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Thyroid dysfunction and thyroid autoimmunity in euthyroid women in achieving fertility

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Abstract. – OBJECTIVE: Thyroid disease is the second most common endocrine condition in women of childbearing age. Thyroid hormones are involved in control of menstrual cycle and in achieving fertility affecting the actions of follicle-stimulating hormone and luteinizing hormone on steroid biosynthesis by specific triiodothyronine sites on oocytes; therefore, affect all aspects of reproduction. It remains controversial if pregnant women should be screened for thyroid dysfunction.

Purpose of this review was to examine recent studies on the assessment of thyroid dysfunction in pregnancy, its treatment and newly perspective of thyroid autoimmunity in pregnant euthyroid women in achieving fertility.

METHODS: An electronic search was conducted using the internet medical databases: Medline/PubMed, EMBASE, EBSCO, and the Cochrane library.

RESULTS: Thyroid gland faces great challenge in pregnancy when many hormonal changes occur. Precondition for normal follicular development and ovulation is pulsate gonadothropin realizing hormone secretion. Thyroid dysfunction in pregnancy is classified as forms of hypothyroidism (positivity of thyroid autoantibody, isolated hypothyroidism, and subclinical or overt hypothyroidism), hyperthyroidism, and autoimmune disease, but also thyroid nodules and cancer, iodine insufficiency and postpartum thyroiditis. These conditions can cause adverse effects on mother and fetus including pregnancy loss, gestational hypertension, or pre-eclampsia, pre-term delivery, low birth weight, placental abruption and postpartum hemorrhage. There is an evidence that thyroid autoimmunity, in thyroid dysfunction adversely affects conception and pregnancy outcomes, but it is unclear what impact has isolated eumetabolic thyroid autoimmunity in achieving fertility, especially in women undergoing *in vitro* fertilization. Treatment of euthyroid pregnant women with positive thyroid peroxides antibodies is still controverse, but not few studies show that levothyroxine substitution is able to lower the chance of miscarriage and premature delivery.

CONCLUSIONS: Further randomized trials are needed to expand our knowledge of physiologic changes in thyroid function during the pregnancy and to reveal mechanisms by which thyroid autoimmunity in euthyroid women affect fertility, especially the success of assisted reproductive technology in achieving the same and validity of levothyroxine administration in thyroid autoimmunity positive women.

Key Words:
Thyroid dysfunction, Thyroid autoimmunity, Female infertility, IVF.

Introduction

Thyroid disease is the second most common endocrine condition in women of childbearing age[1]. If untreated, these conditions may affect mother and fetus. Last few decades knowledge regarding thyroid dysfunction associated with pregnancy was expanded. No less a problem are subclinical forms of disease[2], that are very frequent but not easily recognized without specific screening programs[3]. The effect of thyroid dysfunction on conception, pregnancy and the outcome of the same is a current issue of the recent studies. It is estimated that approximately 8-12% of all pregnancy losses are the result of endocrine factors[4]. At least 2-3% of women have some

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form of thyroid dysfunction during pregnancy, and circa 10% of women have thyroid autoimmune disease despite euthyroidism[5].

Thyroid dysfunction in pregnancy is classified as forms of hypothyroidism (positivity of thyroid autoantibody, isolated hypothyroidism, and subclinical or overt hypothyroidism), hyperthyroidism, and autoimmune disease, but also thyroid nodules and cancer, iodine insufficiency and postpartum thyroiditis that refer to thyroid dysfunction within the first year after delivery or miscarriage, when the known immunosuppressive effect of pregnancy disappears. It is the bidirectional relationship between autoimmunity and reproduction of great interest[6], but detailed medical history and thyroid examination of the pregnant women are needed[7].

