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Hypothyroidism, Oxidative Stress and Reproduction

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1. Introduction

It is well known that in both sexes thyroid hormones influence sexual development and reproductive function; clinical and experimental evidences suggest that the hypothalamic-pituitary-thyroid axis and the hypothalamic-pituitary-ovary axis are physiologically related and act together as unified system in a number of pathological conditions (Doufas & Mastorakos, 2000).

In women, both hyper- and hypo-thyroidism may result in menstrual disturbances. In hyperthyroidism the most common manifestations are simple oligomenorrhea and anovulatory cycles. Hypothyroidism results in changes in cycle length, amount of bleeding, and usually is associated with abnormal menstrual cycles characterized mainly by polymenorrhea and anovulatory cycles (Krassas et al., 1999). Also subclinical hypothyroxinemia can be associated with short luteal phase and insufficient progesterone secretion (Bohnet et al., 1981); similar pictures are present in a variety of situations characterized by low T3 levels (malnutrition, chronic illness, exercise), known as “non-thyroidal illness” (De Groot, 2006).

Interference between thyroid gland function and the ovary are described in three main areas: the secretion of GnRH, the peripheral metabolism of steroids and prolactin secretion. Previous studies demonstrated a direct ovarian effect: TSH possesses a luteotropic activity (Wurfel, 1992) and the expression of thyroid hormone receptors has been documented in all ovarian cell types: surface epithelial cells, oocytes, granulosa and theca cells, stromal cells (Dittrich et al., 2011). Many studies were also performed in males, both in animals and humans and extensively reviewed (Krassas et al., 2010).

Despite the clinical relevance of the association between thyroid and reproductive health, its physiopathological mechanisms are still poorly understood and no definitive trials on thyroid hormone replacement allow unequivocal conclusions. Among the new mechanisms proposed, a link could be related to oxidative stress (OS).

Oxidative stress is defined as the unbalancing between production of free radicals, molecules characterized by high reactivity due to one or more unpaired electrons in the external orbital, and antioxidant defenses in the biological systems. Nowadays, it is considered an important pathogenetic mechanism in different diseases (Halliwell & Gutteridge, 1979). Among free radicals the most important and studied are reactive oxygen species (ROS), of which most *in vivo* production occurs mainly during oxidative processes of energetic substrates in the mitochondrial respiratory chain (Littarru, 1994; Kang & Hamasaki, 2003). However, other important kinds of free radicals exist, besides ROS, among which nitrogen reactive species are the most studied (Lancaster, 1992).

An augmented ROS production can be the consequence of an augmented electronic flow in the respiratory chain, when it is activated by an increased energetic demand or contribution of substrates (Turrens & Boveris, 1980), as occurs in obesity. An uncontrolled production of free radicals is linked to many pathological events, such as rheumatoid arthritis and myocardial infarction (Littarru, 1994), and in general ROS damage occurs in inflamed tissues, characterized by cellular lysis and intracellular content release. Moreover in diabetes mellitus, oxidation accompanies glycation *in vivo*, while antioxidant capacity is decreased, finally resulting in an increased susceptibility to oxidative stress (Wolff et al., 1991).

It is possible to characterize different cellular defensive mechanisms against the free radical damage (Littarru, 1994). The first mechanism is the prevention of production or the rapid inactivation of free radicals, thanks to the action of enzymes, like catalase, peroxidase glutathion complex and superoxydedismutase (SOD), or of transition-metal binding proteins, like transferrin, ferritin and ceruloplasmin. The second mechanism interrupts propagation of the lipid peroxidation chain by a reaction with the intermediate radicals and the consequent neutralization. This mechanism is acted by molecules called "scavengers", which can be water-soluble, such as albumin, bilirubin, ascorbic acid, urates and thiols, or liposoluble, such as vitamin E and coenzyme Q₁₀, the only liposoluble antioxidant synthesized in living organisms. The mobility of scavengers, particularly the liposoluble ones and above all at membrane level, allows to intercept radicals and transform them into more stable molecules and therefore to stop radical chain. The third defensive mechanism uses processes which remove molecules damaged by oxidative attack, allowing the reconstitution of normal structures (e.g. specific phospholypases remove the peroxidized fatty acids, making possible the re-acylation of damaged molecule by an acyl-CoA and the respective enzyme) (Littarru, 1994). Different studies suggest that OS can be present in hypothyroidism and could be a factor involved in infertility associated to thyroid insufficiency.

