

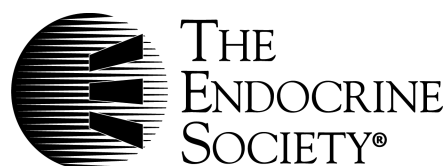
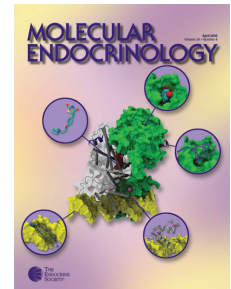
# ENDOCRINE REVIEWS

## Thyroid Function and Human Reproductive Health

G. E. Krassas, K. Poppe and D. Glinoe

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## Thyroid Function and Human Reproductive Health

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Via its interaction in several pathways, normal thyroid function is important to maintain normal reproduction. In both genders, changes in SHBG and sex steroids are a consistent feature associated with hyper- and hypothyroidism and were already reported many years ago. Male reproduction is adversely affected by both thyrotoxicosis and hypothyroidism. Erectile abnormalities have been reported. Thyrotoxicosis induces abnormalities in sperm motility, whereas hypothyroidism is associated with abnormalities in sperm morphology; the latter normalize when euthyroidism is reached. In females, thyrotoxicosis and hypothyroidism can cause menstrual disturbances. Thyrotoxicosis is associated mainly with hypomenorrhea and polymenorrhea, whereas hypothyroidism is associated mainly with oligomenorrhea. Thyroid dysfunction has also been linked to reduced fertility. Controlled ovarian hyperstimulation leads to important increases in estradiol, which in turn may have an adverse effect on thyroid hormones and TSH. When autoimmune thyroid disease is present, the impact of controlled ovarian hyperstimulation may become more severe, depending on preexisting thyroid abnormalities. Autoimmune thyroid disease is present in 5–20% of unselected pregnant women. Isolated hypothyroxinemia has been described in approximately 2% of pregnancies, without serum TSH elevation and in the absence of thyroid autoantibodies. Overt hypothyroidism has been associated with increased rates of spontaneous abortion, premature delivery and/or low birth weight, fetal distress in labor, and perhaps gestation-induced hypertension and placental abruption. The links between such obstetrical complications and subclinical hypothyroidism are less evident. Thyrotoxicosis during pregnancy is due to Graves' disease and gestational transient thyrotoxicosis. All antithyroid drugs cross the placenta and may potentially affect fetal thyroid function. (*Endocrine Reviews* 31: 702–755, 2010)

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### I. Introduction

Two comprehensive review articles on thyroid function and reproductive health were published in *Endocrine Reviews* more than a decade ago (1, 2). In the first article, entitled “Thyroid Hormone and Male Gonadal Function,” Jannini *et al.* (1) concluded that “the classic assumption that adult male gonad is unresponsive to thyroid hormone is no longer tenable; the seminiferous

Abbreviations: AITD, Autoimmune thyroid diseases; ART, assisted reproduction technology; ATD, antithyroid drugs; CH, congenital hypothyroidism; CI, confidence interval; CMI, carbimazole; COH, controlled ovarian hyperstimulation; DE, delayed ejaculation; DHEA, dehydroepiandrosterone; E<sub>2</sub>, estradiol; ED, erectile dysfunction; FT<sub>3</sub>, free T<sub>3</sub>; FT<sub>4</sub>, free T<sub>4</sub>; GD, Graves' disease; Gn, gonadotropin(s); GTT, gestational transient thyrotoxicosis; hCG, human chorionic Gn; HG, hyperemesis gravidarum; HSD, hypoactive sexual desire; hypo-T<sub>4</sub>, hypothyroxinemia; ID, iodine deficiency; IVF, *in vitro* fertilization; KI, potassium iodide; LT<sub>4</sub>, levothyroxine; MMI, methimazole; OD, ovulatory dysfunction; OH, overt hypothyroidism; OHSS, ovarian hyperstimulation syndrome; PCOS, polycystic ovary syndrome; PE, premature ejaculation; PPTD, postpartum thyroid dysfunction; PRL, prolactin; PTU, propylthiouracil; R-<sup>131</sup>I, radioiodine; SCH, subclinical hypothyroidism; SCHAT, subclinical hyperthyroidism; TBG, T<sub>4</sub>-binding globulin; TBII, thyrotropin-binding inhibitory Ig; TG, thyroglobulin; TG-Abs, TG autoantibodies; TH, thyroid hormone(s); Th-Abs, thyroid autoantibodies; TPO, thyroid peroxidase; TPO-Abs, TPO autoantibodies; TR, thyroid receptor; TR-Abs, TSH-receptor antibodies; TS-Ab, thyroid-stimulating antibody.

epithelium of prepubertal testis can now be considered a novel thyroid hormone-responsive tissue” (1). Historically, it was Kendle who reported for the first time in 1905 the development of precocious puberty in a young girl with severe hypothyroidism (3). It has since been largely confirmed that significant associations do exist between thyroid disorders and abnormalities of the reproductive system: both primary hyperthyroidism and hypothyroidism in males and females have been well documented to produce variable degrees of gonadal dysfunction (4–9). Because normal thyroid function is important to maintain normal reproductive functions, the first aim of the present review was to discuss relevant information regarding the effects of hyper- and hypothyroidism on reproduction in males and females; the second aim was to discuss recent information on thyroid function and autoimmunity in relation to infertility and assisted reproduction technology (ART).