It remains controversial if pregnant women should be screened for thyroid dysfunction. Some scientific societies have proposed to assess thyroid function during the first trimester of pregnancy and ideally before week 10 of gestational age[8]. Reasons for screening because of existing high-risk conditions for thyroid diseases in pregnant women should be: history of previous thyroid dysfunction, goiter, positive thyroid antibodies, cervical irradiation, or thyroid surgery, age more than 30 years, family history of thyroid disease, presence of clinical signs or symptoms of hypothyroidism, diagnosis of type 1 diabetes mellitus or any other autoimmune disease, history of repeated abortions, prematurity, or infertility, morbid obesity, treatment with lithium, amiodarone, or recent administration of iodinated contrast and living in an area with moderate to severe deficiency of iodine[9].

Limitations in our current knowledge of physiologic changes in thyroid function during the periconceptional period and the pregnancy enable us to make a consensus over screening, diagnosis and treatment of thyroid disease. The aim of this review was to examine recent studies on the assessment of thyroid dysfunction in pregnancy, its treatment and newly perspective of thyroid autoimmunity in pregnant euthyroid women in achieving fertility.

Methods

An electronic search was conducted using the internet medical databases: Medline/PubMed, EMBASE, EBSCO, and the Cochrane library.

Discussion

Thyroid Gland and Pregnancy

Thyroid gland faces great challenge in pregnancy when many hormonal changes occur. These changes include the estrogen stimulated increase in thyroxin-binding globulin (TBG), resulting in an increase in total thyroxin (TT4), thyroglobulin, and the increase in serum concentration of human chorionic gonadotropin (hCG)[10]. Increased HCG directly stimulates the thyroid gland; increases free thyroxin (FT4), and suppress serum thyroid-stimulating hormone (TSH) concentrations. Also, peripheral metabolism of thyroid hormones is modified, under the impact of the placental "type 3" iodothyronine deiodinase. Iodide and iodothyronines are transported from maternal circulation to the fetus; the recommended iodine intake is 250 μg/day, not more than 500 μg/day[11]. Iodine deficiency cause goiter in mother and fetus. TSH levels increase and reach the highest value in the third trimester, on the other hand free fractions of thyroid hormones decrease. TSH levels are higher in the second half of pregnancy, because of decreased hCG and free thyroid hormones levels. In the last months of pregnancy, FT4 levels were often below the reference interval[12], but an increase in reverse T3 during pregnancy was found. No optimal diagnostic tests for fT4 during pregnancy exist[13]. Thyroid volume is positively correlated with total body water[14], the increased vascularity may be the reason for the increase of thyroid volume[15]. Fetal thyroxin production does not occur until 8-10 week of gestation. Other hormonal changes occur, like increase of mean plasma levels of testosterone and androstenedione, and luteinizing hormone (LH) secretion.

Thyroid hormone, triiodothyronine (T3), receptors are found in the trophoblast. *In vitro* studies show that thyroid hormones act directly on the early development of the placenta, stimulating angiogenesis and promoting invasion and differentiation of embryonic cells. Thyroid receptors (TR) $\alpha 1$ and $\beta 1$ and THRAb are expressed in human endometrium, the highest level is seen in the receptive endometrium, and paracrine factors like leukemia inhibitory factor and leptin are of importance for successful embryo implantation[16].

Abalowich et al[17] established upper limit for thyrotrophin 2.5 mIU/L in the first trimester, and 3.0 mIU/L in the second and third trimesters. The lower physiological limit could be 0.1 mIU/L in

the first trimester, 0.2 mIU/L in the second, and 0.3 mIU/L in the third[18].

Subclinical and Overt Hypothyroidism and Female Infertility

Precondition for normal follicular development and ovulation is pulsate gonadothropin realizing hormone (GnRH) secretion. Thyroid hormone receptors are expressed in human oocytes, cumulus cells and granulose cells[19]. A function of granulose cell is under influence of thyroid hormones through direct effect of follicle stimulating hormone (FSH), facilitating induction of LH/hCG. Hypothyroid women have decreased rates of metabolic clearance of androstenedione and estrange and exhibit an increase in peripheral aromatization. Level of SHBG and its binding activity decreases and therefore in the presence of an ovulation, ovarian androgen production increases with higher biologically active androgens. Decreased levels of factors of coagulation VII, VIII, IX and XI are present. Plasma binding activity of sex hormone binding globulin (SHBG) is decreased, which results in decreased plasma concentrations of both total testosterone and estradiol (E2), but their unbound fractions are increased[1].

