >2.5 mIU/L after LT4 treatment, suggesting a potential benefit on ovarian function; unfortunately, no pregnancy outcome data were provided (20).

Future studies should follow pregnancy rates in women with SCH treated with LT4 vs those in women followed for the progression of their SCH only.

The prevalence of infertility in women with (subclinical) hypothyroidism has not been investigated in longitudinal studies, but only in a few retrospective ones. In one study from 1993, the authors stated that primary and secondary infertility was present in 6% of women, a prevalence compared with that in the general population at those days (21). In another study, the prevalence of infertility, defined as the absence of pregnancy in sexually active women having regular unprotected intercourse for an exposure period of at least 12 months, was 47% in women with autoimmune hypothyroidism; significantly higher compared to the prevalence in the general population (ranging from 7.4 to 24.0% in population-based studies) (22, 23). In the same study, the number of

pregnancies was determined in women prior and after the diagnosis of hypothyroidism. Following the diagnosis, it was 0.67 and prior 1.48 ($P = 0.02$). Noteworthy is that no differences were present between baseline variables and hormonal parameters between fertile and infertile women with hyper- or hypothyroidism (22).

Finally, in one study focusing on the presence of PCOS as a cause of infertility in obese women with and without SCH, its prevalence was similar between both groups (24).

Infertility in euthyroid women with thyroid autoimmunity

A prospective US study in 436 patients reported lower AFCs in women with unexplained infertility, diminished ovarian reserve and increased thyroid peroxidase antibodies (TPOAb) levels (−2.3 follicles, 95% CI: −3.8 to −0.5; $P = 0.01$) (25).

The presence of TAI can lead to infertility via a number of factors direct and/or indirectly related to the presence of the antibodies. An indirect mechanism is via the higher mean age in women with TAI compared to that in women without (26). Age is an independent risk factor for a decreased ovarian reserve and in later stages for miscarriage too. However, in a recent study by Poppe *et al.*, infertile women with TAI were not older compared with women without TAI, nor was there a difference in the use of tobacco (27).

The presence of TAI is probably also a reflection/marker of an immune imbalance that might lead to or be associated with implantation failure. Infertile women with TAI might have a higher prevalence of antiphospholipid antibodies (aPL), and the presence of aPL as such has been associated with implantation failure (28, 29, 30). However, in studies investigating pregnancy outcomes in women with TAI in which the presence of aPL was excluded a priori, higher miscarriage rates remained present; an argument against the impact of aPL (31).

In other studies, in women with TAI and recurrent implantation failure (RIF), abnormal T-lymphocyte function and higher numbers of endometrial T-cells have been reported, as well as decreased percentages of T-cytotoxicity cells (Tc) and an increased Th/Tc ratio ($P < 0.05$). The prevalence of thyroid dysfunction, the absolute number and percentage of T-cells, T- helper (Th) cells, B-cells and natural killer (NK) cells were not different between women with and without TAI (32, 33). Since no difference in serum oestradiol or progesterone levels were observed between groups, these findings could indicate that TAI induces a non-receptive endometrial milieu that may underlie the detrimental effects on embryo implantation (34).

However, in most clinical studies similar implantation rates were noted between women with – and without TAI, although with more first-trimester miscarriages in women with TAI (15, 35). Bottom-line, implantation failure remains a problem that is difficult to document and is due to a number of altered parameters, including male factors (36, 37).

Research should focus on methods to improve the diagnosis of implantation (failure).

Future studies should aim to investigate whether the prevalence of infertility in euthyroid women with TAI is higher compared with that in age-matched women without thyroid disorders. Whether higher levels of increased TPOAb or thyroglobulin (TgAb) in euthyroid women correlate with ovarian reserve and/or implantation and pregnancy rates remain to be investigated too. In daily practice, the presence of TAI may remain unaware since 5–10% of women will have antibodies with a normal function and therefore and will not be screened for it (1).

Thyroid disorders in women with established infertility causes and/or planning an ART procedure

Introduction

Infertility is defined as the absence of clinical pregnancy after at least one year of regular unprotected intercourse (38). The increased public awareness of infertility and treatment options including ART have led to an increased use of ART world-wide, although in 2005, still 70% of ART cycles were performed in Europe and North America (39). Taken into account that guidelines from endocrine (thyroid) societies recommend the systematic screening for thyroid disorders in women of infertile couples, the detection rate/prevalence of infertile women with a concomitant thyroid disorder increased over the years (15, 16, 40).

Female causes of infertility account for 35% with as most important ones the polycystic ovarian syndrome (PCOS), endometriosis and tubal obstruction; male factors for 30% and combined factors for 20%. In 15% of the cases the cause remains unknown (idiopathic or unexplained infertility) (6, 38). Women in the reproductive age group (20–45 years) also have a high prevalence of thyroid disorders (2, 6) and therefore, they can occur together with infertility. However, and despite that connection, establishing causation remains difficult.

Once thyroid dysfunction has been treated and normalised, but a normal menstruation pattern is not followed by pregnancy within at least 6 months of regular intercourse, a workup of infertility should be done to determine the underlying cause(s), that might be purely (fe)male, mixed or remain unexplained. According to the diagnosis, surgery might be necessary and resolve infertility as in case of endometriosis or tubal obstruction, but in most other cases, an ART treatment will be necessary to obtain a pregnancy. In some cases of male infertility or ovulatory dysfunction, a few attempts of intra-uterine insemination might be performed before an ART treatment. The ART procedure starts with an ovarian stimulation (OS), formerly called controlled OS, with the aim to obtain a high ovarian retrieval rate, and avoid an hyperstimulation (syndrome), a severe complication of OS, that can lead to thyroid dysfunction too (41).

Discussion

Thyroid disorders in women with established causes of infertility

TAI is the most common autoimmune disorder in women in the reproductive age range, with an estimated prevalence of around 10% (2, 6). TAI is typically characterised by increased levels of TPOAb often associated with high(er) mean TSH concentrations, and it tends to be more prevalent in women confronted with certain causes of infertility, such as PCOS and primary ovarian insufficiency (POI). In the case of PCOS, the higher prevalence can be due to polymorphisms in the PCOS-related gene for fibrillin 3, altered TGF-β activity (a regulator of immune tolerance), and a higher estrogen-to-progesterone ratio (31, 42).

POI is defined as loss of ovarian function <40 years of age, and affects about 1:10 000 women aged 20 years, and up to 1:100 aged 40 years. Causative mechanisms for POI include genetic factors (20–25%) and autoimmune conditions (4–30%), though the majority remains unexplained (43). Increased prevalence of genetic alterations and autoimmune disease in women with diminished ovarian reserve (DOR) suggest that POI and DOR may represent different stages of the same entity (44, 45). In a prospective study in the US in women with POI, TAI 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 female in the same area; 5.8% ($P < 0.001$; RR: 3.0, 95% CI: 2.3–3.7) (46). Another large cross-sectional study in Chinese infertility patients supports the concept that TAI may be related to idiopathic DOR: 1044 women were grouped to low, normal and high ovarian reserve categories according to age-ladjusted AMH levels. Women with DOR demonstrated higher percentages of TAI (23.3%) when compared to counterparts with normal (14.6%) and high ovarian reserve (10.4%; $P = 0.014$) (47).

Endometriosis has also been associated with a higher prevalence of increased TPOAb levels in one study (6, 31), but that was not the case in another study published a few years thereafter (48). Noteworthy is that in the latter study, the prevalence of TAI in the control group was very high (25%), what might have contributed to the non-significant difference with the patients in which it was 20%. Finally, a meta-analysis of three case–control studies showed a non-significantly increased risk of TAI in women with endometriosis, but with a high I^2 index for heterogeneity (OR: 1.36, 95% CI: 0.54–3.45, $P = 0.52$, $I^2 = 83\%$) (49).

Finally, in a meta-analysis pooling four studies, TAI was more prevalent in euthyroid women with unexplained (idiopathic) infertility (OR 1.5, 95% CI: 1.1–2.0) (35).