In the second article, entitled “Regulation of Thyroid Function in Pregnancy: Pathways of Endocrine Adaptation from Physiology to Pathology,” the author concluded that “our concepts of the complex relationships between pregnancy and thyroid function have evolved importantly over the past years” and that “the assumption that thyroid changes associated with the pregnant state were generally considered minor was far from the truth” (2). In recent years, a wealth of new information has been gained regarding thyroid function and pregnancy, particularly on topics such as the validity of thyroid function tests (10), the role of screening (11), autoimmune thyroid disease (AITD) (12), and management of pregnant women with thyroid diseases (13, 14). Furthermore, international thyroid and endocrine associations have addressed these issues and published expanded guidelines for the management of thyroid disease in pregnancy (15). Therefore, the third aim of the present review was to present and discuss recent concepts on the physiology and physiopathology of thyroid function associated with the pregnant state.

## II. Thyroid Function and Infertility

### A. In males

#### **1. The effects of thyrotoxicosis and hypothyroidism on the male reproductive system: Animal studies**

The effects of thyroid hormone (TH) alterations on the reproductive system have been studied extensively in animals and have generally shown that changes from normal thyroid function resulted in decreased sexual activity and fertility (16, 17). The underlying mechanisms, however,

are not constant throughout all species, and results from different studies disagree.

In intact rats, the administration of  $T_4$  resulted in decreased serum gonadotropin (Gn) levels (18). In immature male mice aged less than 4 wk, the administration of slightly supraphysiological  $T_4$  doses resulted in a tendency toward early maturation and shortening of mice development period. Conversely, larger TH doses resulted in decreased testes weights and seminal vesicles, both in mice and rabbits (16). Direct effects of  $T_4$  resulted in minimal oxygen consumption changes in testes when  $T_4$  was present in testicular slice incubations (19). Administration of excess  $T_4$  to mature male rats also resulted in a decrease in total lipids, cholesterol, and phospholipids in testes, and rats rendered thyrotoxic by  $T_4$  administration were shown to synthesize increased amounts of testosterone (18, 20). Finally, the effects of  $T_4$  on spermatogenesis are conflicting, but it would appear that  $T_4$  does not exert a direct effect on spermatogenesis in mature rats or rams (21).

In the rat,  $T_3$  affects testis maturation, and thyroid receptor (TR) $\alpha$  and TR $\beta$  are known to be expressed in rats' testes (22). TR $\alpha$ 1 is the specific TR isoform that has been proposed to be involved in testis function and development. Maximal Sertoli cell proliferation coincides with maximal  $T_3$  binding capacity in testis, suggesting that the main target of  $T_3$  action is the Sertoli cell. However,  $T_3$  also plays a significant role in differentiation of the seminiferous epithelium, and studies in rodents have shown that  $T_3$  is an important factor in maturation of Leydig cells. The presence of  $T_3$  is necessary to initiate differentiation of mesenchymal cells into Leydig progenitor cells, and  $T_3$  works in concert with other hormones (LH and IGF-I) to promote Leydig cell development (1, 23).

Data from other animal species (such as deer, sheep, cattle, birds, and mink) also suggest that  $T_3$  is a component of the neuroendocrine system that regulates seasonal cycles of reproductive activity (1). Although the underlying mechanisms remain unknown, it has been postulated that  $T_3$  triggers cessation of reproduction at the end of the reproduction season because circulating  $T_3$  levels in deer rise at the time of seasonal transition to the nonbreeding state and thyroidectomy results in the absence of seasonal regression of the testis.  $T_3$  may also interact with and modulate the action of other hormonal systems such as GH and steroids.

Hypothyroidism induced or occurring soon after birth was associated with marked sexual maturation and development delays in animals (1). Rats made hypothyroid transiently by propylthiouracil (PTU) administration (from birth to 24–26 d of age) showed a decrease in testicular size, retardation in Sertoli cell differentiation, and prolongation of Sertoli cell proliferation time (24, 25).

When the rats became older and returned to a euthyroid status, there was an increase in testis size, Sertoli cell number, and sperm production (26). In one interventional study, Hardy *et al.* (27) administered 6-propyl-2-thiouracil (PTU) to suckling rat pups from birth through d 24 postpartum as a 0.1% solution in the mothers' drinking water. They found an increase of adult testis size and sperm production by about 80 and 140%, respectively, without affecting peripheral testosterone levels (27). In other studies where experimental hypothyroidism in rats was left untreated for more than 1 month, there was an arrest of sexual maturity as well as an absence of libido and ejaculate. The longer hypothyroidism persisted, the greater the damage to the testes (28). Induction of hypothyroidism in mature male rat had little effect on histopathology of the testes, spermatogenesis, or serum testosterone concentrations (29). In the adult ram, hypothyroidism was associated with decreased testosterone concentration but normal spermatogenesis (21). It would therefore appear that hypothyroidism affects the immature, but not the mature, testis.

Jiang *et al.* (30) conducted a study to determine whether hypothyroidism in adult male rats induced infertility by impairing sexual behavior or testicular function, whether infertility could be reversed by T<sub>4</sub> treatment, and whether mutant rats could be produced by infertile rats via *in vitro* fertilization (IVF) (30). The results showed that infertility resulted from both defective sexual behavior and testicular dysfunction; no untreated rats mated; the weights of epididymides were significantly reduced, whereas testes weights were not different from those of normal rats. Moreover, no fertilization was detected *in vivo* or *in vitro*. After T<sub>4</sub> administration, which produced markedly increased serum T<sub>4</sub> levels, the weights of the epididymides and testes increased markedly, and there was partial reversion of sexual behavior impairment. When determined both *in vivo* and *in vitro*, sperm fertility characteristics were entirely normalized, and homozygous embryos developed to term after transfer without viability loss (30).

