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Research Article

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Dietary Supplementation Improves Blastocyst Number and Ongoing Pregnancy Rate of IVF Patients with Hashimoto Thyroiditis

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Abstract

In Assisted Reproduction Techniques (ART), autoimmune disorders of the thyroid gland present as common concomitant diseases. Hypothyroidism caused by autoimmune thyroiditis can impair fertility and pregnancy. Hashimoto thyroiditis (HT) is the most common autoimmune thyroid disease (AITD). Patients with HT undergoing IVF/ICSI using the long protocol are thought to benefit from a broad therapeutic concept. We compared the outcome of two different therapeutic schemes for HT patients presenting at our fertility clinic and compared the outcome to ART patients without thyroiditis. TSH level was adjusted to under 2 µIU/mL using L-thyroxine, as required. Concurrent medication from the time of oocyte puncture included daily administration of fragmin (dalteparin) and acetylsalicylic acid (ASA), as well as prednisolone in increasing dosage. One group of these HT patients (group1, n=56) had additionally highly-dosed folic acid, another group (group 2, n=50, referred to as the supplemented group) was alternatively supplemented with a micronutrient preparation containing selenium, high-dose folic acid, B-vitamins, antioxidants and iron. We compared the number of oocytes, fertilization rate, blastocyst formation rate, pregnancy- and ongoing pregnancy rate between the two groups. Also, the ART outcomes of both groups were compared to ART results of non-HT patients within the same age group. We observed a significant increase in the blastocyst rate and demonstrated a substantial rise in ongoing pregnancy rate of the supplemented patients. These also needed less L-thyroxine to achieve optimal TSH level. The outcome of the micronutrient supplemented patients corresponded to the average of healthy IVF patients without HT at our clinic.

Keywords

Autoimmune thyroiditis; IVF/IMSI; Miscarriage; Blastocyst; Ongoing pregnancy; Antioxidative dietary supplement

Introduction

Hashimoto's thyroiditis (HT) is an autoimmune thyroid disease (AITD), which results in chronic inflammation due to the occurrence of auto-antibodies directed against thyroperoxidase (TPO) (sometimes also against thyroglobulin (Tg) and TSH receptor (TSH-R)), with subsequent destruction of thyroid tissue by T-lymphocytes. HT is the commonest autoimmune disorder in humans. It affects an estimated 5-10% of the general population, with women being affected 2 to 5 times more often than males. The incidence of HT is even higher among female patients attending fertility clinics (up to 25%). HT is remarkably the most frequent cause of primary hypothyroidism in women of reproductive age [1]. At the onset of disease, there may be a period of hyperthyroidism due to the progressive destruction of thyroid tissue, causing damage to the integrity of thyroid follicle storage. However, the final state of disease is hypothyroidism, which is highly associated with female infertility.

The reasons for the disorder are various environmental factors which trigger the autoimmune response in genetically susceptible individuals, though the exact mechanisms remain unclear [2]. Severe viral infections have been reported to be involved in the onset of the disease. Besides, other autoimmune diseases or endocrine disorders, as well as environmental pollution, pesticides, xenohormones and many other chemicals with a putative impact on the immune system are suggested to trigger the outburst of the disease [2-4]. Moreover, a few studies proposed increased oxidative stress (OS) in HT, as assessed by elevated lipid peroxidation, and/or decreased antioxidant status [5].

Many women with thyroid dysfunction experience subfertility and increased miscarriage rates [6,7]. Given the fact that for conception, ongoing pregnancy and healthy delivery, various subtle interactions of hormones and components of the immune system are required, this is not surprising. HT, in fact, impairs fertility and reproduction in a multitude of ways.

Recently, Monteleone et al. [8] demonstrated that fertilization, embryo quality and pregnancy rate was lower for female IVF patients with thyroid autoimmunity, and suggested that the presence of anti-thyroid antibodies in ovarian follicles might play a critical role in female infertility. The zona pellucida and thyroid tissue seem to share similar antigens and anti-thyroid antibodies were suggested to alter fertility by targeting zona pellucida, human chorionic gonadotropin receptors and other placental antigens [9].