The prevalence of TAI is based mainly on the presence of high TPOAb levels alone. However, the presence of increased TgAb levels might be important to investigate, as shown in a study in infertile women, in which 5% had isolated positive TgAb (compared with 4% with isolated TPOAb), with significantly higher serum TSH levels compared with women without TAI (50). Data on the prevalence of TAI in infertile women based on ultrasound criteria are absent in the literature. It is known that the earliest stages of TAI can be detected by ultrasound before positive thyroid antibodies are present in the serum (51).

Prospective studies should be performed, taking into account all presenting forms of TAI in infertile women and in controls, before definitive conclusions can be drawn on the (higher) prevalence of TAI in case of infertility.

In a paper by Poppe *et al.*, the prevalence of SCH in women of infertile couples varied between 1 and 43% (31). A number of biases were present such as the different definitions of SCH, the fact that some women were treated with LT4 and finally, comparison with the prevalence of SCH in fertile controls were often lacking. In the study by Unuane *et al.* in 2012, mean serum TSH levels in infertile women were comparable to those in a control group of fertile women that was composed of women consulting for alternative reasons (egg cell donation, single-parent request, etc.) together with male infertility causes (50). More recently, in the study by Dhillon *et al.* in women with infertility and recurrent miscarriage, the prevalence of SCH was 2.4% and that of overt hypothyroidism 0.2% (3). The multiple regression analyses showed an increased OR of SCH (TSH

>4.50 mIU/L) with high BMI ≥35.0 kg/m^2 (aOR: 1.71, 95% CI: 1.13–2.57; $P = 0.01$) and Asian ethnicity (aOR: 1.76, 95% CI: 1.31–2.37; $P < 0.001$), but not with subfertility (3).

An issue in that study is the heterogeneity of the population investigated (infertility and (recurrent) miscarriage; both can be due to a variety of causes), and the lack of fertile controls. Noteworthy is also that infertility was not a risk factor for the presence of increased TPOAb levels either (OR: 0.95, 95% CI: 0.83–1.10; $P = 0.502$).

However, in a recent meta-analysis by Ding *et al.* in infertile women with PCOS, the OR for SCH (serum TSH >4.0 mIU/L) was 3.59 (95% CI: 2.2–5.7) (52). Furthermore, in case of PCOS, the women's higher prevalence of obesity and insulin resistance might have contributed to the higher prevalence of SCH, beyond that of TAI (52).

The prevalence of (subclinical) hyperthyroidism in infertile women has been investigated in a prospective study performed nearly 20 years ago (53). The prevalence of a suppressed serum TSH was 2.1% and comparable to that in the fertile female control population (3%). Subclinical hyperthyroidism was present in 78% of patients with a low serum TSH, and 44% had high TPOAb levels (TSH-r antibodies were not determined). When TPOAb were positive, a suppressed serum TSH was more frequent in all infertile women compared with that in women without (7 vs 1%; $P < 0.05$). In the study by Dhillon-Smith *et al.*, there was no increased prevalence of overt hyperthyroidism either (OR: 0.76, 95% CI: 0.26–2.20); with a prevalence of 0.3 and 1.3% for subclinical hyperthyroidism (3).

In the recent ETA guidelines, it is recommended that all women seeking medical advice for infertility should be screened for TSH and increased TPOAb levels. TgAb can be added systematically or when not allowed according to the local regulatory authorities in women with TSH levels >2.5 mIU/L and no increased TPOAb levels. Treatment with LT4 is suggested in infertile women with TAI and serum TSH >2.5 mIU/L on a case-by-case basis and systematically if TSH levels are >4.0 mIU/L or the ULRR (16).

Thyroid disorders in women planning an ART procedure

Thyroid disorders and ovarian stimulation

Ovarian stimulation (OS) is the first part of the ART procedure. Different schemes exist, but the general principle consists of the pituitary downregulation with GnRH analogues or antagonists, ovarian stimulation with gonadotrophins (Gn) for several days and finally, a single injection of human chorionic gonadotrophin (hCG) for ovulation induction (54). OS induces a rapid and supraphysiologic increase in oestradiol (E2) levels (4000–6000 ng/L), in spontaneous pregnancies only present from the second trimester of pregnancy on. The E2 rise results in an excess of thyroxine-binding globulin (TBG) production and sialylation by the liver and therefore, to a reduced clearance rate of TBG, increasing the total fraction of TH and reducing free TH levels (55, 56). Furthermore, a direct effect of the high E2 levels on the release of thyrotropin-releasing hormone (TRH) has been described and both mechanisms might explain an increase in TSH levels due to the OS (57).

In approximately one third of euthyroid patients, serum TSH levels exceeded 2.5 mIU/L and the elevation lasts 1–3 months after OS (55, 57, 58, 59, 60, 61, 62, 63). The rate of patients with TSH >2.5 mIU/L as well as the magnitude of increase is more pronounced in treated hypothyroid patients (62, 63). During OS, women with positive TPOAb show increased TSH values (decreased FT4 levels) compared with TPOAb negative women (55). In euthyroid women without TAI, the net effect of OS is negligible (57, 59). Nowadays, a hyperstimulation syndrome (HS), characterised by very high E2 levels is an exceptional complication of the OS. It can occur during the luteal phase or during early pregnancy and can be accompanied by severe morbidity and may even be fatal. Complications include electrolytic imbalance, neurohormonal and haemodynamic changes, pulmonary manifestations, liver dysfunction, thromboembolic phenomena, neurological manifestations and adnexal torsion (64). The impact of HS on thyroid function in women without thyroid disorders (no antibodies and not on LT4) is associated with a TSH rise comparable with that in women without HS, but on the other hand, in women with underlying TAI, it can lead to severe overt hypothyroidism (41, 65).

Another effect of OS on thyroid function to be considered is the one possibly exerted by hCG administration since TSH and hCG, as well as their respective receptors, share structural homologies (66). In a Dutch study in more than 7000 patients from two population-based prospective cohorts, the functional response to hCG was different between patients with and without increased TPOAb levels. Healthy patients show a reduction of TSH values and a proportional FT4 increase, whereas the functional trend of patients with TAI is impaired (67). Whether these data can be extrapolated to lower concentrations of hCG as used for the ovulation induction (10 000 IU) remains unknown and deserves further investigation.

The net result of OS in women with TAI is a decrease in FT4 levels and a reactive increase of TSH levels. This is particularly evident in patients with TSH levels >2.5 mIU/L before OS and might be a reason to adapt pre-OS dosage of LT4 to prevent hypothyroidism during early pregnancy stages (63, 68). Recently, in a Chinese study, LT4 treatment before OS/ART did not improve live birth rates in euthyroid women with TAI (69).

Since adverse pregnancy outcomes have been associated with inadequately and untreated maternal hypothyroidism (6), 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 (~6 weeks after the start of OS or 3 weeks after the ovulation induction). Thyroid function serial testing is not necessary in euthyroid women without TAI, unless treated with LT4. LT4 treatment may be considered for TSH levels >2.5 mIU/L with TAI and should be started for TSH levels >4.0 mIU/L or >ULRR. In the recent ETA guideline paper, treatment/follow-up schemes in relation to OS are proposed based on serum TSH and the presence of TAI (16).

Further research is needed with long-term follow-up after OS of thyroid function and if it can induce *de novo* TAI. Besides TPOAb, the presence of increased TgAb levels and/or ultrasound criteria of TAI should be taken into account too. Finally, a remaining question is whether pituitary agonists vs antagonists lead to a different impact on thyroid function.

Thyroid disorders and ART (IVF/ICSI) clinical outcomes

The term 'thyroid autoimmunity' (TAI) and autoimmune thyroiditis (AITD) are used in most papers when at least one type of thyroid Ab is present; in majority TPOAb, sometimes TgAb or finally, both types.