Pekary and Sattin (31) treated young adult Sprague-Dawley male rats for 1 wk with daily ip saline injections, T<sub>4</sub> (5 µg), PTU (3 mg), or castration to investigate the hypothesis that TRH and TRH-derived peptides may contribute to the behavioral and mood changes accompanying hypothyroidism, hyperthyroidism, and hypogonadism. The results showed that both hypothyroidism and castration reduced TRH levels as well as a majority of other TRH-like peptides in entorhinal cortex (31). Finally, rats made hypothyroid had subnormal GH mRNA in the pituitary glands (32, 33). The promoter of rat GH gene has been documented to contain a TH response element (34–36). This important finding provides a possible clue to the mechanism by which TH interacts with the GH genes to

correct GH secretion deficiency that is common in patients with primary hypothyroidism.

## **2. The effects of thyrotoxicosis and hypothyroidism on the male reproductive system: Human studies**

Although the effects of both hyper- and hypothyroidism on female gonadal function have been clearly established, the impact of these disorders on male reproductive function remains controversial (8, 37). This is mainly due to the clinical irrelevance of most signs or symptoms related to gonadal dysfunction in males compared with the well-known systemic effects of both hyper- and hypothyroidism, with the consequence that only a few well-controlled clinical studies have been published.

### **2A. Thyrotoxicosis in males**

*a. Hormonal changes.* An increase in SHBG has been a feature consistently associated with thyrotoxicosis, leading to increased circulating levels of total testosterone and reduction in testosterone metabolic clearance rate (38, 39). By contrast, free testosterone concentrations usually remained normal, although bioavailable testosterone was found subnormal in hyperthyroid males (6). Total and free estradiol (E<sub>2</sub>) concentrations were often elevated, and consequently, the free testosterone/free E<sub>2</sub> ratio was lower in hyperthyroid males compared with normal individuals (4, 6, 40–42). Relative free E<sub>2</sub> elevation may contribute to the higher incidence of gynecomastia observed in hyperthyroid males with decreased libido (43, 44) (Table 1). Another consistent finding has been that LH and FSH responses to GnRH administration were exaggerated in hyperthyroid males, contrasting with a blunted response of Leydig cells to human chorionic Gn (hCG) administration, as assessed by serum testosterone responses (40–42). Such abnormalities of the hypothalamic-pituitary-gonadal axis were significantly correlated with increased serum T<sub>4</sub> levels and were shown to be entirely reversible with restoration of a euthyroid status, hence indicating that no specific treatment is required (Fig. 1).

*b. Spermatogenesis, fertility, and thyrotoxicosis.* Effects of thyrotoxicosis on semen quality have been the subject of only a few studies. Clyde *et al.* (45) investigated three young hyperthyroid males and found that two patients presented marked oligospermia with decreased motility, whereas the third patient had a borderline low sperm count with decreased motility. Kidd *et al.* (46) investigated five hyperthyroid patients and found that all had low total sperm counts. In 1992, Hudson and Edwards (47) had already assessed testicular function in 16 hyperthyroid males, and the results showed that although the mean sperm density did not differ significantly from controls, it was low. In addition, forward progressive sperm mo-

**TABLE 1.** Synopsis of hormonal changes in male and female thyrotoxicosis and hypothyroidism

	Thyrotoxicosis		Hypothyroidism	
	Males	Females	Males	Females
SHBG	↑	↑	↓ or N	↓
E <sub>2</sub>	N or ↑	↑	N	↓
Estrone		↑		↓
Production rate of estrogens		→		→ or ↓
Metabolic clearance rate of estrogens or androgens	↓	↓	↓	↓
Free E <sub>2</sub>	↑	→		N
Testosterone	↑	↑	↓	↓
Δ4-Androstenedione		↑	↓	↓
DHEA	↑	↑	↓	↓
Free testosterone	→		↓	N
Bioavailable testosterone	↑			
Conversion of testosterone to Δ4-androstenedione	↑	→ or ↑	↓	↑
Androgen conversion to estrone	↑	↑		
Progesterone	↑	↓ or →		↓ or →
LH	↑ or →	↑ or →	N	N
FSH	↑ or →	↑ or →	N	N
After GnRH				
LH	↑	↑	↓	↓
FSH	↑	↑	↓	↓

↑, Increase; ↓, decrease; →, no change; N, normal; —, not available.

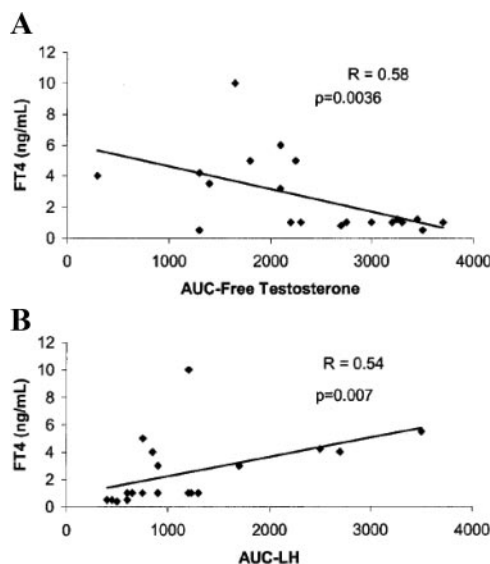
tility in these patients was significantly reduced compared with normal males (47). More recently, Abalovich *et al.* (6) investigated the effect of hyperthyroidism on spermatogenesis in 21 hyperthyroid patients: nine patients (43%)

had low total sperm count, 18 (86%) presented lineal motility defects, and 13 (62%) displayed progressive motility abnormalities.