Patients with primary hypothyroidism often develop hyperprolactinemia, which is detrimental for oocyte maturation. Hyperprolactinemia is triggered in HT by various mechanisms. First, in response to the hypothyroid state, there is a compensatory increase in the discharge of central hypothalamic thyrotropin-releasing hormone, resulting in stimulation of prolactin (PRL) secretion. In addition to this, PRL elimination from the systemic circulation is reduced [10,11], and other reasons for increasing PRL levels in hypothyroidism individuals are also well known [12].

Menstrual irregularities are frequently found in female patients with hypothyroism [13], and its severity is linked to the serum TSH levels [14]. These irregularities are thought to be caused by a change in pulsatile gonadotropin release on the one hand, and by the lack of thyroxin leading to limited luteinizing on the other hand.

Furthermore, a number of other biochemical characteristics associated with HT have been identified. First, patients frequently exhibit elevated homocysteine levels (hyperhomoscysteinemia),

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caused by a reduction of hepatic remethylation of homocysteine into methionine [15,16]. Second, patients have an increased risk of vitamin D deficiency [17]. Also, HT is frequently associated with decreased levels of iron, vitamin B12 and folic acid, even when patients are euthyroid [16,18]. The frequent deficiency of selenium [19-21] or zinc [22] increases the vulnerability to OS, impairing oocyte maturation. All of these specifics have independently been identified as important risk factors for impaired fertility.

Another factor contributing to fertility problems in patients suffering from HT is the fact that HT patients have a higher incidence of endometriosis [23,24], polycystic ovary (PCO) syndrome [6,25], as well as an increased risk for premature ovarian failure (POF) and early miscarriage [23]. POF might be up to the immune system itself. Using a mouse model system, Matalon et al. [26] found that autoimmunity with its hyperactive immune function leads to early reproductive failure.

Miscarriage might be influenced by hypercoagulation and endothelial vascular damage.

Systemic inflammation, as observed in autoimmune diseases, modulates thrombotic responses by suppressing fibrinolysis, up-regulating pro-coagulant and down regulating anti-coagulants [27]. Some of the central features of the hyper-coaguability induced by inflammation are cytokine induction of tissue factor (TF) expression, endothelial dysfunction, suppression of the protein C signal cascade and inhibition of fibrinolysis [27-32].

Finally, there is the risk of hypothyroidism during later pregnancy, even when patients show euthyroidism in early gestation. This is due to the fact that maternal thyroid requirements increase as gestation progresses, but cannot be met [33]. Together with an alteration in renal clearance associated with increased iodine excretion, the rise of the placental type 3 Iodothyronine Deiodinase (D III) and the increase of TBG (Thyroxin Binding Globulin) with subsequent lower levels of free T4 can lead to severe hypothyroidism. This can cause obstetric complications during pregnancy, such as miscarriage, anemia, gestational hypertension, placental abruption, premature delivery and postpartum hemorrhage [6]. Hypothyroidism during pregnancy also elevates the risk for the neonate to be admitted to intensive care, mainly for respiratory stress syndromes [34], and the children are at the risk of poor neurodevelopmental outcome [35].

Data regarding fertilization-, implantation- and pregnancy rates are still inconsistent for women with thyroid autoimmunity [8,36,37]. However, there is a strong association between miscarriage and the presence of auto-antibodies [6].

For these reasons, we hypothesized that HT patients undergoing IVF/ICSI may benefit from a broad therapeutic approach, addressing the wide variety of Hashimoto-associated factors impairing fertility and early pregnancy.

This includes above-normal TSH (<2 µU/mL, optimal TSH: 0.5-1 µU/mL) and PRL adjustment before the start of stimulation, wide anti-coagulation (heparin and ASA) from the day of ovarian pickup (OPU) onwards, immune-modulation using selenium (100-200 µg) and steroids as required (up to 15 mg/day).