For more than a decade, an increased miscarriage rate (MR) in euthyroid women with TAI has been reported, both in spontaneous and assisted pregnancies (70, 71). Three meta-analyses investigated the impact of TAI on ART pregnancy outcomes (70, 71, 72). No effect on the implantation and clinical pregnancy rates was observed, but the first-trimester MR was increased and LBR decreased. Of note is that in the meta-analysis published in 2011 (71), the OR of miscarriage was 3.15, but in the most recent one by Busnelli *et al.* in 2016, it was only 1.44 (72).

The pathophysiological mechanisms underlying an increased MR in women with TAI remain a matter of debate. A first hypothesis is to consider thyroid antibodies as a marker of an immune disorder, thus acting independently of a thyroid dysfunction. In a study in pregnant women, it was shown that there was an abnormal T-helper-1 (Th1)/T-helper-2 (Th2) ratio and a shift to a dominant Th1-type response, activating T-lymphocytes and potentially leading to implantation failure (73). In another similar study, Th1 oriented changes of innate immunity in the peripheral blood were present too, with elevated Natural Killer cells and enhanced natural cytotoxicity (74). Concerning the effects of TAI on the endometrium, evidence is scarce. Kilic *et al.* found no difference in the endometrial volume (as a surrogate to assess endometrial receptivity and the implantation chance), in women with unexplained infertility with- and without TAI (75). The expression of TPO and Tg in the endometrium and the harmful role of TPOAb and TgAb is still a matter of debate (8, 10). Furthermore, TPOAb might be able to recognise other proteins expressed in the uterus such as prostaglandin G/H synthase 2, with a consequence on implantation (8). Finally, in a model of TPO-immunised mice, Lee *et al.* show TPOAb on the surface of their preimplantation embryos (76). However, in most studies on ART pregnancies, similar implantation rates are noted between women with- and without TAI (72, 77).

On the other hand, in the study by Cai *et al.*, implantation failure was associated with lower FT4 levels but not with the presence of thyroid antibodies in the serum or FF (11), leading the authors to conclude that thyroid function might be more important than that of TAI. In the study by Zhong *et al.* lower implantation rates were present in women with TAI (64% vs 74% in women without TAI), but the authors did not determine TSH in their study, rendering the further interpretation of the results difficult (78).

The second hypothesis is an impaired thyroid functional reserve, that might lead to an inadequate production in TH during the first stages of pregnancy. The fact that OS is performed before the embryo transfer might aggravate or unravel an underlying subtle thyroid problem. One of the underlying mechanisms how TAI might impair normal thyroid response to a strain is via an impaired thyroidal response to hCG (67, 79). Furthermore, to explore the hypothesis of a higher mean serum TSH level in women with TAI, Busnelli *et al.* meta-analysed the preconceptional serum TSH levels in six studies. Serum TSH levels were higher in patients with TAI; mean basal TSH was higher by 0.51 mIU/L (95% CI: 0.14–0.88; P = 0.007) in women with TAI compared with the TAI negative group. However, the meta-regression analysis

exploring the possible effect of basal TSH values in the estimated association between TAI and miscarriage failed to document an interaction (72). Another explanation for the latter might have been the fact that in a number of studies included in that meta-analysis, serum TSH cut-offs of 2.5 and 3.0 mIU/L were used to define SCH, based on guidelines from 2012 (72, 77).

A third hypothesis that might go together with the two previous ones is the higher mean age in women with TAI compared with that in TAI – women (72, 79). Older age is a known risk factor for an increased MR and infertility (80). However, in the meta-regression analysis by Busnelli *et al.* (72), the increased MR persisted after correction for age.

Treatments to improve LBR should thus be focused on the first two pathways. Therefore, a primordial question is whether LT4 treatment can increase LBR in euthyroid women with TAI and pregnant after ART.

In pregnant women with TAI, it has been shown that LT4 treatment was able to counteract the Th1/Th2 ratio shift to a Th1-type response, what was not the case in women not treated (73). The authors postulate that this shift might explain in part the beneficial impact of LT4 on pregnancy outcomes, but since they did not report on pregnancy outcomes, this remains to be proven. Furthermore, in the recent TABLET study in euthyroid women with TAI and a history of infertility or recurrent miscarriage, no impact of LT4 on live births was observed; an argument against the immune shift hypothesis induced by LT4 (81). More evidence against this hypothesis comes from a Cochrane systemic review, including two studies and randomising 686 euthyroid women (TSH levels <4.2 and <4.8 mIU/L, respectively) to treatment with LT4 vs placebo/no treatment (69, 82, 83). LT4 treatment had no effect on MR, clinical pregnancy or LBR. The reasons for the absence of a beneficial impact of LT4 on pregnancy outcomes remain speculative, but some hypotheses can be generated based on the results of the meta-analyses published since 2010. In that published in 2011, the OR of miscarriage was 3.15, in that of 2016 it decreased to 1.44 and no increased risk was present in the latest meta-analysis in 2018 (71, 72, 77). Reasons for that decrease can be the difference in the study design (prospective vs retrospective), the inclusion/exclusion criteria (treatment with LT4 or corticosteroids), the OS protocol (agonists vs antagonists, long vs short), and the diagnosis of TAI (defined by the presence of increased TPOAb levels only vs both TPO- and TgAb). Furthermore, noteworthy mentioning is that in the 2018 meta-analysis, women were treated with ICSI only, and that serum TSH levels defining SCH decreased to TSH levels >2.5/3.0 mIU/L compared with >4.0 mIU/L in the studies included in the first meta-analysis (77).

The pivotal study by Wang *et al.* (a negative study on LT4 treatment in euthyroid women with TAI, in an ART setting) was the subject of a number of editorials/comments drawing the attention to subgroups of women that still might benefice from LT4 treatment; more in particular older women with female causes of infertility and high levels of TPOAb (69, 84).

The precise reasons for the observation that LT4 still might be indicated in certain subgroups remain speculative. It is known that women aged >30–35 years and/or with PCOS/POF as the underlying cause of infertility tend to have more TAI/SCH (4, 31, 42). Furthermore, higher levels of thyroid antibodies ('higher levels' as such needs to be defined better) could be associated with an impaired response to exogenous hCG as in case of the ovulation induction at the end of the OS and finally, they may lead to SCH during pregnancy (1, 2, 6, 15, 79). In addition, in the study by Kim *et al.*, it was shown that women in the control group with a miscarriage had higher TPOAb and/or TgAb levels compared to women with ongoing pregnancies (85)

Other issues with the study by Wang *et al.* were the low MR rate (10%) taken into account for the power calculation vs 20–30% in a real-world setting, and finally the exclusion of women with increased TgAb levels only (69, 84).

For the time being, it is suggested that euthyroid women with TAI undergoing IVF/ICSI are not being treated systematically with LT4 (16).

Future research should consist of properly designed, randomised studies of euthyroid women with TAI (taking into account both types of antibodies and ultrasound features), treated with LT4 vs placebo. Outcomes should be corrected for age, the type of OS, thyroid antibody levels, thyroid function, and finally the cause(s) of infertility, including a quantification of the sperm quality, and the type of ART treatment (ICSI/IVF) (80, 86).

Moreover, if the absence of an impact of LT4 on pregnancy outcomes in euthyroid women with TAI would be confirmed, other treatment options could be (re)investigated. In an older small and non-randomised study by Vaquero *et al.* patients receiving intravenous immunoglobulins (IVIG) had some improvement of their pregnancy outcomes, although less than those treated with LT4 (87). In another study, glucocorticoids initiated before the ART procedure, lead to a doubling of the LBR (88). It should be noted that only a small number of women were included, and long-term follow-up data were missing.