In another recent study by one of us (G.E.K.), 23 hyperthyroid males and 15 healthy controls were investigated prospectively by semen examination both before and 5 months after the restoration of euthyroidism by methimazole (MMI) treatment only (in 14 patients) or MMI plus radioiodine (R-I<sup>131</sup>) (in nine patients) (43). Total fructose, Zn, and Mg concentrations were also measured in the seminal plasma in 16 of 23 patients. The results indicated that mean semen volume was within normal range in the patients, but mean sperm density was lower when compared with controls (difference not statistically significant, however). A similar trend was found for the analysis of sperm morphology, but mean sperm motility was lower in hyperthyroid males when compared with controls. After the treatment of thyrotoxicosis, both sperm density and motility improved, although sperm morphology did not change. The type of treatment employed (MMI alone or MMI plus R-I<sup>131</sup>) had no impact on sperm count or morphology. Mean values for seminal plasma fructose, Zn, and Mg concentrations did not differ between controls and patients, before and after restoration of euthyroidism, and the values did not correlate with sperm parameters or with TH levels in the thyrotoxic period (Table 2).

Another interesting aspect concerns the effects of hyperthyroidism on sexual behavior. Despite normal basal testosterone concentrations in hyperthyroid men, anecdotal reports claimed that erectile dysfunction (ED) was observed frequently, with incidence rates reaching 70% (48). Carani *et al.* (49) investigated 34 adult men with hyperthyroidism in a prospective, multicenter, uncontrolled study. The patients were screened for hypoactive sexual desire (HSD), ED, premature ejaculation (PE), and delayed ejaculation (DE) at presentation and again 8–16 wk after restoration of a euthyroid status. Figure 2 shows that hyperthyroidism was associated with a marked increase in the prevalence of HSD, DE, PE, and ED. After restoration of a euthyroid status by treatment, HSD and DE resolved in most cases, and furthermore, the most striking effect was the sharp PE decrease from 50 to 15%, *i.e.*, a figure similar to that found in the general population.

Using the Sexual Health Inventory for Males (SHIM), one of us (G.E.K.) investigated the impact of hyperthyroidism on male sexual health in 27 hyperthyroid male patients (and 71 controls) who participated to a prospective, controlled study (50). The patients were asked to respond to the SHIM five-item questionnaire before and 1 yr after initiation of treatment. A global score between 25



**FIG. 1.** The graphs show the inverse correlation between serum FT<sub>4</sub> concentrations and the area under the curve for free testosterone after hCG administration (A) and the positive correlation between serum FT<sub>4</sub> concentrations and the area under the curve for LH after GnRH therapy (B) in men with variable degrees of thyroid dysfunction. [Reproduced from E. M. Velázquez and G. Bellabarba Arata, Effects of thyroid status on pituitary gonadotropin and testicular reserve in men. *Arch Androl* 38:85–92, 1997 (41), with permission. © 1997, Taylor & Francis.]

**TABLE 2.** Characteristics on quality of semen

First author (Ref.)	No. of patients investigated	Results
In thyrotoxic men		
Clyde (45)	3	Two had severe and one had borderline oligospermia; all had decreased sperm motility.
Kidd (46)	5	All had sperm counts less than $40 \times 10^6$ per ml.
Hudson (47)	16	Sperm densities were low, but not different from controls. Motility was significantly lower in hyperthyroid patients.
Abalovich (6)	21	Nine patients had decreased sperm counts; 18 patients had decreased sperm motility.
Krassas (43)	23	Mean sperm densities were low but did not differ from controls. Sperm motility was significantly lower in hyperthyroid patients.
In hypothyroid men		
Griboff (92)	5	Normal sperm count. Semen exposure to room air produced loss of sperm motility in two patients.
De la Balze (93)	6	Histological abnormalities found in all in testicular biopsies.
Wortsman (94)	8	Seven of eight patients showed varying degrees of testicular atrophy.
Corrales Hernandez (95)	10	No abnormalities found.
Jaya Kumar (96)	8	Five of eight patients had sperm analysis done. No original data.
Krassas (97)	25	Morphology was the only sperm parameter significantly affected. Motility was also affected, but differences were not statistically significant.

and 22 was considered normal, between 21 and 11 was indicative of mild to moderately severe ED, and 10 or less was diagnostic of severe ED. The results showed that 70% of hyperthyroid patients had a SHIM score of 21 or less, compared with only 34% of control individuals completing the questionnaire ( $P < 0.0001$ ). There was a positive correlation between serum free  $T_4$  ( $FT_4$ ) values and SHIM scores ( $P = 0.005$ ). A significant increase of SHIM scores was noted in hyperthyroid patients after treatment. The conclusion was that ED was extremely common in hyperthyroid males and that treatment restored normal erectile function. The authors also recommended thyroid function screening in all men complaining of ED and that, for hyperthyroid males, specific ED treatment could be postponed for at least 6 months after restoring euthyroidism.