2. Thyroid hormones and oxidative stress

Previous studies have shown that both hyperthyroidism and hypothyroidism are associated with enhanced oxidative stress involving enzymatic and non-enzymatic antioxidants (Resch et al., 2002). Besides, some complications of hyperthyroidism are due just to the oxidative stress in target tissues (Asayama & Kato, 1990). Thyroid hormones *per se* can act as oxidants and produce DNA-damage (contrasted by catalase), probably through the phenolic group, similar to that of steroidal estrogens (Dobrzynska et al., 2004). Many other mechanisms, reviewed by Venditti & Di Meo (2006), can be involved: enhanced NOS gene expression

with NO overproduction; activation of hepatic nuclear factor-kB and following increase of cytokines stimulating ROS generation; uncoupling mechanisms involving UCP-2 and UCP-3, regulated by thyroid hormones; increased turnover of mitochondrial proteins; mitoptosis, regulated by peroxisome proliferator-activated receptor gamma coactivator-1, which is upregulated by T3 administration. Thyroid hormones influence lipid composition of rat tissues (Hoch, 1988) and therefore the susceptibility to oxidative stress.

However, there is a specificity in tissue response, and discrepant effects of T3 and T4 are possible. In rat liver, T3-induced hyperthyroidism was found to be associated with altered lipid-peroxidation indices, including elevated levels of TBARS and hydroperoxydes (Fernandez *et al.*, 1985; Venditti *et al.*, 1997; Huth *et al.*, 1998; Venditti *et al.*, 1999). On the contrary, no change in TBARS was found in homogenized livers from rats made hyperthyroid by administration of T4 over a 4-week period (Asayama *et al.*, 1987). As regards testis, no significant change (TBARS or hydroperoxydes) was observed in lipid peroxidation of hyperthyroid adult rats, but hyperthyroidism promoted protein oxidation rate as indicated by an enhanced content of protein-bound carbonyls (Choudhury *et al.*, 2003). In conclusion, we should emphasize the fact of a tissue-linked variability in the effects of hyperthyroidism on the activity of antioxidant enzymes (Mn-SOD or Cu,Zn-SOD, catalase, glutathion-peroxidase) with differential effects of the two thyroid hormones (Venditti & Di Meo, 2006).

At a systemic level, also in humans, hyperthyroidism has been associated with reduced circulating levels of alpha-tocopherol (Ademoglu *et al.*, 1998; Bianchi *et al.*, 1990) and Coenzyme Q₁₀ (Bianchi *et al.*, 1990; Mancini *et al.*, 1991). Coenzyme Q₁₀ showed a trend to increase in hypothyroidism (Mancini *et al.*, 1991); it appeared to be a sensitive index of tissue effect of thyroid hormones, in situations in which drug interference, such as amiodarone (Mancini *et al.*, 1989) or systemic illness inducing a low-T3 conditions (Mancini *et al.*, 2005) complicate the interpretation of thyroid hormone levels.

However, data on hypothyroidism in humans are conflicting. Baskol *et al.* showed in a group of 33 patients with primary hypothyroidism elevated malondialdehyde (MDA) and nitric oxide (NO) levels and low paraoxonase (PON1) activity, while superoxide dismutase (SOD) was not different from controls. Interestingly, thyroid treatment decreased MDA and increased PON1, without reaching levels observed in controls (Baskol *et al.*, 2007). They concluded that a prooxidant environment in hypothyroidism could play a role in the pathogenesis of atherosclerosis in such patients. Elevated MDA levels were also shown in subclinical hypothyroidism (Torun *et al.*, 2009); the increased in OS was attributed to lack of antioxidants but also to altered lipid metabolism, since MDA showed a correlation with LDL-cholesterol, total cholesterol and triglycerides. Total antioxidant status (TAS) was similar in overt hypothyroidism, subclinical hypothyroidism and controls.

Different studies confirmed the NO elevation (Coria *et al.*, 2009; Erdamar *et al.*, 2008). Data on other parameters are more conflicting. As PON-1 is concerned, a decreased activity was observed both in hypo- and hyperthyroidism (Azizi *et al.*, 2003), while not significant differences with controls were shown in other studies (Coria *et al.*, 2009).

Another study (Santi *et al.*, 2010) showed increased levels of thiobarbituric acid reactive substances (TBARS), but also of antioxidants, such as SOD, catalase (CAT) and Vitamin E.

