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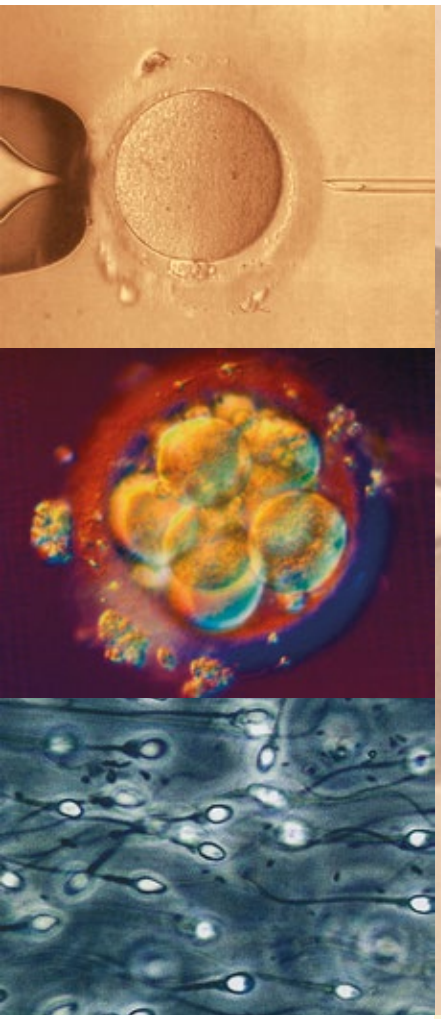

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Prevention and Therapy of Hypothyroidism in Patients Undergoing Fertility Treatment

H. G. Bohnet

In patients undergoing fertility treatment latent (subclinical) hypothyroidism occurs in about 7–12 %; overt hypothyroidism ranges between 2.8 and 5 %. Thus, in many patients thyroid dysfunction may be one reason for infertility. In approximately 15 % autoimmunity is the cause for this disease, i.e. in the majority chronic iodine deficiency may account for hypothyroidism. Most recent studies suggest that a reduced antioxidant defense and expression of selenoproteins, most probably due to Selenium deficiency, trigger autoaggression in the thyroid. As a consequence peroxide, which is necessary for iodide oxidation and tyrosin iodination cannot completely neutralized as oxygen radicals are left.

To prevent thyroid dysfunction women having assisted reproductive technologies should receive a daily dose of 150 µg iodine as well as 75 µg selenium, preferentially given as sodium selenite. The trace elements should be taken after an overnight fast with water half an hour before breakfast as it is also recommended for levothyroxin intake.

Therapy of hypothyroidism is based on the etiology and the extent of the disorder. If the latent form is diagnosed, usually 50–75 µg levothyroxin will restore normal function avoiding a complete suppression of TSH which should be around 1 mU/L. To treat overt hypothyroidism a dosage of 125–150 µg may be warranted. If autoimmunity is excluded, the trace elements iodine and selenium should be given in addition (see above), in particular as the fetus and new-born needs them too. Supplementation of selenium avoids a reduction of the redox system which could result in post-partum-thyroiditis and in exacerbation of a pre-existent Hashimoto's. The treatment of hypothyroidism with 100–200 µg selenium in addition to levothyroxin should result in selenium serum concentrations of approximately 1.4 µmol/L; this level has been shown to prevent further detoriation of the disease.

Key words: sterility, latent, overt hypothyroidsm, iodine, selenium, dosage of levothyroxin

Prävention und Behandlung der Schilddrüsenunterfunktion im Rahmen der Fertilitätstherapie. Im Krankengut von Schwerpunktspraxen für Reproduktionsmedizin wird die Häufigkeit der latenten Hypothyreose mit 7–12 % und die der manifesten Schilddrüsenunterfunktion mit 2,8–5 % veranschlagt und dürfte somit in vielen Fällen zu einer Fertilitätsstörung der Frau beitragen. In etwa einem Sechstel der Fälle ist die Schilddrüsendysfunktion durch eine Autoimmunreaktion in der Schilddrüse hervorgerufen, d. h. bei dem Rest dürfte eine chronische Jodmangelversorgung die Ursache sein. Für die Autoaggression wird nach neuesten Erkenntnissen eine verminderte Antioxydansabwehr aufgrund eines Selenmangels verantwortlich gemacht. Die Folge ist, dass Sauerstoffradikale aus dem Peroxid, welches für die Jodoxidation und für die Tyrosin-Jodisation notwendig ist, nicht abgefangen werden können.