Interestingly, within recent years, the application of multivitamin/mineral supplements in otherwise healthy female patients for improving the outcome of IVF/ICSI treatment has been widely discussed and several promising studies demonstrated that this can have a positive impact [38-40]. Nevertheless, discussion is not without controversy. So far - to our knowledge - this is the first study analyzing the effects of a dietary supplementation on the IVF outcome of patients with autoimmune thyroiditis.

Given that HT patients have an increased risk for a number of micronutrient deficiencies as described above and that OS has been discussed to be involved in the progress of the disease, we supposed that in addition to a broad therapeutic concept as outlined above, supplementing a suitable dietary antioxidative preparation (multivitamin, folic acid, iron, zinc, selenium without iodine) to the diets of women with autoimmune thyroiditis undergoing ART treatment may have a positive impact on treatment outcome.

Materials and Methods

Patients

From January to July 2011, a total of 106 women with a history of HT disease attending the IVF center Prof. Zech were recruited for this study. Participants were randomized and 50 women received a micronutrient containing dietary preparation (Fertilovit®F^{THY}, Table 1) containing selenium, high-dose folic acid, B-vitamins, vitamin D, antioxidants and iron instead of folic acid only. Written consent was obtained from all participants of this study. The control group of 56 women received folic acid only (5 mg/day). Patient's mean age in the supplemented group was 36.1 years and 36.7 years in the non-supplemented group.

Hormonal stimulation schedule and medication

Stimulation was performed using the long protocol [41]. TSH level was adjusted before stimulation to under 2 µIU/mL, using L-thyroxine, as required. Dietary supplementation was started with the beginning of hormonal stimulation. Concurrent medication for HT patients from the time of oocyte pickup included daily administration of dalteparin (2500 IU/day) and ASA (100 mg/day), as well as prednisolone in increasing dosage (7.5 mg-15 mg/day).

Table 1: Substances of content for Fertilovit® F^{THY}. For all patients a daily intake of one capsule was recommended.

Content	Per capsule	Per 100 g	% RDA*
Caloric value	389 kJ (0.94 kcal)	903 kJ (218 kcal)	
Proteins	0.041 g	9.5 g	
Fats	0.035 g	8.6 g	
Carbohydrates	0.06 g	13.86 g	
Vitamin C	100 mg	23.203 g	125
Vitamin E	15 mg	3.48 g	125
Vitamin B1	4 mg	9.28 g	364
Vitamin B2	4.5 mg	1.044 g	321
Pantothenic acid	18 mg	4.177 g	300
Vitamin B6	5.4 mg	1.253 g	386
Vitamin B12	9 µg	2 mg	360
Folic acid	800 µg	186 mg	400
Vitamin D	5 µg	1.16 mg	100
Niacin	17 mg	3.944 g	106
Biotin	180 µg	42 mg	360
Zinc	2.25 mg	522 mg	50
Magnesium	100 mg	23.203 g	26
Iron	7.5 mg	1.740 g	54
Selenium	100 µg	23 mg	181
Coenzyme Q10	20 mg	4.641 g	-

*% of recommended daily allowance (according to EU-guideline)

Oocyte retrieval, fertilization, embryo culture and evaluation of embryo quality

Oocytes were retrieved by ovarian puncture in sedo-analgesia thirty-six hours post human chorionic gonadotropin (hCG) administration, and were fertilized using intracytoplasmic sperm injection (ICSI) or intracytoplasmic morphologically selected sperm injection (IMSI) [42]. Fertilized embryo was identified by the presence of two pronuclei (2PN). Embryo culture was performed in Global medium (LifeGlobal, Ontario, Canada) supplemented with human serum albumin (HSA LifeGlobal, Ontario, Canada) in four-well dishes (Nunc A/S, Roskilde, Denmark) and incubated (Incubator Hera Cell Incubator 240 CO_2) for 5 days, until embryo transfer. On day 5, the embryo quality was evaluated according to Gardner et al. [43]. Blastocysts with a degree of expansion of 2, 3, 4 and 5 and with A-grading for inner cell mass and trophectoderm, or a combination of A- and B-grading, were classified as top blastocysts.