Another question is whether LT4 treatment improves ART outcomes in women with SCH. By definition, SCH is the association of a normal free thyroxine level (FT4) and an increased serum TSH level above the ULRR. Ideally, this upper limit is determined in an assay and population-specific cohort, and in the scope of (in)fertility in women in the age range 20–45 years. Most centres do not have these normative data, and therefore, the upper limit of normality is most often a synonym for the ULRR of the assay used. The most commonly used commercial assays in Europe have a ULRR for serum TSH between 3.60 and 4.31 mIU/L (89). In a recent meta-analysis, altered ART outcomes were present from TSH levels >3.5 mIU/L on, and based on this and the few interventional trials with LT4 that showed an increased LBR when TSH levels exceeded 4.0 and 4.5 mIU/L, respectively, guidelines propose to initiate treatment with LT4 from a TSH cut-off >4.0 mIU/L or >ULRR if the latter is >4.0 mIU/L (16, 90, 91, 92). According to the (strict) Cochrane systemic review criteria, only one study could be included, in which 64 women were scheduled for IVF/ICSI with TSH levels >4.5 mIU/L (>80% of the women had TAI) and randomised to LT4 or no treatment. LT4 treatment was associated with 27–100% chance of live birth compared to 25% in the control group (82, 85). These results are in line with most results in spontaneous pregnancies but need to be confirmed in more studies comparing LBR after ART in women with SCH treated with LT4, with corrections for the type of ART (IVF or ICSI), woman's age, cause of infertility, semen parameters, the severity of SCH and the levels of TPO- and TgAb (80, 86). Therefore, it is noteworthy mentioning that besides the few patients with SCH and no TAI in the study by Kim *et al.*, the evidence on the treatment of infertile women with SCH and no TAI is almost absent (85). In addition, in the meta-analysis by Zhao *et al.*, it was mentioned that increased TPOAb levels could not be eliminated in several of the original papers (90). This particular group of women might have other reasons for a high serum TSH or features of TAI only detectable at ultrasound (4). More research is needed in that group of women, and if other reasons than TAI are underlying the higher TSH levels, another approach might be necessary instead or above LT4 treatment.

Screening/management in daily practice

According to the general principles of screening by Wilson and Jungner, a condition must be an important health problem, with development from a (recognisable) latent to declared disease that is well understood. There should be a suitable test or examination, acceptable to the population; there should be an agreed policy on who to treat as patients with an accepted treatment and facilities for diagnosis and treatment. The cost of case finding (including diagnosis and treatment) should be economically balanced in relation to expenditure on medical care as a whole (93). The case of thyroid disorders and infertility (ART treatment) fulfils most of these prerequisites. Women with PCOS, POI and idiopathic infertility have a higher prevalence of TAI and increased serum TSH levels compared with fertile women (6, 42). Furthermore, the presence of increased TPOAb levels may point out women at risk of developing (subclinical) hypothyroidism after OS or during gestation and are strongly correlated with post-partum thyroiditis (6). Serum TSH levels >3.5 mIU/L are associated with impaired ART outcomes and LT4 treatment can increase LBR in women with TSH levels >4.0 mIU/L (90, 91). In summary, testing for serum TSH and antibodies is easy and widely available; the prevalence of thyroid disorders is high in infertile women and associated with altered pregnancy outcomes, that can be treated with a safe treatment (LT4), able to improve ART outcomes.

The criteria by Wilson and Jungner might need revision, in order not to be applied in a dogmatic way that might lead to unjustified rejection of screening (some) women (94). In the recent ETA guidelines, screening for thyroid dysfunction (TSH) and autoimmunity (TPOAb) is suggested in women of infertile couples planning an ART treatment. The presence of increased TgAb levels can be verified in women with TSH levels >2.5 mIU/L and normal TPOAb levels. In men with ejaculation and erectile dysfunction and/or altered semen parameters, TSH could be measured too (16).

Conclusions

Thyroid dysfunction and autoimmunity are associated with a number of aspects of the reproductive process, by direct actions on reproductive organs or via an interaction with the hypothalamic–pituitary–gonadal axis. Severe thyroid dysfunction with or without the presence of TAI can lead to infertility and its treatment can normalise the menstrual pattern but might not always restore fertility, and in that case, an ART treatment can be considered. Some causes of infertility (ovarian and idiopathic) are associated with a higher prevalence of TAI. Women with thyroid dysfunction prior to an ART procedure should

Table 1 Remaining questions and proposals for future research.

Topic/remaining questions	Proposal for research
Infertility in euthyroid women with TAI	In women with TAI and no immediate pregnancy wish, a long-term follow-up of ovarian reserve parameters (AMH, FSH) should be done, and the prevalence of infertility documented compared with that in euthyroid women without TAI. Furthermore, the type and evolution of thyroid antibody (TPOAb or TgAb) and TSH levels should be followed too. The systematic screening for serum TSH performed in women of infertile couples; should be completed with that of TAI since 5–10% of euthyroid women, might have positive thyroid antibodies.
Higher prevalence of TAI in PCOS, DOR, unexplained infertility and maybe other causes (endometriosis/tubal disorders)	Prospective studies should be performed, taking into account all presenting forms of TAI (including systematically TgAb and ultrasound criteria) before definitive conclusions can be drawn on the higher prevalence of TAI in case of infertility.
The impact of ovarian stimulation/ovulation induction on thyroid function and autoimmunity	An extended long-term follow-up of thyroid function and autoimmune parameters should be performed before definitive conclusions can be made on the importance of the strain of OS on thyroid function and if OS can induce TAI as such. Furthermore, should the type of OS (pituitary antagonists versus agonists) and both types of thyroid antibodies (including ultrasound criteria) be taken into account. To investigate whether the presence of TAI impairs the impact of the ovulation induction (i.e. an hCG injection)
Oocyte (patho)physiology	The role(s) of thyroid antibodies and hormones in the follicular fluid needs to be investigated better, including that of TH - and TSH receptors on the oocytes, the endometrium and the reproductive organs. This knowledge is indispensable before investigating whether LT4 or other (immune modulatory) treatments could improve ART *in vitro* outcomes like the oocyte and embryo quality, the fertilisation rate, and ultimately (spontaneous) pregnancy rates.
Treatment options for euthyroid women (TSH <4.0 mIU/L/ULRR) with TAI	A number of studies should be planned to aim to increase the LBR. These could include the use of ICSI, LT4, immune modulating medications, or a combination of those. However, before recommending the systematically application of ICSI in women with TAI, head-to-head studies are warranted comparing ART *in vitro* outcomes in women with TAI treated either with IVF or ICSI and with corrections for woman's age, cause of infertility, semen parameters, thyroid function and the types/levels of thyroid antibodies (including ultrasound features). Other studies should focus on subgroups of euthyroid women with TAI, in order to decide which women still might benefit from LT4 supplements. Candidates are women with ovarian causes of infertility (DOR, POI), an older age (>35 years), a history of recurrent miscarriage or high levels of thyroid antibodies. A decision to treat should be investigated in relation to an optimal TSH cut-off value for the local population and go beyond fixed TSH cut-offs. The better understanding of genetics underlying thyroid function and the determination (use) of individual TSH setpoint might shed more light on these aspects in the near future. Finally, if these studies would confirm that either in these subgroups, LT4 would not be effective (as it is the case in the only RCT on this subject), other treatments could be investigated (again), such as corticosteroids and immunoglobulins. In the scope of a potentially underlying immune problem in TAI, the implantation window needs to be understood better, including endometrium investigations (histological or radiological ones).
Outcomes/treatment options in women with TSH >4.0 mIU/L/ULRR without TAI	This group of women is probably small and multicentre-based studies will be necessary to reach enough power and randomise women into a group treated with LT4 versus placebo. Before concluding that women with a high TSH/SCH have no TAI based on the absence of thyroid antibodies, an ultrasound should be performed too. Other causes of high TSH must be investigated and eventually taking care of ± LT4 treatment.
Screening criteria	Independent from the available number of RCT's, the criteria by Wilson and Jungner might need revision, in order not to be applied in a dogmatic way that might lead to unjustified rejection of screening.