All these parameters correlated with T3; moreover the correlation between T3 and CAT remained significant also when corrected with total cholesterol. While TBARS elevation was also shown also in some studies (Nanda et al., 2007; Erdamar et al., 2008), other studies did not confirm the datum in overt hypothyroidism (Coria et al., 2009) and in subclinical hypothyroidism (Kebapcilar et al., 2007).

We showed low Total Antioxidant Capacity (TAC) levels in hypothyroid patients (Mancini et al., 2010a) and increased CoQ₁₀ levels also in secondary hypothyroidism (mainly due to its metabolic role in mitochondrial respiratory chain and therefore underutilized in hypothyroid tissue). In the last case, hypothyroidism has a predominant effect on other conditions influencing CoQ₁₀ in opposite direction, such as acromegaly and hypoadrenalism (Mancini et al., 2010a; Mancini et al., 2010b).

Finally, new perspectives concern DUOX (Dual OXidase) genes expression, which is crucial for H₂O₂ generation essential for thyroid peroxidase (TPO)-catalyzed thyroid hormone synthesis (Ohye & Sugawara, 2010). Two oxidases of such family are present in thyroid (DUOX1 and DUOX2) and work together maturation factors (DUOXA1 and DUOXA2), which allow DUOX proteins to translocate to the follicular cell membrane and exert their enzymatic activity (OHYE). Cases of hypothyroidism due to mutation of DUOX or DUOXA genes have been presented in literature (Varela et al., 2006; Ohye et al., 2008). While defects of this system interfere with thyroid hormone synthesis, another new intracellular ROS generating system has been demonstrated in the human thyroid gland: NADPH oxidase 4 (NOX4) (Weyemi et al., 2010); defects in such a system could be associated with thyroid cancer (via activation by H-Ras oncogene) and Hashimoto's thyroiditis (in such a situation increased extracellular production cause an increased ICAM-1 expression and cytokine release) (Sharma et al., 2008).

3. Hypothyroidism and male infertility

Hypothyroidism can cause interference with male fertility, both via endocrine mechanisms and direct effect on spermatogenesis, as recently reviewed (Krassas et al., 2010). The best definite alteration is the decrease in SHBG and total testosterone (T) concentrations, while free T are reduced in approximately 60% of hypothyroid male; thyroxine therapy induces an increase in free T (Donnelly & White, 2000). While in females PRL elevation in hypothyroidism is a crucial phenomenon inducing hypogonadism, in males PRL levels are not frequently augmented. Similarly, gonadotropin levels are often in the normal range, but a blunted gonadotropin (Gn) response to GnRH support the hypothesis of a reduced pituitary responsiveness to hypothalamic stimulation (Velazquez & Bellabarba Arata, 1997). The exaggerated T response to hCG also underlines the role of hypothalamic-pituitary unit rather than a primary testicular effect. A decrease has also been shown in DHEA, DHEAS, androstendiol and pregnenolone sulfate (Tagawa et al., 2001). The endocrine dysfunction partially explain the sexual symptoms complained in such patients, such as decreased libido or erectile dysfunction (Carani et al., 2005; Krassas et al., 2008).

The studies on hypothyroidism and spermatogenesis are not conclusive, since reports concerning small groups of patients are reported in literature (Krassas et al., 2010); the hypothesis that severe and prolonged thyroid deficiency occurring early in life can result in

abnormal testicular biopsies is based on histological and endocrine evaluation of 6 adult hypothyroid men (De la Balze et al., 1962). Similarly, in a group of 8 hypothyroid males, various degrees of testicular atrophy were shown (Wortsman et al., 1987). Another group of 10 hypothyroid patients treated with T4 (with a discontinuation or decrease of therapy for at least a spermatogenetic cycle) presented a decrease in semen volume, progressive forward motility and cumulative percentage of mobile spermatozoa forms, but without significant changes in these parameters during the phase of reinduced hypothyroidism; it was concluded therefore that short-term postpubertal hypothyroidism does not cause severe seminal alterations (Corrales Hernández et al., 1990).

Another prospective, controlled study evaluated semen analysis, biochemical parameters (fructose and acid phosphatase), teratozoospermia index and acridine orange test, in 25 hypothyroid men, before and after 6-9 months T4 treatment (Krassas et al., 2008) in comparison with 15 normal fertile men. The authors concluded that hypothyroidism had an adverse effect on spermatogenesis, with sperm morphology as the only parameter that was significantly affected. These data, therefore, need to be reevaluated, considering the variations in parameters of fertile men which have been introduced by the new version of the WHO manual for semen analysis (WHO, 2010) which are remarkably different from those previously adopted as normal range (WHO, 1999).