#### c. $R\text{-I}^{131}$ treatment for hyperthyroidism and reproduction.

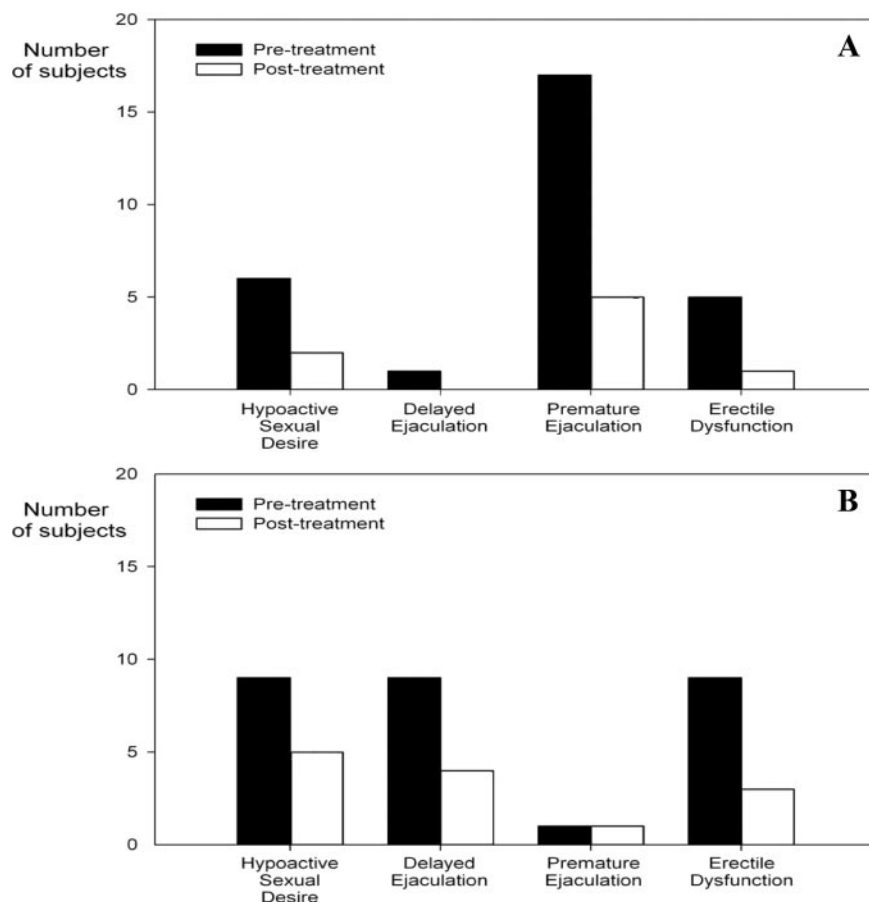
$R\text{-I}^{131}$  is widely used in the treatment of hyperthyroidism (51). Because of potential mutagenic effects of radiation on the gonads, there is a legitimate concern regarding the possible side effects of  $R\text{-I}^{131}$  administration on reproductive function in young patients. Reassuringly, several studies have reported normal reproductive performance in men with thyrotoxicosis after  $R\text{-I}^{131}$  therapy.  $R\text{-I}^{131}$  therapy is therefore justifiably used by clinicians as the first-line treatment for thyrotoxicosis in adults of all ages (52–55).

Ceccarelli *et al.* (56) have evaluated a series of 15 thyrotoxic male patients before and at different times after  $R\text{-I}^{131}$  therapy. Mean basal FSH concentration was within the normal limits and did not change after therapy, although two patients showed substantial FSH increases

lasting for 1 yr (but one of them was already mildly hypogonadal before treatment). Asthenospermia was observed before  $R\text{-I}^{131}$  treatment in 10 of 15 patients, and sperm quality was significantly improved in five of these 10 patients within 1 yr after therapy. Sperm morphology did not show any significant modification. LH was normal and did not change after  $R\text{-I}^{131}$  therapy, whereas testosterone levels were reduced 45 d after  $R\text{-I}^{131}$  therapy and returned to basal values 1 yr later. The inference was that the radiation dose to the testes may account for small and transient damage, both to the germinal epithelium and Leydig cells. However, this damage is difficult to distinguish from that caused by hyperthyroidism *per se*.

For children aged 10 yr or older,  $R\text{-I}^{131}$  administration may also be considered as a first-line therapeutic option. The goal of  $R\text{-I}^{131}$  therapy in children is to achieve hypothyroidism by ablating the thyroid gland, and there is no apparent risk for future fertility (57–59).

Finally, in the context of thyroid cancer treatment, deleterious effects of gonadal irradiation are directly related to the cumulative dose absorbed by the gonads, which is difficult to estimate after multiple  $R\text{-I}^{131}$  doses (60–62). Dose fractionation appears to increase testicular toxicity of irradiation (63). There are only a few reports in literature on spermatogenesis and fertility status in male patients with  $R\text{-I}^{131}$  treatment for thyroid cancer (64–70). Most of those studies have shown that  $R\text{-I}^{131}$  treatment for differentiated thyroid cancer may cause transient impairment of testicular function. Specifically, transient suppression of spermatogenesis or, even complete azoospermia, has been noted as lasting up to 3 yr in



**FIG. 2.** A, Hyperthyroidism before and after treatment. B, Hypothyroidism before and after treatment. The graphs show the prevalence of four features related to sexual dysfunction during hyperthyroidism and hypothyroidism (black columns, before treatment) and after restoration of euthyroidism (white columns, after treatment). [Reproduced from C. Carani *et al.*, Multicenter study on the prevalence of sexual symptoms in male hypo- and hyperthyroid patients. *J Clin Endocrinol Metab* 90:6472–6479, 2005 (49), with permission. © 2005, The Endocrine Society.]

patients that received the higher dose. Sperm cryopreservation before R-I<sup>131</sup> should be addressed in all young men, especially those likely to receive higher and/or cumulative R-I<sup>131</sup> doses (69, 70).

## 2B. Hypothyroidism in males

**a. Hormonal changes.** Hypothyroidism is less common in men than in women and has less clear-cut effects on reproductive function (9, 71–76). Primary hypothyroidism results in a decrease in SHBG and total testosterone concentrations, and free testosterone concentrations are reduced in approximately 60% of males with hypothyroidism (Table 1). In a prospective study of 10 men with primary hypothyroidism, plasma free testosterone levels were low and increased after the onset of levothyroxine (LT<sub>4</sub>) therapy (77). It has been shown that TH administration to hypothyroid men induces a rise in both SHBG and total serum testosterone (78). Boys with congenital hypothyroidism (CH) diagnosed and treated soon after birth have normal sexual development and adult height,

indicating that CH does not produce long-term detrimental effects on gonadal function (79).