Juvenile hypothyroidism cause delay in sexual maturity. Hypothyroidism in adult women causes ovulatory disorders, galactorrhoea, hirsutism, amenorrhea and/or menorrhagia, because of variations in pulsate secretion of LH[18]. Inadequate corpus luteum progesterone secretion occurs when delay in luteotropin hormone is present. It is believed that the cervix changes are the consequence of the decrease of sensitivity to estrogen under the low level of T3 and T4 and increase TSH in plasma, such as molecular atypia of endocervical cells[20]. One of the manifestations of hypothyroidism is subclinical form, presenting with higher level of TSH and normal thyroxin (T4) level.

Subclinical hypothyroidism can cause pregnancy loss, gestational hypertension, or preeclampsia, pre-term delivery, low birth weight, placental abruption and postpartum hemorrhage. Treatment with levothyroxine should be considered, and its requirement increases very early (4-6 week), continues to increase through midge station (16-20 week). Of 394 infertile women, 23.9% were hypothyroid (TSH > 4.2 mIU/l) and after levothyroxine substitution, 76.6% of infertile women conceived within 6 weeks to 1 year according to Verma et al[21].

The Controlled Antenatal Thyroid Screening (CATS) study in the United Kingdom was initiated as a prospective interventional trial wherein women with low serum FT4 or high serum TSH were randomized to no screening *vs.* thyroid testing followed by intervention, administration of levothyroxine (LT4)[22]. Screening pregnant women (or those planning pregnancy) for hypothyroidism remains highly controversial at this time[5]. Current guidelines differ between an case finding approach[10,23-25] versus testing only symptomatic women or those with a personal history of thyroid disease or other associated medical condition[26,27].

The prevalence of overt hypothyroidism in women in the reproductive age (20-40 years) varies between 2% and 4%[28]. The babies born from hypothyroid mothers have reduced intelligence quotient. Normal thyroid function's pivotal role was also demonstrated in the study of Abalowich et al, where it was shown that the rate of early fetal loss decreased from 31% in hypothyroid women at the time of conception to only 4% in those hypothyroid women who started pregnancy with a euthyroid status after adequate levothyroxine administration[29]. Women who never achieved basal TSH < 2.5 mIU/l had lower conception rates[30].

Women with hypothyroidism have a significantly decreased chance of achieving a pregnancy following in-vitro fertilisation (IVF) compared to euthyroid patients, despite levothyroxine substitution[31].

Either subclinical or overt hypothyroidism affects pregnancy and development of fetus and neonatus at each level causing serious consequences, so undouthbly screening is needed, particulary in women trying to achieve pregnancy by IVF. Pregestational maternal thyrotrophic level predicts the risk of hypothyroidism during pregnancy, especially considering women undergoing IVF.

Isolated Hypothyroxinemia

Isolated hypothyroxinemia in pregnancy is defined as the value of FT4 under 2.5th percentile with a normal level of TSH, estimated occurrence of approximately 2% in unselected pregnancies[29]. Iodine deficiency is leading cause of this hormonal variation. The first study dealing specifically with isolated hypothyroxinemia was reported from the Netherlands studies shown that children of mothers with this thyroid disease had mean intelligence and motor scores significantly lower than

children of mothers with no thyroid disease; maternal hypothyroxinemia was defined by FT4 levels below the 10th percentile and concomitant TSH values < 2.0 mU/liter[32-34]. In the other studies, isolated hypothyroxinemia is defined by FT4 values below the 2.5th percentile, but by TSH values ≤ 3.0mU/liter[35,36], or by values that fall below the upper gestational specific limit[37,38]. Still, treatment with levothyroxine is not recommended, but iodine supply is advised. In the paper by Morreale De Escobar et al, it is suggested that levothyroxine treatment should be prescribed in women whose fT4 concentrations fall below the 10th percentile value, provided that they are also given adequate iodine supplements[39,40].

