Review Article

Subclinical Hypothyroidism & Infertility: A Review

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Abstract

Subclinical hypothyroidism (SCH) may be of greater clinical importance in women with "unexplained" infertility, especially when the luteal phase is inadequate, and such patients should be investigated for thyroid dysfunction in detail. To date, studies investigating the association between SCH and infertility are still based on the high serum thyroid stimulating hormone (TSH) levels while some older studies are based on the presence of an abnormal serum TSH after a thyrotropin releasing hormone (TRH) stimulation test. The recommendation in the current guidelines to treat subclinical hypothyroidism is based on minimal evidence and it is thought that with treatment the potential benefits outweigh the potential risks. Thyroxine-replacement therapy should be started in patients with SCH caused by conditions which are at high risk of progression to overt hypothyroidism.

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Introduction

Sub-fertility or infertility is a common condition having important psycho-social and economic impact. Prevalence of this condition is 12-14%. Studies that estimated prevalence of sub-fertility included primary infertility (i.e., inability to conceive) and secondary infertility (i.e., inability to conceive again after one or more pregnancy). Nevertheless, many authors distinguish sub-fertility from infertility, the latter being the absolute inability to conceive due to absence of sperm, premature menopause, complete tubal obstruction etc.[1-6] Thyroid dysfunction is a known contributing cause of infertility. Abnormal thyroid hormones affect normal menstrual pattern. Thyroid disorders is associated with an increased risk of miscarriage and possible long-term health consequences for the child.[7] The impact of screening and treatment of subclinical thyroid disorders for infertility management has not extensively been documented in the literature. Hence, this review attempts to identify the impact of subclinical hypothyroidism on female infertility, and to propose guidelines for screening and treatment when indicated.

Infertility

Infertility is defined as inability to conceive after one year of regular normal sexual activity without any contraceptive measures.[8] This definition was based on a study conducted on 5574 women during the period between 1946 and 1956 who had unprotected intercourse and ultimately conceived. Among these women 85% conceived within 12 months, 72% within first 6 months, and 50% within first 3 months. Two more recent prospective population-based studies showed that 50% of healthy women having unprotected intercourse become clinically pregnant during the first two cycles, and 80–90% during the first 6 months.[9,10] Though these studies may not represent the general population

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globally, but these indicate that under appropriate circumstances, most females are likely to conceive early.[11] The prevalence of infertility has been found stable over the recent decades.[12]

Causes of infertility among couples can be subdivided into four (4) broad categories: female infertility (35%), male infertility (30%), a combination of both (20%), and unexplained or 'idiopathic' infertility (15%).[13,14]

Causes of female infertility comprise endometriosis, tubal damage and ovulatory dysfunctions. Excepting tubal disorders which is more prevalent in Africa due to infections, all other causes of infertility have similar worldwide prevalence.[15] Endometriosis is only considered as a cause of infertility when the disease exceeds stage I (as defined by the American Society for Reproductive Medicine).[16] The cause of ovulatory dysfunction is further divided according to criteria established by World Health Organization (WHO) into: hypogonadotrophic - with low level of endogenous gonadotophins (Group -I), normogonadotrophic - with lnormal endogenous gonadotophins (Group -II) and hypergonadotrophic defective ovulation (Group -III).[17] Age and smoking habit of woman also constitute important prognostic factors.[18-21]

Regarding male infertility, there are many factors which cannot be evaluated properly. Thus evaluation of sperm quality, its transport, and semen analysis remain of limited value as a predictor of fertilizing ability.[22] The work-up of female infertility includes: a medical history, gynaecological examination, transvaginal ultrasonography, hormone profile, screening for infectious disease and, when indicated, hystero-salpingography and/or laparoscopy.[23,24] In the presence of a normal spermogram and a normal female work-up, the cause of a couple's infertility is considered idiopathic.

Sub clinical hypothyroidism (SCH)

In a Consensus Development Conference held in September, 2002 the American Association of Clinical Endocrinologists(AACE), American Thyroid Association (ATA) and The Endocrine Society (TES) have defined SCH as a disorder with high serum thyroid-stimulating hormone (TSH) level above upper limit of the reference range with normal serum free thyroxine (FT_4) level.[25] The third National Health and Nutrition Examination Survey (NHANES III)[26] screened 13,344 disease-free, euthyroid participants who were thyroid antibody negative. In this population, the median TSH concentration was1.39 mIU/L [95% CI: 0.45-4.12 mIU/L]. This was accepted as normal by the above mentioned consensus conference on sub clinical thyroid diseases[25] and Surks *et al*.[27] agreed with this reference range. In contrast, the National Academy of Clinical Biochemistry[28] suggested 0.4–2.5 mIU/L as the normal range, while Wartofsky and Dickey[29] and the AACE suggested 0.3–3.0 mIU/L as normal.[30] According to United States Preventive Services Task Force (USPSTF) Guidelines defined SCH to have high serum TSH 2.5-10 mIU/L with a normal FT_4 concentration.