ART, assisted reproductive technology; DOR, diminished ovarian reserve; hCG, human chorionic gonadotrophin; ICSI, intracytoplasmic sperm injection; IVF, in vitro fertilization; OS, ovarian stimulation; POI, primary ovarian insufficiency; TgAb, thyroglobulin antibodies; TPOAb, thyroid peroxidase antibodies; TSH, thyroid stimulating hormone.

always be treated. The ovarian stimulation leads to a strain on thyroid function that is more severe if TAI is present. Pregnancy outcomes are impaired in women with SCH (TSH >4.0 mIU/L and most often concomitant TAI) and might be improved with LT4 treatment. Screening for thyroid disorders is essential in the work-up of women of infertile couples, even if not for every thyroid disorder an adequate treatment is available yet, it might point out patients with higher pregnancy morbidity and at higher risk to develop thyroid dysfunction in the long run.

Many questions remain unanswered in this field and are awaiting the results of upcoming studies to improve fertility issues associated with or due to thyroid disorders (Table 1).

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References

1 Valdés S, Maldonado-Araque C, Lago-Sampedro A, Lillo JA, Garcia-Fuentes E, Perez-Valero V, Gutierrez-Repiso C, Ocon-Sanchez P, Goday A, Urrutia I, et al. Population-based national prevalence of thyroid dysfunction in Spain and associated factors: Di@bet.es Study. *Thyroid* 2017 **27** 156–166. (https://doi.org/10.1089/thy.2016.0353)
2 Hollowell JG, Staehling NW, Dana Flanders W, Harry Hannon W, Gunter EW, Spencer CA, Braverman LE & Serum TSH. T4, and thyroid antibodies in the United States population (1988 to 1994): national Health and Nutrition Examination Survey (NHANES III). *Journal of Clinical Endocrinology and Metabolism* 2002 **87** 489–499. (https://doi.org/10.1210/jcem.87.2.8182)
3 Dhillon-Smith RK, Tobias A, Smith PP, Middleton LJ, Sunner KK, Baker K, Farrell-Carver S, Bender-Atik R, Agrawal R, Bhatia K, *et al*. The prevalence of thyroid dysfunction and autoimmunity in women with history of miscarriage or subfertility. *Journal of Clinical Endocrinology and Metabolism* 2020 **105** dgaa302. (https://doi.org/10.1210/clinem/dgaa302)
4 Veltri F & Poppe K. Variables contributing to thyroid (dys)function in pregnant women: more than thyroid antibodies? *European Thyroid Journal* 2018 **7** 120–128. (https://doi.org/10.1159/000488279)
5 Dong AC & Stagnaro-Green A. Differences in diagnostic criteria mask the true prevalence of thyroid disease in pregnancy: a systematic review and meta-analysis. *Thyroid* 2019 **29** 278–289. (https://doi.org/10.1089/thy.2018.0475)
6 Krassas GE, Poppe K & Glinoer D. Thyroid function and human reproductive health. *Endocrine Reviews* 2010 **31** 702–755. (https://doi.org/10.1210/er.2009-0041)
7 Zhang C, Xia G & Tsang BK. Interactions of thyroid hormone and FSH in the regulation of rat granulosa cell apoptosis. *Frontiers in Bioscience* 2011 **3** 1401–1413. (https://doi.org/10.2741/342)
8 Vissenberg R, Manders VD, Mastenbroek S, Fliers E, Afink GB, Ris-Stalpers C, Goddijn M & Bisschop PH. Pathophysiological aspects of thyroid hormone disorders/thyroid peroxidase autoantibodies and reproduction. *Human Reproduction Update* 2015 **21** 378–387. (https://doi.org/10.1093/humupd/dmv004)
9 Aghajanova L, Lindeberg M, Carlsson IB, Stavreus-Evers A, Zhang P, Scott JE, Hovatta O & Skjöldebrand-Sparre L. Receptors for thyroid-stimulating hormone and thyroid hormones in human ovarian tissue. *Reproductive Biomedicine Online* 2009 **18** 337–347. (https://doi.org/10.1016/S1472-6483(10)60091-0)
10 Colicchia M, Campagnolo L, Baldini E, Ulisse S, Valensise H & Moretti C. Molecular basis of thyrotropin and thyroid hormone action during implantation and early development. *Human Reproduction Update* 2014 **20** 884–904. (https://doi.org/10.1093/humupd/dmu028)
11 Cai YY, Lin N, Zhong LP, Duan HJ, Dong YH, Wu Z & Su H. Serum and follicular fluid thyroid hormone levels and assisted reproductive technology outcomes. *Reproductive Biology and Endocrinology* 2019 **17** 90. (https://doi.org/10.1186/s12958-019-0529-0)
12 Eggan K, Jurga S, Gosden R, Min IM & Wagers AJ. Ovulated oocytes in adult mice derive from non-circulating germ cells. *Nature* 2006 **441** 1109–1114. (https://doi.org/10.1038/nature04929)
13 De S & Pearce EN. Autoimmune thyroid disease during pregnancy. *Lancet Diabetes and Endocrinology* 2018 **6** 575–586. (https://doi.org/10.1016/S2213-8587(17)30402-3)
14 ESHRE Guideline Group on RPL, Bender Atik R, Christiansen OB, Elson J, Kolte AM, Lewis S, Middeldorp S, Nelen W, Peramo B, Quenby S, et al. ESHRE guideline: recurrent pregnancy loss. *Human Reproduction Open* 2018 **2018** hoy004. (https://doi.org/10.1093/hropen/hoy004)
15 Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, Grobman WA, Laurberg P, Lazarus JH, Mandel SJ, *et al*. 2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. *Thyroid* 2017 **27** 315–389. (https://doi.org/10.1089/thy.2016.0457)
16 Poppe K, Bisschop PH, Fugazzola L, Mintziori G, Unuane D & Weghofer A. European Thyroid Association guideline on thyroid disorders prior to and during assisted reproduction. *European Thyroid Journal* 2020 9 281-295. (https://doi.org/10.1159/000512790)
17 Weghofer A, Barad DH, Darmon S, Kushnir VA & Gleicher N. What affects functional ovarian reserve, thyroid function or thyroid autoimmunity? *Reproductive Biology and Endocrinology* 2016 **14** 26. (https://doi.org/10.1186/s12958-016-0162-0)
18 Rao M, Wang H, Zhao S, Liu J, Wen Y, Wu Z, Yang Z, Su C, Su Z, Wang K, *et al*. Subclinical hypothyroidism is associated with lower ovarian reserve in women aged 35 years or older. *Thyroid* 2020 **30** 95–105. (https://doi.org/10.1089/thy.2019.0031)
19 Polyzos NP, Sakkas E, Vaiarelli A, Poppe K, Camus M & Tournaye H. Thyroid autoimmunity, hypothyroidism and ovarian reserve: a cross-sectional study of 5000 women based on age-specific AMH values. *Human Reproduction* 2015 **30** 1690–1696. (https://doi.org/10.1093/humrep/dev089)
20 Kuroda M, Kuroda K, Segawa T, Noh JY, Yoshihara A, Ito K, Osada H, Takeda S & Teramoto S. Levothyroxine supplementation improves serum anti-Müllerian hormone levels in infertile patients with Hashimoto's thyroiditis. *Journal of Obstetrics and Gynaecology Research* 2018 **44** 739–746. (https://doi.org/10.1111/jog.13554)
21 Joshi JV, Bhandarkar SD, Chadha M, Balaiah D & Shah R. Menstrual irregularities and lactation failure may precede thyroid dysfunction or goitre. *Journal of Postgraduate Medicine* 1993 **39** 137–141.
22 Quintino-Moro A, Zantut-Wittmann DE, Tambascia M, MacHado Hda C & Fernandes A. High prevalence of infertility among women with Graves' disease and Hashimoto's thyroiditis. *International Journal of Endocrinology* 2014 **2014** 982705. (https://doi.org/10.1155/2014/982705)
23 Slama R, Hansen OKH, Ducot B, Bohet A, Sorensen D, Giorgis Allemand L, Eijkemans MJC, Rosetta L, Thalabard JC, Keiding N, *et al*. Estimation of the frequency of involuntary infertility on a nation-wide basis. *Human Reproduction* 2012 **27** 1489–1498. (https://doi.org/10.1093/humrep/des070)
24 Zhang B, Wang J, Shen S, Liu J, Sun J, Gu T, Zhu D & Bi Y. Subclinical hypothyroidism is not a risk factor for polycystic ovary syndrome in obese women of reproductive age. *Gynecological Endocrinology* 2018 **34** 875–879. (https://doi.org/10.1080/09513590.2018.1462319)
25 Korevaar TIM, Mínguez-Alarcón L, Messerlian C, Poortere RA De, Williams PL, Broeren MA, Hauser R & Souter IC. Association of thyroid function and autoimmunity with ovarian reserve in women seeking infertility care. *Thyroid* 2018 **28** 1349–1358. (https://doi.org/10.1089/thy.2017.0582)