For evaluation of treatment outcome, we compared the number of oocytes, fertilization rate, blastocyst formation rate, pregnancy rate and ongoing pregnancy rate between the two groups and the average results of healthy IVF-patients. Pregnancy rate (PR) was determined by urinary ß-hCG level 14 days after ET. Ongoing pregnancy rate (oPR) was defined as observation of foetal heartbeat(s) by ultrasound 6-8 weeks after ET. Differences in the fertilization-, blastocyst- and pregnancy rates were evaluated using Pearson's chi-squared test. Between-group comparisons of normally distributed variables were assessed using Student's t-test.

Results

The results of this study are summarized in Tables 2 and 3. While there was no difference between the two groups regarding the number of retrieved oocytes and fertilization rate, there was a significant increase in the blastocyst rate (Table 2), within the supplemented group. In addition, patients of the supplemented group required less L-thyroxine to achieve the TSH value aimed for ($p<0.01$). Moreover, the supplemented HT-patient group also demonstrated a substantial increase in the ongoing pregnancy rate detected by foetal heart beat (Table 2) after ET. Pregnancy rate was also slightly, yet not significantly elevated. This data of supplemented patients corresponds to the IVF outcome of non-HT patients (Table 3).

Discussion

Despite the low number of patients, this study demonstrates that IVF patients with chronic lymphocytic thyroiditis benefit significantly from a broader therapeutic concept within ART therapy. Dietary supplementation with an iodine-free micronutrient combination, including selenium and vitamins, seems to be markedly beneficial in terms of the number of blastocysts at day 5 of embryo culture. Considering the similar number of retrieved oocytes and the higher rate of top-blastocysts, these findings indicate that the micronutrient supplementation increases the competence of oocytes to develop to the blastocyst stage.

Another crucial aspect is the finding of a higher ongoing pregnancy rate following embryo transfer of the supplemented patients, although there was no significant difference in pregnancy rate detected. We, therefore, postulate that this is due to either

Table 2: Comparison of data from dietary supplemented and non-supplemented (control group) HT-patients.

	Supplemented group	Non-supplemented group	p-value
Number of patients	50	56	
BMI (kg/m²) (mean) +/- s.d.	22.3 +/-4.2	22.7 +/-3.7	n.s.
Age at the begin of stimulation (years) (mean) +/- s.d.	36.1 +/- 3.5	36.7 +/- 4.2	n.s.
L-Thyroxine Dosage needed for adjustment (µg) (mean) +/- s.d.	66.2 +/- 31.9	86.5 +/- 38.5	**<0.01 ****
Stimulation period (days) (mean) +/- s.d.	11.6 +/-1.41	11.4 +/-1.8	n.s.
Stimulation dose (IU)	2484 +/-891.5	2592+/-924	n.s.
Number of Oocytes retrieved (mean) +/- s.d.	11.1 +/- 6.7	10.9 +/- 6.2	n.s.
Number of Mature Oocytes M II oocytes (mean) +/- s.d.	9.08 +/- 5.6	8.78 +/- 6.1	n.s.
Fertilization rate %	73.7	76.3	n.s.
Blastocyst rate %	48.6	38.5	**<0.01 ****
Top Blastocysts rate %	27.2	30.5	n.s.
Embryos transferred (mean) +/- s.d.	1.72 +/- 0.53	1.68 +/-0.60	n.s.
Pregnancy rate (PR) %	48.0	39.3	n.s.
Ongoing pregnancy rate (oPR) %	44.0	32.1	**<0.05 ***

s.d: Standard Deviation
*p-value<0.05; **p-value<0.01; ***p-value<0.001

Table 3: Comparison of IVF outcome from supplemented HT patients and non- HT patients from the year 2011 within the same age class.