As serum TSH varies over time in healthy people with occasional abnormal values, repeated serum TSH along with FT_4 measurements within 3–4 months is required to confirm diagnosis of SCH.[31-33] If an elevated serum TSH concentration is confirmed with normal FT_4, the diagnosis of SCH is made, and transient forms of SCH should be excluded. Normal serum free thyroxine concentrations may also be found among hospital in-patients with elevated serum TSH concentrations.

Serum TSH during pregnancy

Evidence based literatures strongly suggest that reference range for TSH is lower throughout pregnancy, both the lower and upper normal limit of serum TSH are decreased by about 0.1-0.2 mIU/L and 1 mIU/L respectively, compared with the customary TSH reference interval of 0.4–4.0 mIU/L in non-pregnant women. The largest decrease in serum TSH is observed during the first trimester which is transient, apparently related to hCG levels. (Table 1)

The American Thyroid Association Taskforce on Thyroid Disease During Pregnancy and Postpartum recommends that if trimester-specific reference ranges for TSH are not available in the laboratory, the following reference ranges will be 0.1–2.5 mIU/L in first trimester, 0.2–3.0 mIU/L in second trimester, and 0.3–3.0 mIU/L in third trimester.

Sub clinical hypothyroidism (SCH) has recently been challenged. Variations of FT_4 within the reference range in individual is less than that observed in a population. These data might reflect an abnormally low FT_4 value for patients who present with a mildly

Table-1: *Trimester-Specific Serum TSH Reference Intervals*

References	Serum TSH mIU/L [median (percentiles)		
	First Trimester	Second trimester	Third trimester
Haddow *et al*. (2004)[34]	0.94 (0.08–2.73)	1.29 (0.39–2.70)	-
Stricker *et al*. (2007)[35]	1.04 (0.09–2.83)	1.02 (0.20–2.79)	1.14 (0.31–2.90)
Panesar *et al*. (2001)[36]	0.80 (0.03–2.30)	1.10 (0.03–3.10)	1.30 (0.13–3.50)
Soldin *et al*. (2007)[37]	0.98 (0.24–2.99)	1.09 (0.46–2.95)	1.20 (0.43–2.78)
Bocos-Terraz *et al*. (2009)[38]	0.92 (0.03–2.65)	1.12 (0.12–2.64)	1.29 (0.23–3.56)
Marwaha *et al*. (2008)[39]	2.10 (0.60–5.00)	2.40 (0.43–5.78)	2.10 (0.74–5.70)

NB: *Median TSH in mIU/L, with data indicating 5th and 95th percentiles[34,36,39] or 2.5th and 97.5th percentiles[35,37,38].*

increased serum TSH.[40,41] Many authors have proposed serum TSH 2·5 mIU/L as upper normal limit. However, there is no general agreement among the endocrinologists about the most appropriate normal (i.e. physiologically relevant) upper limit serum TSH.[42]

Sub clinical hypothyroidism (SCH) and infertility

Studies investigating the association between SCH and infertility are still based on the high serum TSH levels and some older studies are based on the presence of an abnormal serum TSH after a TRH stimulation test. Table 2 summarizes the most relevant studies on the prevalence of SCH in women with infertility. In the study by Bohnet *et al*., SCH was considered as an infertility factor by itself because treatment with L-thyroxine 50 ì g/day had normalized their mid progesterone secretion and two among the eleven treated women became pregnant.[43] Bals-Pratsch *et al*. did not observe corpus luteum insufficiency in infertile women with SCH.[44] Gerhard *et al*. reported a positive correlation between basal TSH, LH and testosterone concentrations in the early follicular phase. Women with an elevated serum TSH had a lower pregnancy rate than the women with a normal TRH stimulated serum TSH. Eighty out of 185 infertile women had an abnormal TRH test, but only one woman had an increased basal serum TSH (0·5%).[45] In the study by Shalev *et al*., the prevalence of SCH was 0·67% in 444 infertile women, all with ovulatory dysfunction.[46] Grassi *et al*. investigated 129 women of infertile couples with ovulatory dysfunction, idiopathic and male infertility.[47] Six patients (4·6%) had a basal serum TSH level >4·5 mU/L and five of these six women had Autoimmune Thyroid Disease (AITD). The authors noted that the mean duration of infertility was significantly longer in the patients having thyroid disorders like abnormal TSH and/or AITD compared to those without any abnormality (3·8 vs. 2·6 years; P=0·005). In a case control study, Poppe *et al* investigated the prevalence of SCH (serum TSH >4·2 mU/l) in women of infertile couples (n = 438) who came for the first time to the centre of reproductive medicine. The control population consisted of 100 age-matched fertile women. The prevalence of a high serum TSH was comparable in both the study group and controls (<1%; P=ns).[48] Overall, the studies investigating the association between SCH and infertility were poorly controlled. Considering the largest cohorts published, the prevalence of SCH in infertile women ranged from 1% to 4% and most cases with SCH were associated with ovulatory dysfunction.