Finally, even if the topic of autoimmune thyroid disease (AITD) is extensively studied in females (see the following paragraph), some data in males are reported. The prevalence of thyroid antibody positivity in a population of infertile men was found to be 7.5%; there was no difference in prevalence of abnormal thyroid function tests in normozoospermic vs pathozoospermic patients (11.1 vs 11.8%), but when correlating thyroid autoimmunity with semen parameters, the authors found a significantly higher presence of TPO-Abs in pathozoospermic and asthenozoospermic vs normozoospermic infertile men (6.7% and 7.2% respectively vs 1.6%) (Trummer et al., 2001). This datum was not confirmed in other studies (Krassas et al., 2010). The causal effect of thyroid autoimmunity is far to be understood; only one study showed the presence of TPO-Abs in men with serum sperm autoantibodies (Paschke et al., 1994).

The hypothesis that OS, which is well known to interfere with male fertility (Iwasaki & Gagnon, 1992; Aitken & Krausz, 2001; Agarwal & Saleh, 2002), can be related to thyroid dysfunction induced us to perform a case-control study, evaluating TAC and seminal parameters in an unselected group of infertile man and controls (Mancini et al., 2009) and correlating these values with systemic hormones. TAC was measured using the system H_2O_2 -metmyoglobin as source of radicals. They interact with the chromogenous compound 2,2',-azinobis (3-ethylbenzothiazoline-6-sulphonate) (ABTS) generating its radical cationic form ($ABTS^{\bullet+}$) which can be spectroscopically and kinetically detected (Rice-Evans & Miller, 1994; Meucci et al., 2003). This colorimetric assay was compared with the enhanced chemiluminescence one, which is the most commonly used method for measuring TAC in seminal plasma (Said et al., 2003). The colorimetric assay was found to be a reliable and accurate method, simpler and cheaper than the chemiluminescence one. Antioxidants induce a "lag time" in accumulation and appearance of $ABTS^{\bullet+}$ which is proportional to the antioxidant concentration itself, so that TAC can be expressed as Lag

phase. The possible release of intracellular antioxidants from broken cells was preliminarily excluded by measuring the enzyme LDH in seminal plasma specimens (Mancini et al., 1994).

The correlation analysis between hormones and seminal parameters showed an inverse correlation between PRL and sperm motility, and a direct correlation of TAC with PRL and FT4, but not with gonadotropins or gonadal steroids. Our data suggest that systemic hormones may play a role in regulating seminal antioxidant capacity. This is interesting also because some hormones, such as thyroid and pituitary ones, are not usually tested in the first level evaluation of male patients with fertility problems.

4. Hypothyroidism and female infertility

Hypothyroidism is frequently associated with infertility, due to different reasons: altered peripheral estrogen metabolism, alterations in GnRH secretion causing abnormal pulsatile LH release, hyperprolactinemia and defects in hemostasis (Krassas, 2000).

Similarly to what observed in males, plasma SHBG is decreased, with lowering of total T and estradiol, but their unbound fractions are increased. The metabolism is profoundly affected, with decrease of metabolic clearance rate of androstendione and estrone and increase in peripheral aromatization (Redmond, 2004; Longcope et al., 1990). The $5\alpha/\beta$ ratio of androgen metabolism is decreased and there is an augmented excretion of 2-oxygenated estrogens (Gallagher, 1966). The alterations in steroid metabolism are corrected by replacement therapy (Gordon & Southren, 1977). As in male, gonadotropin levels are usually normal (Larsen, 1998), but with blunted or delayed response to GnRH (Marino et al., 2006; Valenti et al., 1984). Hyperprolactinemia can be induced by augmented TRH secretion, also causing galactorrhea in some patients, reversible with thyroid therapy (Honbo et al., 1978). Finally, decreased levels of clotting factors VII, VIII, IX and XI have been shown and can contribute to polymenorrhea and menorrhagia (Ansell, 1996).

Many studies have been performed also in subclinical hypothyroidism (SCH); the prevalence of SCH in infertile women was 11% in one study (Bohnet et al., 1981), but not considered as an infertility factors by others (Bals-Pratsch et al., 1997). A positive correlation was found in early follicular phase between basal TSH, LH and T; moreover women with elevated TSH response to TRH had lower pregnancy rate than women with normal TSH response (Gerhard et al., 1991). In a controlled prospective study of 438 women with infertility of various origin, the median TSH levels were significantly higher than controls (Poppe et al., 2002). Moreover more frequent miscarriages were observed in women with higher basal TSH levels, irrespective of the presence of AITD (Raber et al., 2003).