Isolated hypothyroxinemia was associated with preterm birth, infants weighing more than 4000 g and gestational diabetes, but in another cohort isolated maternal hypothyroxinemia has no adverse effects on perinatal outcome[41]. Some association has also been seen with neonatal intraventricular hemorrhage, but this association was based on a very limited sample size[35], with poorer neuropsychological development in the offspring.

Thyroid Autoimmunity and Infertility

There is an evidence that thyroid autoimmunity (TAI) in thyroid dysfunction adversely affects conception and pregnancy outcomes[41,42], but it is unclear what impact has isolated eumetabolic thyroid autoimmunity in achieving fertility. TAI with the incidence of 5-10% in pregnant women is the most common thyroid disorder and cause of thyroid failure. The effects of thyroid autoimmunity on conception's failure are particularly interesting. Pregnancy itself causes significant variation in immune tolerance, which may trigger thyroid autoimmunity in susceptible individuals with appropriate genetic background, excessive iodine intake and other environmental risk factors[11]. TAI is associated with impaired cellular and humoral immune responses in women with pregnancy failure[43], and the higher number of endometrial T cells confirming in studies with improved pregnancy outcomes in women with TAI who received immunoglobulines. Study conducted on 3593 women shown an increase in very preterm delivery (< 34 week gestation at delivery) and respiratory distress in women who were thyroid antibody positive[44]. Women positive for thyroid peroxidase (TPO Ab) and thyroglobulin antibodies (Tg Ab) have 3-5 times higher risk for spontaneous miscarriage, placental abruption, preeclampsia, preterm delivery, fetal loss, recurrent abortion, and still in investigation respiratory distress[45]. Causes of miscarriage in euthyroid women with autoimmune thyroid disease (AITD) can be a subtle degree of hypothyroidism, the presence of thyroid antibodies underlying overall autoimmune disbalance, resulting recurrent abortion or thyroid auto antibodies with their direct influence, or older age of AITD euthyroid women, as an immunological factor. The presence of TPO antibodies is strongly associated with postpartum thyroiditis and long-term with overt hypothyroidism. The recent study shown that first-trimester positive thyroid antibodies were a risk factor for prenatal death rather than the thyroid hormone status per se[29]. In another study by Benhadi et al[46], an opposite conclusion was reached because in that study even a slightly increased serum TSH remaining within the normal range was associated with an increased miscarriage rate that was independent of AITD presence. The study of Potlukova et al[47] published in 2013, indicate that functional deficiency of mannan-binding lectin (MBL) has been associated with adverse pregnancy outcome and serum MBL levels in the first trimester of pregnancy are influenced by autoimmune thyroid disease, even in its subclinical form. MBL deficiency has been found to be associated with the production of antiphospholipid antibodies and to predispose to thrombotic events, thus increasing the risk of late pregnancy loss.

A meta-analysis of prospective cohort studies included eleven prospective cohort studies involving 35 467 participants[48], showing that the presence of TPO-Ab in pregnant women significantly increases the risk of preterm delivery.

Treatment of euthyroid pregnant women with positive thyroid peroxides antibodies is still contraverse, but it is undouthable that levothyroxine substitution is able to lower the chance of miscarriage and premature delivery[49]. It is shown that treatment with selenium had no benefit for preeclampsia or preterm delivery. However, because women who are TPO Ab+ and euthyroid in the first trimester have an increased risk for developing hypothyroidism as pregnancy progresses, ongoing TSH monitoring during pregnancy is recommended[50].