Recently, Raber *et al*. Investigated prospectively a group of 283 women with infertility.[49] All patients underwent a TRH stimulation test (SCH was defined as a serum TSH >15 mU/L). Women with a diagnosis of SCH were treated with thyroxine and followed prospectively over a 5-year period. Among these women 34% had SCH, an unusually high prevalence reflecting the specific referral pattern. Among the women who became pregnant during the follow-up period, over 25% still had SCH. Furthermore, the women who never achieved a basal serum TSH<2·5 mU/L or a TRH-stimulated TSH<20 mU/L became pregnant less frequently than those who could achieve. More frequent abortions were also observed in the women with a higher basal serum TSH (independent of the presence of autoimmunity). Arojoki *et al* found elevated serum TSH levels (>5·5 mU/L) in 4% women presenting with infertility for the first time.[50] The prevalence of

having an increased serum TSH was highest in the group with ovulatory dysfunction (6·3%). Prior to infertility examinations, 10 of 299 women were already receiving L-thyroxine for primary hypothyroidism. The incidental finding of an elevated serum TSH value in patients with infertility was therefore reduced to four among 299 women (1·3%), and this was in the range of the prevalence of SCH in the general population in Finland (2–3%).

In the studies summarized in Table 2, three included a control (fertile population) and the prevalence of SCH was comparable between the study group and controls.

The prevalence of SCH was considerably higher in the studies based on a TRH stimulation test to detect SCH compared with the studies that were based only on the upper limit of basal serum TSH. This difference might indicate that in older studies, using less sensitive measurements of serum TSH, the actual TSH reference levels are perhaps slightly higher in the setting of infertility. In a study, basal and TRH-stimulated TSH concentrations were measured in 834 infertile women, and 20% had abnormal results.[51] Postcoital tests and spontaneous conceptions were significantly poorer in women with SCH than in controls. Staub *et al*.[52] suggested that secondary hyperprolactinemia could be a cause of infertility in SCH women. In contrast, menstrual function in SCH patients and controls was similar, such as luteinizing hormone pulse patterns, 24-h mean serum luteinizing hormone, TSH, and prolactin concentrations.[53] Lincoln *et al*. reported a 2.3% prevalence of elevated serum TSH concentrations in 704 women with infertility for at least 1 year. Eleven out of sixteen hypothyroid patients' had ovulatory dysfunction. TSH values were not determined in the control group.[54]

Treatment interventions and guideline for subclinical/clinical hypothyroidism

Some studies used levothyroxine as treatment. Five studies reported the effect of treatment interventions for clinical and/or subclinical hypothyroidism. A randomized non-placebo controlled trial reported that after treatment with L-thyroxine subclinical hypothyroid women undergoing IVF/ICSI had a significantly higher embryo implantation rate (RR: 1.8, 1.00–3.25; P ¼ 0.05) and live birth rate (RR: 2.13, 1.07–4.21; P ¼ 0.03) compared to untreated women.[55] No significant differences were found for clinical pregnancy (RR: 1.42, 0.81–2.45; P ¼ 0.22) or miscarriage rate (RR: 0.8, 0.00–1.36; P ¼ 0.08).

Two cohort studies reported on pregnancy complications for women with clinical or sub clinical hypothyroidism who were adequately, and who were not adequately treated.[56,57] Not adequately treated hypothyroid women had higher TSH and a lower than normal thyroxine level, despite treatment. In the case of subclinical hypothyroidism, a TSH higher than the reference interval despite treatment was defined as not adequately treated. The first study showed no significant difference in the prevalence of gestational hypertension in 68 women not adequately treated for subclinical or clinical