Although prolactin (PRL) elevation is the common link between primary hypothyroidism and gonadal dysfunction in females, males with primary hypothyroidism seldom exhibit elevated serum PRL concentrations, except those with long-standing and severe hypothyroidism. Severe primary hypothyroidism results in pituitary tumors in men with hyperprolactinemia and hypogonadotropic hypogonadism. Replacement therapy with TH reverses all of these abnormalities (48, 80, 81). A mechanism for hypogonadism associated with primary hypothyroidism without PRL elevation has been investigated. Most studies indicated that hypothyroid men with hypogonadism have normal LH and FSH levels, suggesting that the primary defect is not in Leydig cells and presumably results from a defect at the hypothalamus and/or pituitary level. Blunted Gn responses to GnRH support this notion, and it would therefore seem that primary hypothyroidism impairs the ability of the pituitary gland to respond to GnRH (41). Another finding that supports the above notion is that hCG produces an exaggerated response of serum testosterone in such patients, which is in contrast with what is expected if the primary defect was in Leydig cells. The latter may also be explained in part from the impaired clearance of hormones and drugs with which hypothyroidism is associated (82, 83). The net consequence of an impaired hypothalamic-pituitary-gonadal axis is that free testosterone levels are subnormal in men with primary hypothyroidism.

Dehydroepiandrosterone (DHEA), DHEA sulfate, estrogenic metabolites of DHEA (androstenediol and its sulfate), and pregnenolone sulfate are decreased in the serum of men with hypothyroidism, compared with normal controls (84).

Hypothyroidism is associated with a variety of endocrine disorders depending on age and severity of primary hypothyroidism (85–87). In children, hypothyroidism is associated with growth retardation and alterations in GH secretion and action (86). Hyposecretion of ACTH and cortisol has also been reported in primary hypothyroid-

ism, although cortisol levels remain normal (77, 85, 88, 89). The discrepancy between serum cortisol concentrations and its secretion rate has been attributed to diminished cortisol clearance (86). Both provocative tests and sleep-induced GH secretion have been reported to be subnormal in male patients with primary hypothyroidism and are reversible by TH replacement (86, 90). Primary hypothyroidism produces delayed or precocious puberty in prepubertal boys and hypogonadism in postpubertal individuals (90). As mentioned already, boys with CH do not show impaired adult height or sexual development alterations when they have been treated with TH since the neonatal period (48).

**b. Spermatogenesis, fertility, and hypothyroidism.** Hypothyroidism is associated with decreased libido or impotence (9, 91). In the studies of Carani *et al.* (49) and Krassas *et al.* (50), described above for the effects of hyperthyroidism on sexual behavior, sexual behavior was also investigated in males with hypothyroidism, both before and after TH treatment. In the Carani study (49), 14 adult hypothyroid males showed an overall 64% prevalence for HSD, DE, and ED and 7% prevalence for PE. After euthyroidism was reached, half of the patients with DE had no complaints, ED almost disappeared, and patients with HSD found a significant improvement of symptoms while on therapy (Fig. 2). In the Krassas study (50), 44 hypothyroid patients and 71 controls were investigated with the SHIM questionnaire. Thirty-seven of 44 (84%) hypothyroid patients had a SHIM score of 21 or less, compared with only 24 of 71 controls (33.8%;  $P < 0.0001$ ). Thirteen patients (35.1%) with ED had a SHIM score of 10 or less, indicative of severe ED, compared with only six (25%) controls ( $P < 0.01$ ). Negative correlations were found between the SHIM scores and serum TSH levels ( $P < 0.001$ ). After treatment of hypothyroidism, a significant increase of SHIM scores was noted. As concluded for the case of hyperthyroidism in males, the conclusion of this part of the study was that ED was also common in hypothyroid males and that treatment restored normal erectile function, indicating again that screening for thyroid dysfunction is recommended in all men presenting with ED.

Little is known about the effects of hypothyroidism on human spermatogenesis and fertility. Griboff (92) investigated five patients with primary hypothyroidism (aged 30–64 yr) and, whereas all patients demonstrated normal sperm counts, semen exposure to room air revealed a rapid drying of the material and sperm motility loss in two of five specimens. Another study by De la Balze *et al.* (93) investigated six adult hypothyroid males (aged 17–59 yr) and showed that all patients demonstrated features of hypogonadotropic hypogonadism, with testicular biopsies revealing

histological abnormalities. Of notice, thyroid insufficiency had occurred before puberty in five of them, whereas it occurred during childhood in the sixth patient. It was concluded that severe and prolonged thyroid insufficiency occurring early in life resulted in moderate failure of pituitary Gn secretion and abnormal testicular biopsies.

Wortsman *et al.* (94) investigated eight hypothyroid male patients aged 37–77 yr. All patients had evidence of hypogonadism, five were hypergonadotropic, and three were hypogonadotropic. Seven patients showed various degrees of testicular atrophy, but sperm analysis was not performed. Serum testosterone and SHBG concentrations were low in four patients. The authors concluded that gonadal function abnormalities were common in men with primary hypothyroidism. Corrales Hernández *et al.* (95) studied spermatogenesis in 10 hypothyroid patients treated with  $T_4$ , in whom hypothyroidism was reinduced by discontinuing (or decreasing) the daily  $T_4$  dose over at least one spermatogenic cycle. A decrease in seminal volume, progressive spermatozoa forward motility, and cumulative percentage of mobile spermatozoa forms was observed. No abnormality in sperm density or the percentage of spermatozoa with normal morphology was observed. Reinduction of hypothyroidism did not lead to seminal changes, when compared with the same patients in the euthyroid state. Serum concentrations of testosterone and Gn were normal during the hypothyroid phase. It appears, therefore, that short-term postpubertal hypothyroidism does not cause seminal alterations of sufficient intensity to impair male fertility. Jaya Kumar *et al.* (96) studied reproductive and endocrine function in eight males with primary hypothyroidism during the hypothyroid phase and again after achieving euthyroidism with  $T_4$ . The authors found high mean Gn levels, low serum testosterone, low SHBG, and subnormal testosterone responses to hCG. Semen analysis was performed in five patients; results were not reported, but the authors claimed that “some improvement in sperm count and motility was observed.”