Thyroid Autoimmunity and Assisted Reproductive Technology

Infertility is defined as inability of conception after one year of regular intercourse without contraception[51]. Primary infertility is in women who

have never achieved a pregnancy, and the secondary ones in those women who at least once in their life had become pregnant[52]. According to Mayo Clinic, USA, the causes of infertility are many: male factor infertility (which is present in 25-40% of cases), female factor infertility (which is present in 40-55% of cases), common factors of infertility (in 10% of cases), unclear (idiopathic) infertility, which occurs in 10% of cases[53]. The essence of all assisted reproduction procedures is to cause ovulation and delivery of prepared seed in more or less close to the egg cells in the body (artificial insemination – AIH or IUI) or out of a woman – *in vitro* fertilization (IVF). IVF is carried out as infertility treatment only when there is no other simple way of treating infertility. AIH applies as the first method, and if it fails, IVF is recommended. IVF involves two techniques, classical method of IVF and intracytoplasmic sperm injection, or microfertilisation (ICSI). ICSI is the technique of choice in cases of male infertility.The medical preparation for IVF is called controlled ovarian hyperstimulation (COH)[28]. Using gonadotrophin relasing hormone (GnRH) agonists or antagonists down-regulation of the pituitary gonadal axis, and stimulation of the ovaries with (recombinant) FSH is achieved. Treatment is discontinued and 10 000 units of hCG are given to induce ovulation, when three or more large follicles are seen on echography. Then follicles puncture and oocytes aspiration should be done. When the insemination is done, approximately 14-18 hours after oocytes are reviewed to determine whether fertilization has occurred, and 24 hours later to check that there is a proper division. Two weeks later βHCG in the blood can show us if biochemical pregnancy occurred. When morphological criteria are achieved 2-3 embryos are transferred. Hormones like estrogen and progesterone, but also adhesion molecules, growth factors and cytokines determine implantation and development of an embryo. Mature (MII) oocytes from women undergoing IVF demonstrate the presence of TRα1, TRα2, TRβ1, and TRβ2 mRNA, supporting the hypothesis that T3 has a direct effect on the human oocyte, and deiodinases types 2 and 3 in combination with activation of cAMP by TSH indicates a possibility of conversion of peripheral T4 on ovarian tissue[16].

Anti-thyroid antibodies were suggested to be independent markers for the failure of assisted reproductive techniques and their presence cause lower oocyte fertilization[54]. Lack of vitamin D was suggested as a predisposing factor to autoimmune diseases, and it is reduced in TAI[55]. The presence of thyroid autoimmunity adversely affects the outcome of the ART, leading to an increased risk for spontaneous miscarriage in subfertile women achieving a pregnancy through an IVF procedure[56]. On the other hand, TAI per se does not influence ICSI outcome according to Tan et al[57].

TAI has a negative effect on the early outcome of COH, but this negative influence may be avoided with adequate levothyroxine therapy aimed at keeping TSH < 2.5 mU/L according to Magri et al[58]. Other studies shown in Table I, indicating that levothyroxine substitution increases the conception rate among hypothyroid women undergoing IVF[31,59,60].

This procedure elevates estrogen and TBG levels, changing levels of free thyroid hormone and steroid, and cytokines action fall in order to maintain the pregnancy. After one cycle of ART, the live birth rate among women aged 30-35 years ranges from 25-30%[61]. Euthyroid women with thyroid autoimmunity unlikely become hypothyroid during controlled ovarian hyperstimulation and the early implantation phase[62]. It is described a case of a woman with an unknown subclinical autoimmune hypothyroidism who developed overt and transient hypothyroidism as a consequence of COH[63]. Despite evidence for a pattern of dissociation for higher serum TSH and lower serum FT4 in women with TAI compared with those without TAI after ART-induced pregnancies, the clinical importance of the changes provoked by gonadotropins in terms of miscarriage risk appears to be minimal, acoording to the meta-analysis[64]. Table II presents two studies[59,60] trying to establish the impact of ovarian hyperstimulation syndrome on thyroid function in women without thyroid disorders and to compare it with that in women with uncomplicated COH, showing that serum TSH levels increased significantly after COH[65,66].

The first one who described association between thyroid autoimmunity and ART were Stagnaro-Green et al[67] indicating three- to five-fold increase in overall miscarriage rate. Thyroid function and autoimmunity should be determined in infertile women before ART. There is an association between organ-specific thyroid and ovarian autoantibodies and reproductive failure after IVF. Unuane et al[68] showed the prevalence of TAI was higher in infertile women as compared to fertile. Serum TSH levels have shown to be a

Table I. The effect of levothyroxine substitution on the conception rate among hypothyroid women undergoing IVF.