Table-2: *Prevalence of subclinical hypothyroidism in infertile women*

Reference	Prevalence of SCH in patients	Prevalence of SCH in controls	SCH defined by	Type of study
Bohnet et al. (1981)[43]	11% (20/185)	No controls	Basal TSH > 3 mU/l or peak TSH‡ > 15 mU/l	P
Gerhard et al. (1991)[45]	43%* (80/185)	No controls	Peak TSH‡ > 20 mU/l	P
Shalev et al. (1994)[46]	0·7% (3/444)	No controls	Basal TSH > 4·5 mU/l	R
Grassi et al. (2001)[47]	4·6% (6/129)	Controls	Basal TSH > 4·5 mU/l	P
Poppe et al. (2002)[48]	0·9% (4/438)	< 1%	Basal TSH > 4·2 mU/l	P
Raber et al. (2003)[49]	34% (96/283)	No controls	Basal TSH > 4 mU/l or peak TSH‡ > 15 mU/l	P
Arojoki et al. (2000)[50]	1·3% (4/299)	2–3%†	Basal TSH > 5·5 mU/l	R

SCH: *sub clinical hypothyroidism; P: prospective; R: retrospective. *One in 185 patients had a basal serum TSH >6 mU/L (0·5%). †Prevalence in the Finnish population. ‡Peak serum TSH after TRH-stimulation test.*

hypothyroidism compared with 38 women who remain still hypothyroid despite treatment (RR: 0.14, CI: 0.01–2.20: P ¼ 0.16) for clinical hypothyroidism, (RR: 0.41, CI:0.11–1.62:P¼0.21) for subclinical hypothyroidism.[56] The second study reported no significant difference in Neonatal Intensive Care Unit (NICU) admissions (RR:0.31, CI:0.08–1.2: P¼0.09). A significant difference was found in low birth weight (RR:0.31, CI: 0.11–0.92: P¼ 0.04) for 127 women with subclinical hypothyroidism with normal TSH level with levothyroxine treatment compared with 40 women with abnormal TSH levels in the first trimester despite levothyroxine treatment, while Caesarean section rates were almost similar in the two groups, respectively 27.5% and 29.1%.[57] One case control study on 38 women with hypothyroidism treated with levothyroxine during pregnancy reported no significant difference in the IQ level, verbal performance or cognitive performance between the 19 children of subclinically hypothyroid mothers despite treatment and 19 children of mothers who were euthyroid with treatment.[58]

European Society of Clinical Pharmacy (ESCP) guideline recommends levothyroxine replacement in women with subclinical hypothyroidism, given the fact that the potential benefits outweigh the potential risks. For obstetrical outcome, United States Preventive Services Task Force (USPSTF) recommendation level is B, evidence is fair (Grade 1). For neurological outcome, USPSTF recommendation level is I, evidence is poor (Grade: 0). The European Society of Human Reproduction and Embryology (ESHRE) and the Royal College of Obstretians ans Gynaecologists (RCOG) do not employ guidelines on sub clinical hypothyroidism in pregnancy. Only one among the seven studies on hypothyroidism reported separate data on subclinical hypothyroidism. This study showed that gestational hypertension was more commonly found in not adequately treated women than in adequately treated women, though the difference was not significant. The recommendation in the current guidelines to treat subclinical hypothyroidism is based on minimal evidence. It is thought that with treatmant the potential benefits outweigh the potential risks. L-Thyroxine replacement therapy should be started in patients with SCH caused by conditions which are at high risk of progression to overt hypothyroidism. The main controversy revolves around the upper limits of the serum TSH concentration beyond which therapy should be started. Patients with SCH should always be given thyroid-replacement therapy when serum TSH concentrations are persistently above 10 mIU/L. In SCH patients presenting with persistently elevated serum TSH concentrations less than 10 mIU/l, L-thyroxine replacement therapy should be started in presence of at least one of the following conditions: pregnancy, childhood, elevated anti-thyroid autoantibody, evidence of hypo-echoic thyroid gland on ultrasound, women with persistent infertility, diffuse or nodular goitre, or symptoms of hypothyroidism. In patients with a serum TSH above normal but below 10 mIU/L and who do not have any of these conditions, L-thyroxine therapy remains controversial.[59-61]

Conclusion

Severe hypothyroidism is commonly associated with failure of ovulation. Ovulation followed by pregnancy can occur in case of mild hypothyroidism. However, these pregnancies are often associated with abortions, stillbirths, or pre-maturity. Subclinical hypothyroidism may be of greater clinical importance in women with "unexplained" infertility, especially when the luteal phase is inadequate, and such patients should be investigated in depth for thyroid dysfunction. Treatment with levothyroxineis is recommended for women with clinical hypothyroidism because it lowers the risk for miscarriage and preterm delivery. Our review shows that for subclinical hypothyroidism there is insufficient evidence to recommend for or against the universal treatment with levothyroxine. But in case of infertility it is always a preferable option to start levothyroxine as it not only enhance the fertility but also ensures euthyroid state which is very important to continue the pregnancy till delivery.

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