The effects of hypothyroidism on male spermatogenesis were investigated in a recent prospective, controlled study. A total of 25 hypothyroid men and 15 normal individuals were investigated, with semen analysis, fructose and acid phosphatase measurements, teratozoospermia index, and acridine orange test determined both before and 6–9 months after treatment with  $T_4$  (97). The conclusion was that hypothyroidism had an adverse effect on human spermatogenesis, with sperm morphology the only parameter that was significantly affected. Screening for thyroid dysfunction in males who present with a defect in spermatogenesis is strongly advised, and, when hypothy-



roidism is diagnosed, response to TH ought to be evaluated before initiating other treatments (Table 2).

Although the impact of thyroid dysfunction and/or AITD has been studied extensively in the females of infertile couples, few studies have addressed the question of whether thyroid dysfunction and/or AITD was more frequent in the males (of infertile couples) with altered semen characteristics, compared with men with normal semen, and whether systematic screening should be advised. Trummer *et al.* (98) investigated 305 men who underwent evaluation for infertility. Semen analysis and measurements of FT<sub>4</sub>, FT<sub>3</sub>, TSH, and thyroid antibodies, including thyroid receptor antibodies, were carried out. A total of 179 of the men (*i.e.*, 59%) had pathozoospermia. Clinically, no evident thyroid dysfunction was found. With regard to abnormal thyroid function tests, their frequency was distributed equally between normozoospermic and pathozoospermic patients (11.1 *vs.* 11.8%). Furthermore, there was no correlation between elevated or decreased TSH, FT<sub>4</sub>, and FT<sub>3</sub> values with semen analysis results. The only difference observed in that study concerned thyroid autoimmunity features. Thyroid antibodies were positive in 23 patients (7.5%). When correlated with semen analysis, the prevalence of positive thyroid peroxidase (TPO)-Abs was significantly higher in patients with pathozoospermia (6.7 *vs.* 1.6%;  $P = 0.04$ ) and asthenozoospermia (7.2 *vs.* 1.6%;  $P = 0.5$ ), compared with normozoospermia. The inference of this study is that the presence of thyroid antibodies correlated significantly with patho- and asthenozoospermia. However, it remains unclear whether thyroid antibodies influenced semen parameters directly or were present simultaneously with other potentially detrimental autoantibodies, such as sperm antibodies. The latter hypothesis was supported by the observations of Paschke *et al.* (99), who noted that TPO-Abs were only present in men with serum sperm antibodies.

One of us (K.P.) investigated 299 men, subdivided according to the presence of normal ( $n = 39$ ) or abnormal ( $n = 253$ ) semen characteristics (100). Thyroid function was assessed by measuring serum TSH, FT<sub>4</sub>, and TPO-Abs. The results showed that the prevalence of thyroid dysfunction and autoimmunity features was not different when comparing men with normal or abnormal semen characteristics. On the basis of the above data, systematic screening for thyroid disorders in infertile men consulting a tertiary referral center is not recommended.

## 2C. Summary

Hyper- and hypothyroidism are the main diseases that may adversely affect male reproductive function. Changes in SHBG and sex steroids are a consistent feature of these disorders, and most studies concur to indicate that male hyperthyroid patients have abnormalities in seminal pa-

rameters (mainly sperm motility), whereas male hypothyroid patients have abnormalities in sperm morphology. These abnormalities improve or normalize when euthyroidism is restored. Finally, many patients with ED display thyroid dysfunction, and the normalization of thyroid function with treatment restores normal erectile function.

## B. In females

### 1. The effects of thyrotoxicosis and hypothyroidism on the female reproductive system: Animal studies

In laboratory animals, T<sub>3</sub> levels have been shown to affect estrous cycle regulation, behavior, pregnancy maintenance, fetal growth, and lactation. Mating behavior in ovariectomized rodents stimulated by E<sub>2</sub> administration is inhibited by T<sub>3</sub> administration, suggesting that estrogen-mediated reproductive behavior is negatively influenced by T<sub>3</sub> (101). The thyroid gland is also necessary for the transition to the anestrus state in seasonally breeding animals. For instance, in ewes, the presence of normal serum T<sub>3</sub> concentrations is required at the end of the breeding season to initiate anestrus, although T<sub>3</sub> does not intervene to maintain anestrus and timing of the subsequent breeding season (101). Pregnancy alters thyroid status in rodents. In the rat, pregnancy results in decreased total T<sub>4</sub> and T<sub>3</sub> concentrations and enlarged thyroid gland volume. However, unlike the case of humans, iodine uptake is decreased in pregnant rats, and urinary iodide excretion remains unaltered the last days of gestation (102–104).

There are few data on the effects of excess TH on fetal development of the female reproductive tract. Small TH doses given to young female mice resulted in early sexual maturity attainment, with early vaginal opening and onset of estrous cycles (105). The ovaries of mice receiving excess TH revealed multiple corpora lutea and follicles. In contrast, the administration of large T<sub>4</sub> doses to neonatal rat resulted in delaying vaginal opening and first estrus (106). Due to the short period of TH administration (5 d only), which was followed by a period of hypothyroidism, it is uncertain whether it was the excess T<sub>4</sub> or subsequent hypothyroidism that caused delay in sexual maturation in these experimental conditions. In adult female rats, administration of high T<sub>4</sub> doses resulted in long periods of diestrus with few mature follicles or corpora lutea (107). Moreover, the administration of excess TH was shown to produce an increase (or no change) in pituitary LH with a decrease in serum LH (108). Finally, a synergistic effect of TH with FSH to stimulate differentiation of porcine granulosa cells was also reported (109).