We want to focus our attention on luteal deficiency, on one side, and AITD, the most prevalent associated etiology in patients of reproductive age, on the other one.

Progesterone secreted by the corpus luteum plays an important role in the maintenance of early pregnancy. Immediately after implantation, under the influence of human chorionic gonadotropin (hCG) secreted by the trophoblast, the corpus luteum receives a signal to continue to producing 17- α -progesterone along with estradiol, estrone, and relaxin (Szlachter et al., 1980; Bigazzi et al., 1981). The corpus luteum maintains its capacity to synthesize progesterone almost throughout the pregnancy, but at approximately 7 weeks

gestation, its functional ability decreases markedly at the start of the luteoplacental transition. The removal of the corpus luteum before the eighth week of gestation results in abortion, whereas after the ninth week it does not (Csapo et al., 1973). Abnormalities of the luteal phase have been reported to occur in up to 35% of women with recurrent pregnancy losses (Insler, 1992). There are several causes for luteal phase deficiency, including stress, exercise, weight loss, hyperprolactinemia, and menstrual cycles at the onset of puberty or perimenopause.

Luteal phase deficiency (LPD) presents without any significant change in menstrual cycle length, despite prolonged follicular phases and shortened progesterone-deficient luteal phases (De Souza et al., 1998). Clinically, LPD is associated with abnormal corpus luteal function, which includes the mentioned short luteal phases and inadequate progesterone production, and also inappropriate endometrial stimulation and maturation (Ginsburg, 1992). These luteal phase alterations cause asynchronous follicular growth, compromised oocyte maturation, and differentiated (out of phase) function of the endometrium, which is associated with low rates of cycle fecundity and high rates of embryonic loss, i.e. infertility and spontaneous abortion (Ginsburg, 1992).

As above stated, hypoactive thyroid hormone is associated with infertility, even if severe forms of hypothyroidism rarely complicate pregnancy because they are associated with anovulation. However, in mild hypothyroidism, pregnancies can occur and are associated with higher rates of pregnancy loss and maternal complications (Davis et al., 1988; Stray-Pedersen & Stray-Pedersen, 1984). Even if an association exists between low thyroid function and pregnancy loss, a direct evidence for a causal role is missing (Clifford et al., 1994). One hypothesis for this correlation is that luteal phase defect has been linked to thyroid hypofunction. In consideration that production of progesterone is a pivotal element of a successful pregnancy, it is possible that pregnancy loss could be related to a deficient corpus luteum action (Daya et al., 1988).

An important study was published by Negro et al (2006) showing, in a large cohort of women, that patients with positive thyroid autoantibodies (TPO-ab), even if euthyroid at the early stages of pregnancy, would benefit from L-thyroxine administration to improve outcome of pregnancy, and namely the rate of spontaneous miscarriage and premature delivery. Ab-positive women were significantly older than control population (suggesting that AITD could delay conception due to its relation with infertility) but exhibit a mean serum TSH, although normal, significantly higher than controls; women were randomly assigned to two groups, one without treatment, and the other with L-thyroxine treatment. In group without therapy, serum TSH progressively increased during gestation, in the meantime serum free T4 (FT4) decreased by 30%, suggesting reduced functional thyroid reserve due to AITD. On the contrary, in treated group, the miscarriage rate was reduced by 75% and frequency of premature delivery by 69%. Similar results were reported by other authors showing that age, TPO positivity and high TSH levels were independently associated with the risk of miscarriage in multivariate analysis (Siero Netto et al., 2004). An association between miscarriage and AITD had been previously described (Stagnaro-Green et al., 1990; Glinoeer et al., 1991) and support in other population studies, confirming this association also in the case of apparent normal thyroid function (Poppe & Glinoeer, 2003). A recent review separately considered association of AITD and miscarriage, AITD and recurrent miscarriage and finally AITD and early pregnancy loss after in vitro fertilization

(Stagnaro-Green & Glinioer, 2004). Finally another confirmation came from a meta-analysis of all case-controlled and longitudinal studies, with an increased risk by 3-fold. Poppe et al. performed a prospective cohort study in women undergoing the first Assisted Reproduction Technology (ART) cycle, excluding over thyroid dysfunction. The prevalence of antiTPO was 14%, without differences in TSH, FT4 and age; in this positive group, pregnancy rate was 53% vs 43%, with an odds ratio of 0.67, but in pregnant group the miscarriage rate was 53% and 23% respectively, with and odds ratio of 3.77 (Poppe et al., 2003). Autoimmune thyroiditis are clearly associated with clinically relevant events occurring before, during and after pregnancy (Muller & Berghout, 2003). The hypothesis to explain this strong association were, of course, based on the concept of a generalized autoimmune disorders or a subtle thyroid hormone deficiency.