Zur Prävention von Schilddrüsenfunktionsstörungen sollten alle Frauen mit Kinderwunsch, sofern sie als „schilddrüsengesund" gelten, täglich 150 µg Jod und 75 µg Selen, letzteres am besten als Natriumselenit, nüchtern mit Wasser, am besten eine halbe Stunde vor dem Frühstück einnehmen, so wie auch Levothyroxin eingenommen werden muss.

Die Therapie einer Hypothyreose richtet sich nach dem Ausmaß und der Ursache der Störung. Bei der latenten Form liegt die durchschnittlich erforderliche Levothyroxin-Substitutions-Dosis zwischen 50 und 75 µg pro Tag; dadurch wird erfahrungsgemäß eine völlige Suppression des TSH verhindert, was unbedingt zu vermeiden ist. Das TSH sollte bei der Kontrolle um 1 mE/L liegen. Bei der manifesten Hypothyreose sind selten höhere Dosen als 125–150 µg erforderlich. Ist eine Immunthyreopathie ausgeschlossen, ist die zusätzliche Gabe von Jod und Selen sinnvoll (s. o.), zumal in einer nachfolgenden Schwangerschaft der Fetus ebenfalls mit diesen Spurenelementen versorgt werden muss. Durch die Verabreichung von Selen wird eine Verminderung des Redoxpotenzials in der Schilddrüse verhindert; ein drastischer Abfall begünstigt die Erstmanifestation einer postpartalen bzw. eine Exazerbation einer präexistenten Immunthyreopathie. Bei nachgewiesener Hashimoto-Thyreoiditis wird neben Levothyroxin 100–200 µg Selen verabreicht, womit ein Serum-Selenspiegel von etwa 1,4 µmol/L angestrebt wird, welcher erfahrungsgemäß ein optimales Redoxpotenzial gewährleistet. **J Reproduktionsmed Endokrinol 2009; 6 (Sonderheft 1): 10–2.**

Schlüsselwörter: Sterilität, Hypothyreose, Jod, Selen, Levothyroxin

Introduction

Among sterility patients the latent (subclinical) form of hypothyroidism is more common than overt dysfunction; based on a TSH cut-off of 3 mU/L the incidence has been reported to occur between 7–12 % and 2.8–5.1 % respectively [1–3]. TSH and antithyroxin-peroxidase antibody (anti-TPO) measurements in our own fertility clinic laboratory over approximately one decade revealed that in about 17 % cases anti-TPO is positive, when TSH exceeds 3 mU/L suggesting Hashimoto thyroiditis. In Figure 1, our own data are shown. Thus, most probably iodine deficiency accounts for more than 80 % for hypothyroidism. Most recent preliminary data [4] show that TSH concentrations increased significantly during controlled ovarian hyperstimulation for IVF suggesting an instable, vulnerable thyroid function in this condition; a detoriation may even occur when these patients become pregnant. Therefore a strategy to prevent hypothyroidism is necessary. Treatment of thyroid dysfunction is based upon its pathophysiology, i.e. either autoimmunity or iodine deficiency as well as upon the degree of thyroid malfunction.

Prevention and Treatment of Hypothyroidism Due to Iodine Deficiency

To prevent thyroid malfunction a daily intake of 200 µg iodine is required; in pregnant women 250 µg are needed. During the last 10 years iodine supply of the German population has been considerably improved; an average intake of approximately 150 µg a day was achieved.

However, greater variations can be seen, in particular among different social groups. Thus, the difference to the opti-

Correspondence: Prof. Dr. med. Heinz G. Bohnet, Postfach 54 07 22, D 22507 Hamburg; E-Mail: Prof.Dr.HGBohnet@gmx.net

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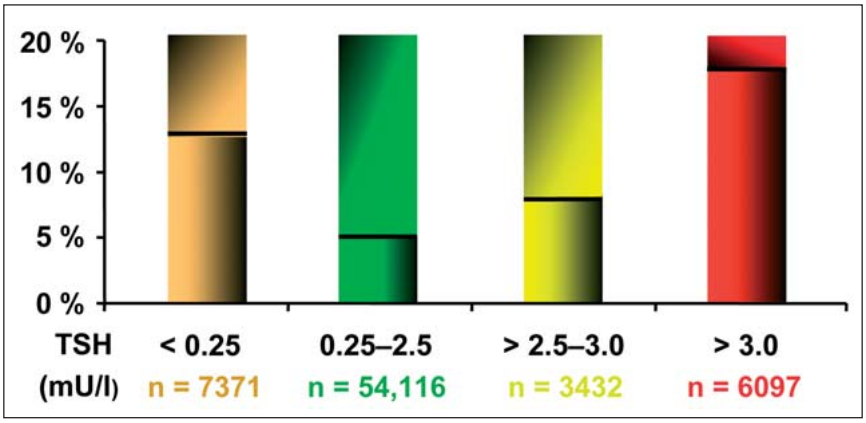