Author, year	Design, sample size, study period	TSH limit	IVF protocol	Results
Busnelli A, 2013	Randomized control trial, 137 tretaed hypothyroidism and 274 controls, 3 years	≤ 2.5 mIU/L.	ICSI	Lower fertilization rate (75% vs. 86%, $p = 0.017$), the clinical pregnancy rate per started cycle, 36% vs. 34% ($p = 0.93$)
Velkeniers B, 2013	Meta analysis included 3 trials with data on 220 patients	–	IVF/ICSI	LT4 treatment resulted in a significantly higher delivery rate, with a pooled relative risk (RR) of 2.76 LT4 treatment significantly lowered miscarriage rate with a pooled RR of 0.45 LT4 treatment had no effect on clinical pregnancy
Scoccia B, 2012	Randomized control trial, 21 treated hypothyroidism and 219 controls, 4 years	0.35-4.0 μU/mL	IVF/ICSI	Significantly decreased chance of achieving a pregnancy in women with hypothyroidism

significant predictor of fertilization failure in women undergoing IVF. One of the reasons of failure after IVF in AITD women could be as an increased number of CD5/20-positive B cells or an abnormal T-cell function or a subtle deficiency in thyroid hormones or an inability of the thyroid to adapt to increased estrogen levels, ovarian hyperstimulation or pregnancy. During investigations it was noticed that in women with AITD miscarriages occur mainly in the first trimester of gestation. It could be that women with AITD have a subtle underlying fertility problem, leading to conception at a later age (3-4 years older, on average)[28]. TAI per se does not alter the implantation of embryo[28]. Monteleone et al[69] in recent study tried to verify whether anti-thyroid antibodies are present in the follicular milie of euthyroid infertile women with thyroid autoimmunity undergoing in vitro fertilization (IVF) and whether IVF outcome is different in affected

Table II. Thyroid function in women without thyroid disorders in complicated and noncomplicated ovarian hyperstimulation.

Author, year	Design, sample size	Results
Gracia CR, 2012	• Prospective control study • 57 women • TSH, total and free T(4), E(2), and thyroxine-binding globulin (TBG), measured at six time points from before stimulation to 2 weeks after serum pregnancy test.	1 week after hCG administration compared with baseline (2.44 vs. 1.42 mIU/L), as did free T(4) (1.52 vs. 1.38 ng/dL) and TBG (32.86 vs. 21.52 μg/mL) Estradiol levels increased, peaking at hCG administration (1743.21 vs. 71.37 pg/mL). 22/50 (44.0%) women with baseline TSH ≤ 2.5 mIU/L, had a subsequent rise in TSH to > 2.5 during or after COH
Poppe K, 2011	• Retrospective analysis • 77 women • 25 developed OHSS – ovarian hyperstimulation syndrome and 52 had no OHSS, TSH and free T4 (fT4) evels were measured before and 2, 4, and 6 weeks after embryo transfer (ET), and thyroid peroxidase and thyroglobulin antibody levels were measured before ET to exclude thyroid autoimmunity	Serum TSH and fT4 levels increased 2 weeks after embryo transfer-ET in both study groups compared with prestimulation levels In the OHSS group: TSH, 1.9 ± 0.8 mIU/L vs. 3.1 ± 1.9 mIU/L; fT4, 12.3 ± 1.4 ng/L vs. 13.4 ± 2.1 ng/L In the no-OHSS group: TSH, 2.1 ± 1.1 mIU/L vs. 2.6 ± 1.9 mIU/L; fT4, 13.0 ± 1.7 ng/L vs. 13.8 ± 1.6 ng/L

women with respect to negative controls. The characteristics of the follicular fluid, providing micro environment of the greatest importance for the developing oocytes depend on thyroid hormones. In TAI positive women antithyroid antibodies were found in the ovarian follicular fluid, providing antibody mediated cytotoxicity in the growing ovarian follicle and damage to the maturing oocyte. The antithyroid antibodies cause an alteration of the zone pellucida, damaging its functional role. Table III shows that the clinical pregnancy rate, live birth rate and miscarriage rate were similar among women with or without TAI[70,71].