In this sense, a light is brought by studies performed with the administration of L-thyroxine. Vaquero et al (2000) included patients with Ab positivity and two previous first-trimester miscarriage, achieving a greater pregnancy outcome than untreated patients (81% vs 55%). Negro reported a reduction of miscarriage rate after L-thyroxine treatment in Ab positive infertile women who underwent in vitro fertilization (Negro et al., 2006). Finally, Abalovich et al. (2002) underlined the importance of adequate hormone treatment, comparing patients with hypothyroidism already known before pregnancy (adequate treatment) and patients with uncompletely adjusted replacement therapy: the pregnancy ended with abortion in 60% and 71% of cases, respectively.

In conclusion we believe it is prudent to screen for thyroid disease and normalize thyroid functions, when these are found abnormal, prior to conception or to return to a “normal” menstrual cycle, moreover Ab+ women should be carefully evaluated before pregnancy for subclinical hypothyroidism.

We report here some personal data on subclinical hypothyroidism, in couples users of Billings Ovulation Method (BOM); it is based on vulvar observation of the “Mucus Symptom”, whose pattern is an accurate and precise marker of the ovarian function (Billings, 1972), validated by laboratory research and field trials (Billings, 1991; Brown et al., 1987). BOM can be useful in studying subtle abnormalities in thyroid-gonadotropin interaction; the simple identification of the mucus peak and the evaluation of luteal phase length allow to detect a precise timing to perform hormonal assays. Therefore, we used BOM to evaluate the prevalence of subclinical hypothyroidism in women, users of the method for achieving or spacing pregnancy, and whose cycle abnormalities were not referred to cervical pathology. Preliminary data, still unpublished, but presented at the World Congress on Fertility & Sterility (Giacchi et al., 2007) were collected in 42 couples consulting our Center: 22 exhibited an history of infertility (1-4 ys), with a range age of women: 26-42 ys. Criteria of exclusion were male infertility and cervical pathology. Evaluation of progesterone levels was performed on the 6th-7th day after the “peak of mucus symptom”, or on the 6th-7th day before the expected menses, when no peak occurred. We evaluated basal plasma levels of FT3, FT4, TSH, PRL and performed a TRH test (200 ug iv, with TSH evaluation at 0, 30, 60 min) when TSH was normal or high normal. The presence of anti-TPO and anti-thyroglobulin autoantibodies was also evaluated. Progesterone (P), FT3 and FT4 were assayed by RIA; TSH was assayed by IRMA method. Coefficients of variation: intra-assay CV 2.6% for P, 3.8% for FT3, 4.1% for FT4, 4.5% for TSH; inter-assay CV 3.9% for P, 3.9% for FT3, 4.9% for FT4, 3.4% for TSH. Normal ranges: Progesterone: 7-30 ng/ml; FT3: 2.3-4.2

pg/ml; FT4 8.5-15.5 pg/ml; TSH 0.35-2.80 μ UI/ml. TRH (Relefact 200 μ g) was furnished by Hoechst, Italy. Subclinical hypothyroidism was defined as TSH peak response > 15 μ g/ml, according to previous studies and comparison with age-matched controls (Giacchi et al., 2001). Women were classified in three groups according to the BOM mucus symptom different patterns: Anovulatory pattern of the mucus symptom (n=2), post-peak phases shortened and/or affected by spotting (n=22), normal length of luteal phase, but P in the lower range of postovulatory values (n=18); among these two presented hypermenorrhea. Mean \pm levels of the studied hormones are reported in table 1. Normal PRL levels were present in this group of patients. The prevalence of subclinical hypothyroidism, as above defined, in this group was 80%; prevalence of thyroid autoantibodies: 10%. After L-thyroxine treatment, we observed a clear and significant increase in progesterone levels (evaluated 6-7 day after the "peak" of the "mucus symptom") and the resumption of ovulation in the two women with anovulatory cycles (Fig. 1), strongly supporting a pathogenetic role of hypothyroidism in anovulation or luteal failure.