26 Prummel MF & Wiersinga WM. Thyroid autoimmunity and miscarriage. *European Journal of Endocrinology* 2004 **150** 751–755. (https://doi.org/10.1530/eje.0.1500751)

27 Poppe K, Autin C, Veltri F, Sitoris G, Kleynen P, Praet JP & Rozenberg S. Thyroid disorders and in vitro outcomes of assisted reproductive technology: an unfortunate combination? *Thyroid* 2020 **30** 1177–1185. (https://doi.org/10.1089/thy.2019.0567)

28 Kwak-Kim J, Park JC, Ahn HK, Kim JW & Gilman-Sachs A. Immunological modes of pregnancy loss. *American Journal of Reproductive Immunology* 2010 **63** 611–623. (https://doi.org/10.1111/j.1600-0897.2010.00847.x)

29 Versini M. Thyroid autoimmunity and antiphospholipid syndrome: not such a trivial association. *Frontiers in Endocrinology* 2017 **8** 175. (https://doi.org/10.3389/fendo.2017.00175)

30 Bellver J, Soares SR, Álvarez C, Muñoz E, Ramírez A, Rubio C, Serra V, Remohí J & Pellicer A. The role of thrombophilia and thyroid autoimmunity in unexplained infertility, implantation failure and recurrent spontaneous abortion. *Human Reproduction* 2008 **23** 278–284. (https://doi.org/10.1093/humrep/dem383)

31 Poppe K, Velkeniers B & Glinoer D. The role of thyroid autoimmunity in fertility and pregnancy. *Nature Clinical Practice. Endocrinology and Metabolism* 2008 **4** 394–405. (https://doi.org/10.1038/ncpendmet0846)

32 Matalon ST, Blank M, Ornoy A & Shoenfeld Y. The association between anti-thyroid antibodies and pregnancy loss. *American Journal of Reproductive Immunology* 2001 **45** 72–77 11216877. (https://doi.org/10.1111/j.8755-8920.2001.450202.x)

33 Huang C, Liang P, Diao L, Liu C, Chen X, Li G, Chen C & Zeng Y. Thyroid autoimmunity is associated with decreased cytotoxicity T cells in women with repeated implantation failure. *International Journal of Environmental Research and Public Health* 2015 **12** 10352–10361. (https://doi.org/10.3390/ijerph120910352)

34 Wu Z, Cai Y, Xia Q, Liu T, Yang H, Wang F, Wang N, Yu Z, Yin C, Wang Q, *et al*. Hashimoto's thyroiditis impairs embryo implantation by compromising endometrial morphology and receptivity markers in euthyroid mice. *Reproductive Biology and Endocrinology* 2019 **17** 94. (https://doi.org/10.1186/s12958-019-0526-3)

35 Van den Boogaard E, Vissenberg R, Land JA, Van Wely M, Van der Post JAM, Goddijn M & Bisschop PH. Significance of (sub)clinical thyroid dysfunction and thyroid autoimmunity before conception and in early pregnancy: a systematic review. *Human Reproduction Update* 2011 **17** 605–619. (https://doi.org/10.1093/humupd/dmr024)

36 Timeva T, Shterev A & Kyurkchiev S. Recurrent implantation failure: the role of the endometrium. *Journal of Reproduction and Infertility* 2014 **15** 173–183.

37 Bellver J & Simón C. Implantation failure of endometrial origin: what is new? *Current Opinion in Obstetrics and Gynecology* 2018 **30** 229–236. (https://doi.org/10.1097/GCO.0000000000000468)

38 Vander Borght M & Wyns C. Fertility and infertility: definition and epidemiology. *Clinical Biochemistry* 2018 **62** 2–10. (https://doi.org/10.1016/j.clinbiochem.2018.03.012)

39 Präg P & Mills MC. Cultural determinants influence assisted reproduction usage in Europe more than economic and demographic factors. *Human Reproduction* 2017 **32** 2305–2314. (https://doi.org/10.1093/humrep/dex298)

40 Lazarus J, Brown RS, Daumerie C, Hubalewska-Dydejczyk A, Negro R & Vaidya B. 2014 European Thyroid Association guidelines for the management of subclinical hypothyroidism in pregnancy and in children. *European Thyroid Journal* 2014 **3** 76–94. (https://doi.org/10.1159/000362597)

41 Poppe K, Glinoer D, Tournaye H, Devroey P & Velkeniers B. Impact of the ovarian hyperstimulation syndrome on thyroid function. *Thyroid* 2008 **18** 801–802. (https://doi.org/10.1089/thy.2007.0304)

42 Romitti M, Fabris VC, Ziegelmann PK, Maia AL & Spritzer PM. Association between PCOS and autoimmune thyroid disease: a systematic review and meta-analysis. *Endocrine Connections* 2018 **7** 1158–1167. (https://doi.org/10.1530/EC-18-0309)

43 Coulam CB, Adamson SC & Annegers JF. Incidence of premature ovarian failure. *Obstetrics and Gynecology* 1986 **67** 604–606. (https://doi.org/10.1097/00006254-198703000-00020).

44 Weghofer A, Brill H, Feichtinger R, Barad D & Gleicher N. Does autoimmunity play a role in the pathophysiology of premature ovarian ageing? *Reproductive Biomedicine Online* 2008 **16** 830–834. (https://doi.org/10.1016/S1472-6483(10)60149-6)

45 Osuka S, Iwase A, Goto M, Takikawa S, Nakamura T, Murase T, Kato N, Bayasula, Kotani T & Kikkawa F. Thyroid autoantibodies do not impair the ovarian reserve in euthyroid infertile women: a cross-sectional study. *Hormone and Metabolic Research* 2018 **50** 537–542. (https://doi.org/10.1055/a-0637-9430)

46 Bakalov VK, Gutin L, Cheng CM, Zhou J, Sheth P, Shah K, Arepalli S, Vanderhoof V, Nelson LM & Bondy CA. Autoimmune disorders in women with turner syndrome and women with karyotypically normal primary ovarian insufficiency. *Journal of Autoimmunity* 2012 **38** 315–321. (https://doi.org/10.1016/j.jaut.2012.01.015)

47 Chen CW, Huang YL, Tzeng CR, Huang RL & Chen CH. Idiopathic low ovarian reserve is associated with more frequent positive thyroid peroxidase antibodies. *Thyroid* 2017 **27** 1194–1200. (https://doi.org/10.1089/thy.2017.0139)

48 Petta CA, Arruda MS, Zantut-Wittmann DE & Benetti-Pinto CL. Thyroid autoimmunity and thyroid dysfunction in women with endometriosis. *Human Reproduction* 2007 **22** 2693–2697. (https://doi.org/10.1093/humrep/dem267)