The possible mechanism thyroid autoimmunity affecting IVF outcomes and leading to the failure of itself remains largely unkown. The fact is, that existence of thyroid antibodies represents generalized activation of whole immune system. Maternal thyroid hormones are of the extreme importance in the first trimester of pregnancy, so it is not suprising that miscarriage indeed happens when the lack of these hormones can harm the fetus the most or when the autoimmune balance is affected.

Do the thyroid antibodies directly affect placenta, are these antibodies present in follicular fluid? Is that a reasone of miscarriage or simply their presence delay a conception? Is maybe the psychological moment of great importance for women undergoing IVF? Or maybe it is their age or comorbidities? Is their body and their immune system more vulnebrale because of years trying to become pregnant, or is titer of thyroid antibodies higher during years because the body is expose to many different influencing envitomental factors? Or is it just a matter of time when the gene predisposition for some disease will become manifest? Serum TSH level increased during the pregnancy probably the same in TPO positive and TPO negative women, so the effect of these antibodies could be totally independent of TSH level.

Can we decrease miscarriage rate by administrating levothyroxine to TPO positive women and is it the way of healing the cause or the consequence? Is possible to disturb the hormonal balance? Maybe the presence of these antibodies is not just reflection of thyroid disease. Do we know what actually we treat adiminstrating levothyroxine at that moment? Is it notable that there is no available studies discussing the effect of TRAb on miscarriage rate. We can not predict something that is so unclear, but it is for sure that those women require special attention and monitoring during pregnancy.

Subclinical and Overt Hyperthyroidism and Female Infertility

Clinical hyperthyroidism is not uncommon in pregnancy, with a reported prevalence of 0.1 to 0.4%[63]. The diagnosis of hyperthyroxinemia implies elevated serum level of free thyroxin, leading to augmentation of SHBG production, estrogen metabolism and conversion of androgens to estrogens, gonadotropin response to GnRH and baseline gonadothropin concentrations. It also affects factor of coagulation VIII causing the decrease in menstrual flow. Hyperthyroid women usually maintain ovulation[28]. Graves' hyperthyroidism is the most common cause of hyperthyroidism in pregnancy[72], affecting up to 0.4% of pregnant women, and others causes including gestational transient thyrotoxicosis (GTT), au-

Table III. The clinical pregnancy rate, live birth rate and miscarriage rate among women undergoing IVF with or without TAI.

Author, year	Design, sample size	Results
Chai J, 2014	• Retrospective study • 627 women • Pre-IVF archived blood serum samples were tested for TAI and thyroid function tests	The clinical pregnancy rate, live birth rate and miscarriage rate were similar among women with or without TAI and/or subclinical hypothyroidism using a TSH threshold 4·5 mIU/l Thyroid autoantibody level did not affect these IVF outcomes
Mintziori G, 2014	• Retrospective design • 158 euthyroid women • Underwent IVF, evaluate the association of TSH concentrations and presence of TAI with the live birth rate in euthyroid women undergoing IVF	No difference in the live birth rate was found between the TSH (low: 34.2% vs. high: 36.8%, p = 0.763) or TAI (present: 26.7% vs. absent: 34.3%, p = 0.568) subgroups