Figure 1: Rate of thyroid antibodies depending on serum TSH levels. Note that in hypothyroidism (TSH > 3 IU/l) the greatest percentage was observed.

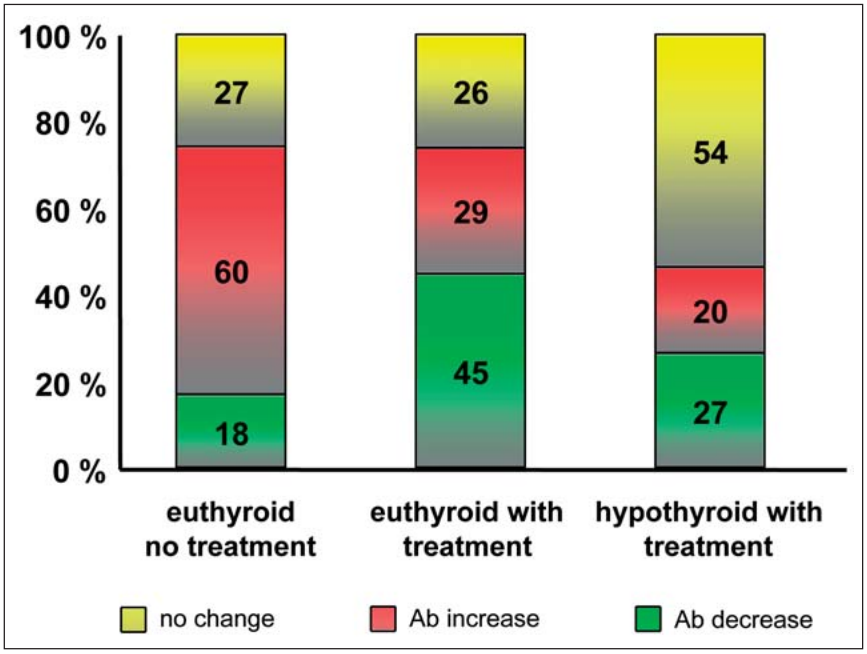

Figure 2: Change in thyroid antibody titers within 6 months. Note that the highest increase was observed, when no levothyroxin was given.

mum of daily iodine supply may account for an increased incidence of goitrous thyroids and/or instable thyroid function. To cope iodine depletion of the thyroid gland, it takes at least 3 months. The German Society for Nutrition recommends a daily supplement of 150 µg iodine. To prevent the development of a goiter and/or hypthyroidism in women who want to become or in those being pregnant. This also applies to patients with a basal TSH exceeding 2 mU/L [3]. Therefore, a strategy for thyroid iodine replenishment is warranted.

Most often hypothyroidism is diagnosed during the sterility work-up. Therefore, a period of 3 months of iodine supplementation appears to be a relative long time, in particular as it does not guarantee to establish normal thyroid function. It has been widely documented that in contrary to children, juveniles and young adults, iodine supplemention does not always result in a normalisation of an increased thyroid volume nor in restitution of normal function. Therefore a combination of both, levothyroxin plus iodine, should be preferred (see below).

An European study revealed the trace element selenium (Se) as a protective against goiter [5]. In addition, Se plays a role in antioxidant defense against peroxide, which is necessary for thyroid hormone synthesis. Therefore, supplementation of Se in a daily dose of 50–75 µg, given as sodium selenite [6], is recommended in addition to an iodine supplement.

This seems to be important, as during pregnancy maternal levels of these trace elements decrease as a result of fetal needs [7, 8].

The aim of treatment of hypothyroidism is to render the patient quickly back to an euthyroid state, in particular, women who want to become pregnant. A presumed sufficient dose of levothyroxin combined with iodine (and Se) is given to lower TSH to the normal reference range (< 2.5 mU/L). This depends a.o. on the extent of previous TSH elevation and on the body weight of the patient. In latent hypothyroidism a daily dose of 50–75 µg of levothyroxin is usually adequate, whereas in overt hypothyroidism a dosage up to 125 µg may be needed.