49 Shigesi N, Kvaskoff M, Kirtley S, Feng Q, Fang H, Knight JC, Missmer SA, Rahmioglu N, Zondervan KT & Becker CM. The association between endometriosis and autoimmune diseases: a systematic review and meta-analysis. *Human Reproduction Update* 2019 **25** 486–503. (https://doi.org/10.1093/humupd/dmz014)

50 Unuane D, Velkeniers B, Anckaert E, Schiettecatte J, Tournaye H, Haentjens P & Poppe K. Thyroglobulin autoantibodies: is there any added value in the detection of thyroid autoimmunity in women consulting for fertility treatment? *Thyroid* 2013 **23** 1022–1028. (https://doi.org/10.1089/thy.2012.0562)

51 Pedersen OM, Aardal NP, Larssen TB, Varhaug JE, Myking O & Vik-Mo H. The value of ultrasonography in predicting autoimmune thyroid disease. *Thyroid* 2000 **10** 251–259. (https://doi.org/10.1089/thy.2000.10.251)

52 Ding X, Yang L, Wang J, Tang R, Chen Q, Pan J, Yang H, Chen X, Chen Z & Mu L. Subclinical hypothyroidism in polycystic ovary syndrome: a systematic review and meta-analysis. *Frontiers in Endocrinology* 2018 **9** 700. (https://doi.org/10.3389/fendo.2018.00700)

53 Poppe K, Glinoer D, Steirteghem A Van, Tournaye H, Devroey P, Schiettecatte J & Velkeniers B. Thyroid dysfunction and autoimmunity in infertile women. *Thyroid* 2002 **12** 997–1001. (https://doi.org/10.1089/105072502320908330)

54 Gallos ID, Eapen A, Price MJ, Sunkara SK, Macklon NS, Bhattacharya S, Khalaf Y, Tobias A, Deeks JJ, Rajkhowa M, *et al*. Controlled ovarian stimulation protocols for assisted reproduction: a network meta-analysis. *Cochrane Database of Systematic Reviews* 2017 **3** CD012586. (https://doi.org/10.1002/14651858.CD012586)

55 Poppe K, Glinoer D, Tournaye H, Schiettecatte J, Devroey P, van Steirteghem A, Haentjens P & Velkeniers B. Impact of ovarian hyperstimulation on thyroid function in women with and without thyroid autoimmunity. *Journal of Clinical Endocrinology and Metabolism* 2004 **89** 3808–3812. (https://doi.org/10.1210/jc.2004-0105)

56 Ain KB, Mori Y & Refetoff S. Reduced clearance rate of thyroxine-binding globulin (TBG) with increased sialylation: a mechanism for estrogen-induced elevation of serum TBG concentration. *Journal of Clinical Endocrinology and Metabolism* 1987 **65** 689–696. (https://doi.org/10.1210/jcem-65-4-689)

57 Mintziori G, Goulis DG, Toulis KA, Venetis CA, Kolibianakis EM & Tarlatzis BC. Thyroid function during ovarian stimulation: a systematic review. *Fertility and Sterility* 2011 **96** 780–785. (https://doi.org/10.1016/j.fertnstert.2011.06.020)

58 Muller AF, Verhoeff A, Mantel MJ, Jong FH De & Berghout A. Decrease of free thyroxine levels after controlled ovarian hyperstimulation. *Journal of Clinical Endocrinology and Metabolism* 2000 **85** 545–548. (https://doi.org/10.1210/jcem.85.2.6374)

59 Poppe K, Glinoer D, Tournaye H, Schiettecatte J, Haentjens P & Velkeniers B. Thyroid function after assisted reproductive technology in women free of thyroid disease. *Fertility and Sterility* 2005 **83** 1753–1757. (https://doi.org/10.1016/j.fertnstert.2004.12.036)

60 Gracia CR, Morse CB, Chan G, Schilling S, Prewitt M, Sammel MD & Mandel SJ. Thyroid function during controlled ovarian hyperstimulation as part of in vitro fertilization. *Fertility and Sterility* 2012 **97** 585–591. (https://doi.org/10.1016/j.fertnstert.2011.12.023)

61 Reinblatt S, Herrero B, Correa JA, Shalom-Paz E, Ata B, Wiser A, Morris D & Holzer H. Thyroid stimulating hormone levels rise after assisted reproductive technology. *Journal of Assisted Reproduction and Genetics* 2013 **30** 1347–1352. (https://doi.org/10.1007/s10815-013-0081-3)

62 Benaglia L, Busnelli A, Somigliana E, Leonardi M, Vannucchi G, Leo S De, Fugazzola L, Ragni G & Fedele L. Incidence of elevation of serum thyroid-stimulating hormone during controlled ovarian hyperstimulation for in vitro fertilization. *European Journal of Obstetrics, Gynecology, and Reproductive Biology* 2014 **173** 53–57. (https://doi.org/10.1016/j.ejogrb.2013.11.003)

63 Busnelli A, Somigliana E, Benaglia L, Sarais V, Ragni G & Fedele L. Thyroid axis dysregulation during in vitro fertilization in hypothyroid-treated patients. *Thyroid* 2014 **24** 1650–1655. (https://doi.org/10.1089/thy.2014.0088)

64 Delvigne A & Rozenberg S. Review of clinical course and treatment of ovarian hyperstimulation syndrome (OHSS). *Human Reproduction Update* 2003 **9** 77–96. (https://doi.org/10.1093/humupd/dmg005)

65 Poppe K, Unuane D, D'Haeseleer M, Tournaye H, Schiettecatte J, Haentjens P & Velkeniers B. Thyroid function after controlled ovarian hyperstimulation in women with and without the hyperstimulation syndrome. *Fertility and Sterility* 2011 **96** 241–245. (https://doi.org/10.1016/j.fertnstert.2011.04.039)

66 Noppen M, Poppe K, D'Haese J, Meysman M, Velkeniers B & Vincken W. Interventional bronchoscopy for treatment of tracheal obstruction secondary to benign or malignant thyroid disease. *Chest* 2004 **125** 723–730. (https://doi.org/10.1378/chest.125.2.723)

67 Korevaar TIM, Rijke YB de, Chaker L, Medici M, Jaddoe VWV, Steegers EAP, Visser TJ & Peeters RP. Stimulation of thyroid function by human chorionic gonadotropin during pregnancy: a risk factor for thyroid disease and a mechanism for known risk factors. *Thyroid* 2017 **27** 440–450. (https://doi.org/10.1089/thy.2016.0527)

68 Busnelli A, Vannucchi G, Paffoni A, Faulisi S, Fugazzola L, Fedele L & Somigliana E. Levothyroxine dose adjustment in hypothyroid women achieving pregnancy through IVF. *European Journal of Endocrinology* 2015 **173** 417–424. (https://doi.org/10.1530/EJE-15-0151)

69 Wang H, Gao H, Chi H, Zeng L, Xiao W, Wang Y, Li R, Liu P, Wang C, Tian Q, *et al*. Effect of levothyroxine on miscarriage among women with normal thyroid function and thyroid autoimmunity undergoing in vitro fertilization and embryo transfer a randomized clinical trial. *JAMA* 2017 **318** 2190–2198. (https://doi.org/10.1001/jama.2017.18249)

70 Toulis KA, Goulis DG, Venetis CA, Kolibianakis EM, Negro R, Tarlatzis BC & Papadimas I. Risk of spontaneous miscarriage in euthyroid women with thyroid autoimmunity undergoing IVF: a meta-analysis. *European Journal of Endocrinology* 2010 **162** 643–652. (https://doi.org/10.1530/EJE-09-0850)

71 Thangaratinam S, Tan A, Knox E, Kilby MD, Franklyn J & Coomarasamy A. Association between thyroid autoantibodies and miscarriage and preterm birth: meta-analysis of evidence. *BMJ* 2011 **342** d2616. (https://doi.org/10.1136/bmj.d2616)

72 Busnelli A, Paffoni A, Fedele L & Somigliana E. The impact of thyroid autoimmunity on IVF/ICSI outcome: a systematic review and meta-analysis. *Human Reproduction Update* 2016 **22** 775–790. (https://doi.org/10.1093/humupd/dmw019)