	Non-HT patients (control group)	Supplemented patients	p-value
Number of patients	274	50	n.s.
Age at stimulation start (years) +/- s.d.	36.1 +/- 3.1	36.1 +/- 3.5	n.s.
Number of oocyte retrieved (mean) +/- s.d.	11.6 +/- 6.0	11.1 +/- 6.7	n.s.
% MII oocytes	81.0	83.0	n.s.
Fertilization rate %	72.0	73.7	n.s.
Blastocyt rate %	49.9	48.6	n.s.
Pregnancy rate (PR) %	51.2	48.0	n.s.
Ongoing pregnancy rate % (oPR) %	42.9	44.0	n.s.

s.d: Standard Deviation.
*p-value<0.05; **p-value<0.005; ***p-value<0.001

an improved embryo competence or improved intrauterine environment, both of which may reduce the risk of early abortion. In fact, as mentioned before, there is a strong association of HT, implantation failure and (recurrent) foetal loss [6].

As a secondary effect, dietary supplemented patients obviously require less L-thyroxine to achieve the TSH levels aimed for, which is desirable, as it lowers the patient's risk for side effects, such as cardiac arrhythmias, insomnia or hypertension.

How these changes are brought about is currently not known and beyond the scope of this study. However, a few crucial aspects of micronutrients should be mentioned that might hint to possible mechanisms of action. One micronutrient with a substantial impact on thyroid function is undeniably iodine. Whereas a sufficient intake has been shown to be critical for normal thyroid function, for women with autoimmune thyroiditis, it has been observed that higher iodine concentrations may have detrimental effects, as well. Autoimmune thyroiditis worsens with iodine excess [44], whereas improvements have been reported in several studies when the iodine content of patients' diet was low [45-47].

Several other trace elements have been identified to be essential for normal thyroid hormone metabolism. Among these, iron and selenium are most worth to be mentioned. Deficiencies of these elements can restrain thyroid function markedly. Iron deficiency impairs thyroid hormone synthesis by reducing the activity of heme-dependent thyroid peroxidase [48]. Erdal et al. [49] demonstrated that basal levels of iron in patients with subclinical hypothyroidism were significantly lower when compared to a control group.

Under physiological conditions, thyroid gland retains high selenium concentrations and expresses many known seleno-cysteine containing proteins, which are needed for the (in)activation of thyroid hormones, responsible for normal development, growth and metabolism. Furthermore, seleno-cysteine can be often found in the catalytic center of enzymes protecting the thyroid from OS [50]. Adequate selenium-rich nutrition has been shown to be important for efficient thyroid hormone synthesis and metabolism, and protects the thyroid gland from damage by excessive iodide exposure. Various studies indicate other beneficial effects of selenium supplementation in patients with HT, such as modulation of the immune system by reducing thyroid antibody titers [19,51]. Positive effects of selenium supplementation during pregnancy in terms of reduced thyroid inflammatory activity have also been reported [52].

Recently, it was demonstrated that the GSH levels in HT patients are markedly lower compared to healthy controls. Even though the pathways of the autoimmune thyroiditis are not fully understood, OS has been found to be an additional important contributing factor [53,54], and the imbalance of ROS/antioxidants might be a responsible factor for a spectrum of HT symptoms.

Meanwhile, high susceptibility of oocytes to ROS is well established. ROS impair the membrane and interfere with protein synthesis, as well as energy production, and have also been associated with various problems throughout pregnancy [54]. Several studies revealed that patients with autoimmune thyroiditis have increased OS levels and a decrease in antioxidants [5]. The present study indicates that supplementation of antioxidants would be beneficial to the diets of HT-patients. In addition, a study comprising 115 patients with autoimmune thyroid disease demonstrated that this patient collective also has an increased risk of having a vitamin B12 deficiency [18]. Together with folic acid and vitamin B6, vitamin B12 is vitally needed for proper homocysteine metabolism.

Vitamin D deficiency was also suggested as a pre-disposing factor for autoimmune diseases and can also be observed in autoimmune thyroiditis patients [17]. Given that vitamin D deficiency has been linked to infertility and pregnancy loss [55], this is an important issue.

Conclusion

Although the detailed mechanisms in HT disease are still unclear, patients with HT undergoing fertility treatment (IVF/ICSI) obviously benefit from taking a dietary supplement, including selenium, iron, vitamins, as well as antioxidants, in addition to other supportive medication, such as ASA, dalteparin and prednisolone. This therapeutic regimen results in a marked increase of ongoing pregnancy rate, while requiring less L-thyroxine.

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