Not before six weeks of treatment thyroid function should be re-evaluated, which must include serum TSH und free thyroxin (fT4), as further fine-tuning of TSH inside the reference range (0.5–1.5 mU/L) may be needed for individual patients. It is however a preriquisite to avoid TSH suppression.

Prevention and Treatment of Hypothyroidism Due to Autoimmunity

The reason for autoimmunity to the thyroid has not been clarified. Thus, there is no specific treatment available so far. Infiltration of lymphocytes into the thyroid gland, paralleled by production of antibodies to microsomes and thyroxin-peroxidase (anti-TPO), respectively as well as to thyroglobulin, is apparent and may not only result in destruction of the thyroid gland, but finally also in hypothyroidism. A logical consequence was and still is to substitute thyroxin to restore and maintain normal thyroid function.

In most recent years data have been accumulated that in a not suppressive dose levothyroxin given to still euthyroid subjects with thyroid antibodies will prevent development of hypothyroidism [2, 7]; in particular, women with fertility problems due to thyroid immunity appear to have a benefit.

Early treatment of latent hypothyroidism, however, as an option recommended in a consensus paper by the German Endocrine Society [9] may prevent

detoriation of the autoimmunic process, i.e. anti-TPO-Titers decrease or stay stable. In overt hypothyroidism an increase of thyroid antibodies may occur despite thyroid treatment. In Figure 2 our own data are presented.

Recently, several studies reported on the advantages of a daily supplement of 200 µg Se in thyroid autoimmunity [10, 11]; serum titers of anti-TPO-antibodies decreased and patients' self-assessment of the disease improved significantly. Moreover, Negro and co-workers [2] reported that Se supplementation during pregnancy resulted in a lowered abortion rate and in less cases developing hypothyroidism within one year post partum. Best effects were seen when mean Se serum concentrations leveled at about 1.4 µmol/L [2].

Treatment Monitoring

It is widely recognized that more than 80 % of euthyroid subjects with a normal thyroid gland, as judged by ultrasound, exhibit a basal TSH ranging between 0.5 and 1.5 mU/L [3]. As a consequence hypothyroid patients should receive an adequate dose of levothyroxin resulting in a TSH of approximately 1 mU/L. As pointed out above, in latent hypthyroidism therapy can be initiated with the assumed full dose of levothyroxin (50–75 µg a day). It is a rule that the hormon is taken after an overnight fast half an hour before breakfast, as this guaranties a perfect absorption. A control of TSH should not be performed before six weeks of treatment. As a standard levothyroxin should be taken after the necessary bloodsample was withdrawn. If TSH is not in the favorable range, a further step-wise increase of levothyroxin for about 12.5 µg is advised for fine tuning. In iodine deficient patients the equivalent of 150 µg iodine and in subjects with thyroid immunity at least 100 µg Se should be taken along with thyroxin [8].

In overt hypythyroidism half of the assumed necessary dose of levothyroxin should be administered for about 2–4 weeks; thereafter usually the full dose can be given. Not before 6–8 weeks TSH und fT4 should be controlled to verify normal thyroid function. A further increase of the dosage may also be required. In patients with Hashimoto's thyroiditis Se should be supplemented. As it appears that there is an inverse relationship between Se levels and thyroid immunity, 200 µg Se might be given as a starting dose. However, three months after initiation of the supplementation Se serum levels should be estimated to judge whether a favorable concentration of about 1.4 µmol/L is established.

Following fertility treatment the dose of levothyroxin must be increased for about 25 % as soon as pregnancy is documented by an ultrasound.

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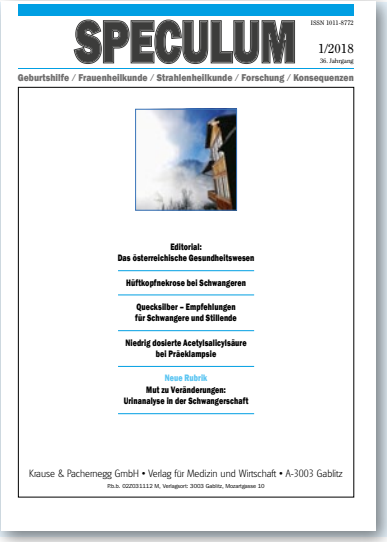

Speculum

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