73 Turhan Iyidir O, Konca Degertekin C, Sonmez C, Atak Yucel A, Erdem M, Akturk M & Ayvaz G. The effect of thyroid autoimmunity on T-cell responses in early pregnancy. *Journal of Reproductive Immunology* 2015 **110** 61–66. (https://doi.org/10.1016/j.jri.2015.04.002)

74 Miko E, Meggyes M, Doba K, Farkas N, Bogar B, Barakonyi A, Szereday L, Szekeres-Bartho J & Mezosi E. Characteristics of peripheral blood NK and NKT-like cells in euthyroid and subclinical hypothyroid women with thyroid autoimmunity experiencing reproductive failure. *Journal of Reproductive Immunology* 2017 **124** 62–70. (https://doi.org/10.1016/j.jri.2017.09.008)

75 Kilic S, Tasdemir N, Yilmaz N, Yuksel B, Gul A & Batioglu S. The effect of anti-thyroid antibodies on endometrial volume, embryo grade and IVF outcome. *Gynecological Endocrinology* 2008 **24** 649–655. (https://doi.org/10.1080/09513590802531112)

76 Lee YL, Ng HP, Lau KS, Liu WM, O WS, Yeung WS & Kung AW. Increased fetal abortion rate in autoimmune thyroid disease is related to circulating TPO autoantibodies in an autoimmune thyroiditis animal model. *Fertility and Sterility* 2009 **91**(Supplement) 2104–2109. (https://doi.org/10.1016/j.fertnstert.2008.07.1704)

77 Poppe K, Autin C, Veltri F, Kleynen P, Grabczan L, Rozenberg S & Ameye L. Thyroid autoimmunity and intracytoplasmic sperm injection outcome: a systematic review and meta-analysis. *Journal of Clinical Endocrinology and Metabolism* 2018 **103** 1755–1766. (https://doi.org/10.1210/jc.2017-02633)

78 Zhong YP, Ying Y, Wu HT, Zhou CQ, Xu YW, Wang Q, Li J, Shen XT & Li J. Relationship between antithyroid antibody and pregnancy outcome following in vitro fertilization and embryo transfer. *International Journal of Medical Sciences* 2012 **9** 121–125. (https://doi.org/10.7150/ijms.3467)

79 Hou Y, Liu A, Li J, Wang H, Yang Y, Li Y, Fan C, Zhang H, Wang H, Ding S, *et al*. Different thyroidal responses to human chorionic gonadotropin under different thyroid peroxidase antibody and/or thyroglobulin antibody positivity conditions during the first half of pregnancy. *Thyroid* 2019 **29** 577–585. (https://doi.org/10.1089/thy.2018.0097)

80 Chua SJ, Danhof NA, Mochtar MH, Van Wely M, McLernon DJ, Custers I, Lee E, Dreyer K, Cahill DJ, Gillett WR, et al. Age-related natural fertility outcomes in women over 35 years: a systematic review and individual participant data meta-analysis. *Human Reproduction* 2020 **35** 1808–1820. (https://doi.org/10.1093/humrep/deaa129)

81 Dhillon-Smith RK, Middleton LJ, Sunner KK, Cheed V, Baker K, Farrell-Carver S, Bender-Atik R, Agrawal R, Bhatia K, Edi-Osagie E, *et al*. Levothyroxine in women with thyroid peroxidase antibodies before conception. *New England Journal of Medicine* 2019 **380** 1316–1325. (https://doi.org/10.1056/NEJMoa1812537)

82 Akhtar MA, Agrawal R, Brown J, Sajjad Y & Craciunas L. Thyroxine replacement for subfertile women with euthyroid autoimmune thyroid disease or subclinical hypothyroidism. *Cochrane Database of Systematic Reviews* 2019 **6** CD011009. (https://doi.org/10.1002/14651858.CD011009.pub2)

83 Negro R, Mangieri T, Coppola L, Presicce G, Casavola EC, Gismondi R, Locorotondo G, Caroli P, Pezzarossa A, Dazzi D, et al. Levothyroxine treatment in thyroid peroxidase antibody-positive women undergoing assisted reproduction technologies: a prospective study. *Human Reproduction* 2005 **20** 1529–1533. (https://doi.org/10.1093/humrep/deh843)

84 Poppe K, Veltri F & Autin C. Does levothyroxine improve pregnancy outcomes in euthyroid women with thyroid autoimmunity

undergoing assisted reproductive technology? *Thyroid Research* 2018 **11** 7. (https://doi.org/10.1186/s13044-018-0052-y)

85 Kim CH, Ahn JW, Kang SP, Kim SH, Chae HD & Kang BM. Effect of levothyroxine treatment on in vitro fertilization and pregnancy outcome in infertile women with subclinical hypothyroidism undergoing in vitro fertilization/intracytoplasmic sperm injection. *Fertility and Sterility* 2011 **95** 1650–1654. (https://doi.org/10.1016/j.fertnstert.2010.12.004)

86 Loutradi KE, Tarlatzis BC, Goulis DG, Zepiridis L, Pagou T, Chatziioannou E, Grimbizis GF, Papadimas I & Bontis I. The effects of sperm quality on embryo development after intracytoplasmic sperm injection. *Journal of Assisted Reproduction and Genetics* 2006 **23** 69–74. (https://doi.org/10.1007/s10815-006-9022-8)

87 Vaquero E, Lazzarin N, Carolis C De, Valensise H, Moretti C & Romanini C. Mild thyroid abnormalities and recurrent spontaneous abortion: diagnostic and therapeutical approach. *American Journal of Reproductive Immunology* 2000 **43** 204–208. (https://doi.org/10.1111/j.8755-8920.2000.430404.x)

88 Litwicka K, Arrivi C, Varricchio MT, Mencacci C & Greco E. In women with thyroid autoimmunity, does low-dose prednisolone administration, compared with no adjuvant therapy, improve in vitro fertilization clinical results? *Journal of Obstetrics and Gynaecology Research* 2015 **41** 722–728. (https://doi.org/10.1111/jog.12615)

89 Barth JH, Luvai A, Jassam N, Mbagaya W, Kilpatrick ES, Narayanan D & Spoors S. Comparison of method-related reference intervals for thyroid hormones: studies from a prospective reference population and a literature review. *Annals of Clinical Biochemistry* 2018 **55** 107–112. (https://doi.org/10.1177/0004563217691549)

90 Zhao T, Chen BM, Zhao XM & Shan ZY. Meta-analysis of ART outcomes in women with different preconception TSH levels. *Reproductive Biology and Endocrinology* 2018 **16** 111. (https://doi.org/10.1186/s12958-018-0424-0)

91 Velkeniers B, Van Meerhaeghe A, Poppe K, Unuane D, Tournaye H & Haentjens P. Levothyroxine treatment and pregnancy outcome in women with subclinical hypothyroidism undergoing assisted reproduction technologies: systematic review and meta-analysis of RCTs. *Human Reproduction Update* 2013 **19** 251–258. (https://doi.org/10.1093/humupd/dms052)

92 Practice Committee of the American Society for Reproductive Medicine. Subclinical hypothyroidism in the infertile female population: a guideline. *Fertility and Sterility* 2015 **104** 545–553. (https://doi.org/10.1016/j.fertnstert.2015.05.028)

93 Wilson JM & Jungner YG. Principles and practice of mass screening for disease. *Boletin de la Oficina Sanitaria Panamericana. Pan American Sanitary Bureau* 1968 **65** 281–393. (https://doi.org/10.1001/archinte.1969.00300130131020)

94 Dobrow MJ, Hagens V, Chafe R, Sullivan T & Rabeneck L. Consolidated principles for screening based on a systematic review and consensus process. *CMAJ* 2018 **190** E422–E429. (https://doi.org/10.1503/cmaj.171154)

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