		women number	P (ng/ml)	FT3 (pg/ml)	FT4 (pg/ml)	basal TSH levels μ U/ml	TSH peak μ U/ml	PRL (ng/ml)
No peak anovulatory cycles		2	0,3 \pm 0,2	3,6 \pm 1,5	9,0 \pm 0,5	3,4 \pm 0,8	24,5 \pm 1,5	19,5 \pm 1,0
post peak phase lenght	< 11 g	22	10,7 \pm 1,1	4,0 \pm 1,0	10,1 \pm 0,8	2,7 \pm 0,2	21,2 \pm 1,5	16,1 \pm 1,6
	\geq 11 g	18	9,1 \pm 0,8	3,8 \pm 1,0	9,1 \pm 0,8	3,0 \pm 0,2	22,5 \pm 1,3	17,5 \pm 1,2

Table 1. Mean \pm SEM hormone levels in patients consulting our Center for infertility and monitored by Billings' Ovulation Method.

An hypothesis linking thyroid dysfunction and luteal deficiency is that concerning OS. Oxidative stress is associated with decreased female fertility in animals and in vitro models, but some observations in humans also reinforces this concept. Exposures associated with OS (extremes of body weight, alcohol, tobacco and caffeine intake) may induce pregnancy complications (e.g. preeclampsia); while intake of antioxidants nutrients, included use of multivitamins, have a beneficial role in female fertility (Ruder et al., 2009). More recently, it has been hypothesized that the exposure to environmental pollutants in fetal life may alter DNA methylation, causing altered gene expression in adult life (Li et al., 1997; Anway et al., 2005); therefore this widespread condition should be added to the factors favouring OS. A role of reduced antioxidant defence has also been hypothesized in polycystic ovary, unexplained infertility and outcome of in vitro fertilization (Ruder et al., 2008).

When specifically considering luteal function, it has been shown than the corpus luteum has a high concentrations of antioxidants, especially β -carotene, to which is related the bright yellow color (Rodgers et al., 1995); other carotenoids and vitamins C and E are also present and may contribute to ROS scavenging (Aten et al., 1992; Matzuk et al., 1998; Behrman et al., 2001). Moreover ROS are produced during luteal regression (Behrman et al., 2001), in part through cytochrome P450 enzymes involved in the first step of steroidogenesis (Rodgers et al., 1995).