tonomous toxic adenoma, sub acute painful and nonpainful thyroiditis, drug induced such as iodine, amiodarone, lithium and iatrogenic excessive thyroxin ingestion, while struma ovarii and hyperplacentosis are extremely uncommon during pregnancy. Graves' hyperthyroidism can be present first time in pregnancy either as an active disease on antithyroid drug therapy or recurrence of disease previously treated with antithyroid drug, administration of $_{131}$I or in women who have given birth to an infant with thyroid dysfunction[73]. Women with pregestational hyperthyroidism had better outcomes than those diagnosed with it during pregnancy[74]. Potential complications are as follows: maternal-miscarriages, gestational hypertension, preeclampsia, congestive heart failure and even thyroid storm; obstetrical: premature delivery, placenta abruption, premature rupture of membrane, gestational hypertension including preeclampsia and postpartum bleeding; fetal: congenital malformations, developmental dysplasia of the hip associated with first-trimester maternal hyperthyroidism irrespective of the cause of her hyperthyroidism, intrauterine growth restriction (IUGR), small for gestational age (SGA) infants, prematurity, and stillbirth; and neonatal: neonatal morbidity is related to prematurity and thyroid dysfunction and neonatal central hypothyroidism has been reported in infants whose mothers remained hyperthyroid throughout their pregnancies[41]. Gestational thyrotoxicosis usually happens in the first half of pregnancy and resolves spontaneously and is often associated with the syndrome of hyperemesis gravidarum. Transient hyperthyroidism of hyperemesis gravidarum (THHG) characterized by severe nausea and vomiting between 4 and 8 weeks' gestation, weight loss of at least 5 kg, ketonuria, in severe cases abnormal liver function tests, and hypokalemia is the most common cause of hyperthyroidism[53]. Fetal health may be affected by poor control of maternal hyperthyroidism, titer of maternal TRAb, and unadequate use of ATD[74]. Newborns of mother with Graves' disease had a subclinical course with abnormal FT4 levels that peaked at fifth day, associated with low weight gain[76]. Women with active disease and this post ablation should be advised to measure maternal serum anti thyrotrophic receptor antibodies (TRAb) level between 20 and 24 weeks gestation. The presence of TRAb increases 3-5 times the risk of fetal and/or neonatal thyrotoxicosis[77]. These antibodies are capable of stimulating growth and function of both maternal and fetal thyroid glands. Fetal hyperthyroidism, which occurs in less than 0.01% of pregnancies, may lead to tachycardia, fetal goitre, accelerated bone maturation, growth retardation, low birth weight and malformations. Maternal overtreatment with ATD therapy may produce fetal goiter and hypothyroidism. Infants of untreated hyperthyroid mothers may be born with congenital hypothyroidism of central origin, because high maternal thyroxin values crossing the placenta barrier suppressed fetal TSH[78].

Thyroid function tests should be monitored at regular intervals for the first year starting at 6 weeks postpartum[18]. ATD administration should probably be reserved for a minority of patients with extremely severe GTT. The spontaneous improvement usually observed in pregnant women with GD, can be due to association of the pregnancy and immunosuppression with a progressive decrease in TRAb; the rapid and marked rise in serum TBG in the first trimester increasing SHBG capacity for both T4 and T3, and so decrease FT4 and FT3; pregnancy is also associated with iodine losses. Management of hyperthyroidism during pregnancy requires carefull implementation to avoid any adverse effects on the mother and fetus[79-81].

TRAb and hyperthyroidism during pregnancy are considered as risk factors, requiring extra attention of diagnosis and management to avoid avderse outcomes.

Conclusions

Thyroid hormones are involved in control of menstrual cycle and in achieving fertility affecting the actions of follicle-stimulating hormone and luteinizing hormone on steroid biosynthesis by specific T3 sites on oocytes, therefore affect all aspects of reproduction. Further randomized trials are needed to expand our knowledge of physiologic changes in thyroid function during the pregnancy, so pathological changes should be better analyzed. It is necessary to delineate women with thyroid dysfunction, including thyroid autoimmunity in euthyroid women, who require treatment and follow up during pregnancy. Further studies are needed to reveal mechanisms by which thyroid autoimmunity in euthyroid women affect fertility, especially the success of assisted reproductive technology in achieving the same and validity of levothyroxine administration in TAI positive women.

Conflict of Interest

The authors hereby declare that have not received nor shall receive any financial benefits from publishing the paper, have received any financial incentive from a third party. The authors hereby declare that they are not in any situation which could give rise to a conflict of interest.

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