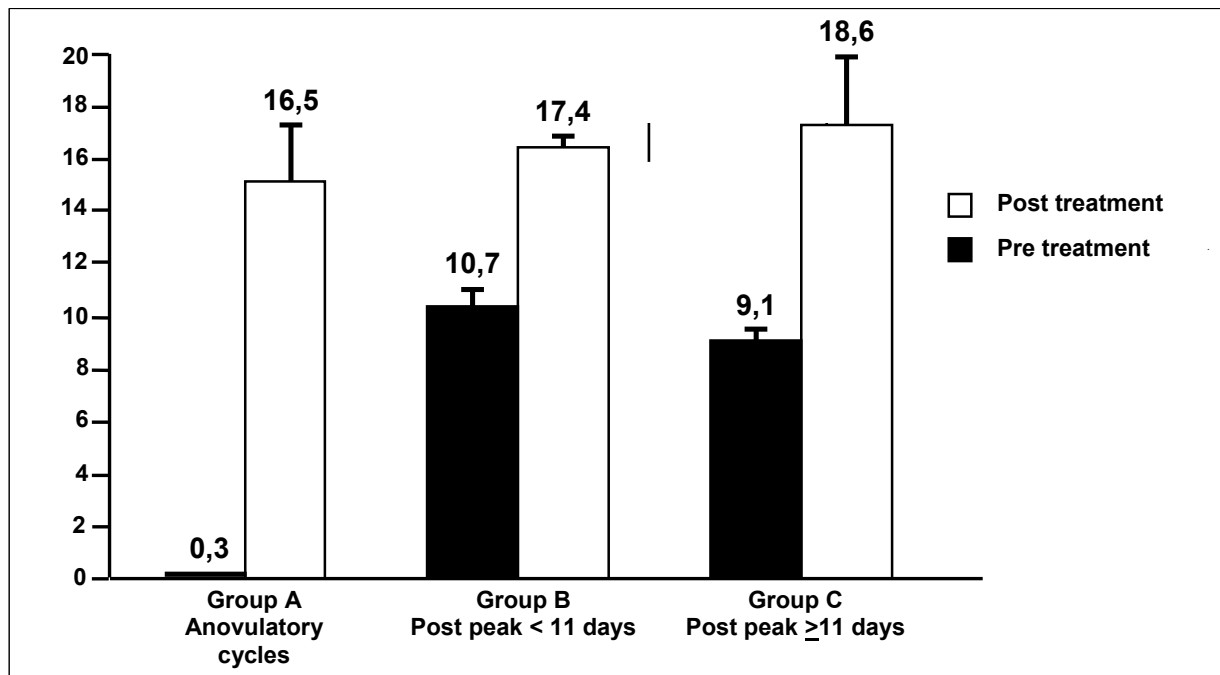


Fig. 1. Post-peak (according to BOM) Progesterone levels (ng/ml) before and after replacement l-T4 treatment .

However, the role of ROS in ovary is particularly complex. On one side, they play a physiological role: regulated ROS generation by the pre-ovulatory follicle is an important promoter of ovulatory sequence; in particular, the resumption of meiosis I (MI) induced by hormonal factor after puberty, is induced by ROS and inhibited by antioxidants (Takami et al., 1999; Kodman & Behrman, 2001). Another beneficial effects could be related to a ROS involvement in intracellular signalling between hypoxia and angiogenic response (Basini et al., 2004). Surprisingly, antioxidants are, on the contrary, beneficial for MII, which arises in response to periovulatory LH peak (Behrman et al., 2001). Follicular ROS initiate apoptosis whereas follicular glutathione (GSH), in addition to FSH, protect against apoptosis in cultured preovulatory rat follicles (Tsai-Turton & Luderer, 2006). Moreover, cyclical ROS production may contribute to oophoritis associated with autoimmune premature ovarian failure (Behrman et al., 2001). It has been suggested that ROS under moderate concentrations play a role in signal transduction processes involved in growth and protection from apoptosis (Basini et al., 2004). In rat thecal-intestinal cells, which regulate steroidogenesis and follicle growth in secondary follicle, ROS induced a biphasic effect on proliferation (positive at lower and negative at higher concentrations). Therefore controlled ROS levels may be needed to maintain DNA synthesis, cell proliferation and growth of ovarian mesenchyme in such animal model (Duleba et al., 2004). Finally, epidemiologic data suggest a positive role of dietary antioxidants (Ruder et al., 2008): preconceptional multivitamin supplementation may enhance fertility, perhaps increasing menstrual cycle regularity (Czeizel et al., 1994; Dudas et al., 1995) or via prevention of ovulatory disorders (Chavarro et al., 2007). Despite all these evidences, it must be reminded the difference by in vitro models and in vivo conditions and the need of more data of antioxidants levels in hypothyroidism, which could be useful for therapeutic purposes.

5. Conclusions

Taken together, all the reported data confirm the role of thyroid hormones in human fertility; also subclinical hypothyroidism should be considered in the evaluation of an infertile couple, even if it is not routinely evaluated in the first level approach to this problem. Oxidative stress could be a phenomenon linking hypothyroidism, also in subclinical form, with altered sperm motility, in males, and luteal phase deficiency in females, even if more experimental data are needed to give statistical evidence to this fascinating hypothesis.

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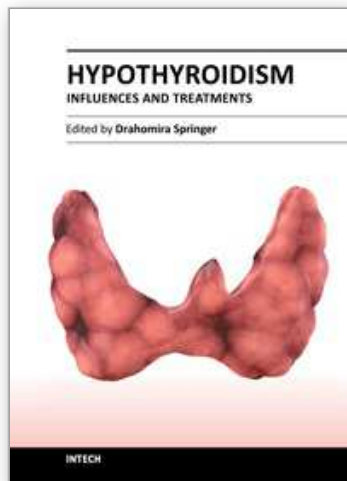
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Hypothyroidism is the most common thyroid disorder and it is significantly more frequent than presented - millions of people suffer from this disease without knowing it. People with this condition will have symptoms associated with slow metabolism. Estimates of subclinical hypothyroidism range between 3 to 8 %, increasing with age, whereas it more likely affects women than men. About 10% of women may have some degree of thyroid hormone deficiency. Hypothyroidism may affect lipid metabolism, neurological diseases or other clinical conditions. The book includes studies on advancements in diagnosis, regulation and replacement therapy, thyroid ultrasonography and radioiodine therapy for hypothyroidism. "Hypothyroidism - Influences and Treatments" contains many important specifications, results of scientific studies and innovations for endocrine practice.

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