TH receptors are present in rat uterus. Therefore, one would expect to observe changes in the uterus after the administration of TH. Indeed, excess TH given to mice

induces a thickened endometrium,  $T_4$  administration decreased the uptake and retention of  $E_2$  by rat uterus, and a reduced uterine response to estrogen was reported in thyrotoxic rats (110–112).

In the rat, fetal hypothyroidism results in small ovaries that are deficient in lipid and cholesterol (113). PTU-induced hypothyroidism (and thyroidectomy) in sexually immature rats resulted in delayed vaginal opening and sexual maturation with smaller ovaries and follicles, as well as poorly developed uterus and vagina (114). Adult female rats, made hypothyroid, had irregular estrous cycles and ovarian atrophy (115, 116). Also, an enhanced response to hCG with development of large cystic ovaries — but few corpus lutea — was also described in hypothyroid rats (117). In mature female rats, hypothyroidism did not result in sterility but interfered with gestation, especially in its first half, with resorption of the embryo and subsequent reduction in litter size and increase in stillbirths (118, 119). Ruh *et al.* (111) reported increased  $E_2$  binding to the uteri of hypothyroid rats, a finding that was not confirmed by others (120).

Female hypothyroid mice are infertile, although the reason for infertility has not yet been fully elucidated. Jiang *et al.* (121) observed that infertility occurred in mature, rather than immature, hypothyroid mice and was probably due to impaired follicular development that was reversible by  $T_4$  administration before mating. In sheep, fetal hypothyroidism did not interfere with reproductive tract development. The uterus in hypothyroid sheep showed endometrial hyperplasia and smooth muscle hypertrophy, perhaps related to the estrous prolongation noted in hypothyroid ewes (122).

## **2. The effects of thyrotoxicosis and hypothyroidism on female reproductive system: Human studies**

In the United States, a large survey performed in the 1970s estimated the prevalence of Graves' disease (GD) to be 0.4% (123). A similar prevalence (0.6%) was found in the Pescopagano study in Italy (124). The Whickham survey in the United Kingdom suggested a prevalence of 1.1 to 1.6% (*i.e.*, about 3- to 4-fold higher) for thyrotoxicosis of all causes, of which GD was presumably the most frequent (125). A meta-analysis of various studies has estimated the general prevalence of the disorder to be about 1% (126), which makes it one of the most frequent clinically relevant autoimmune disorders.

Regarding primary hypothyroidism, the most extensive epidemiological data have been obtained from a population-based study of subjects 18 yr and older in Whickham County in northeast United Kingdom (125, 127). The data seem representative of other countries inasmuch as similar figures have been reported from Sweden, Japan, and the United States (128). The most striking features were the

high prevalence of hypothyroidism [especially subclinical hypothyroidism (SCH)], the marked female preponderance, and the increasing occurrence with advancing age. Most cases are due to chronic autoimmune thyroiditis (incidence of 3.5 per 1000 women per year), followed by destructive treatment for thyrotoxicosis (incidence of 0.6 per 1000 women per year). The probability of spontaneous hypothyroidism developing in women at a particular time increases with age from 1.4 to 14 per 1000 per year at ages 20 to 25 and 75 to 80 yr.

Specific risk factors for progression from SCH to overt hypothyroidism (OH) are the presence of thyroid antibodies and an already elevated TSH.

### **2A. Thyrotoxicosis in females**

*a. Hormonal changes.* Thyrotoxicosis results in increased serum levels of SHBG. Also, estrogen levels may be 2- to 3-fold higher in hyperthyroid women (compared with normal women) during all phases of the menstrual cycle (129). Whether increased estrogen levels are entirely attributed to SHBG changes or whether there is an actual increase in free estrogen levels (as is the case in hyperthyroid males) remains to be determined. In favor of the first hypothesis, the metabolic clearance rate of  $E_2$  is decreased in hyperthyroidism and is thought to be largely due to increased binding of  $E_2$  to SHBG (130).

Changes also occur in androgen metabolism in hyperthyroid women. Mean plasma levels of testosterone and androstenedione increase, and the production rates of testosterone and androstenedione are significantly elevated in hyperthyroid women. The conversion ratio of androstenedione to estrone, as well as of testosterone to  $E_2$ , is increased in hyperthyroid women (16, 131, 132).

Akande and Hockaday (133) found that the mean LH levels in both the follicular and luteal phases of the menstrual cycle are significantly higher in hyperthyroid women than in normal women. Pontikides *et al.* (134) found similar results when they studied women in the middle of the luteal phase of the cycle. Zähringer *et al.* (42) studied seven women with GD and six controls, sampling blood every 10 min for an 8-h period in the early follicular phase of the menstrual cycle. The authors found that LH secretion was increased, whereas the pulsatile characteristics of LH and FSH secretion did not differ in patients when compared with controls. However, LH peaks may be absent in patients with amenorrhea. Serum LH levels decrease to normal after a few weeks of treatment with antithyroid drugs (ATD) (135). Baseline FSH levels may be increased, although data on this are limited (134, 136). However, some reports claim that FSH levels remain normal in thyrotoxic women (42, 137). The mechanism for the increase in serum LH and FSH in hyperthyroid women is unclear. Tanaka *et al.* (136) reported that hyperthyroxine-

mia results in an augmented Gn response to GnRH. Others, however, have been unable to confirm these findings (137).

Pontikides *et al.* (134) investigated 37 thyrotoxic women, all of reproductive age with normal periods, and the same number of age- and weight-matched euthyroid controls. In all patients and controls, LH, FSH, and PRL levels were measured before and 30 and 60 min after a combined administration of TRH and GnRH. In all patients, the same procedure was repeated 4 months after the initiation of ATD, when the patients were euthyroid. The authors found that the Gn response was increased before treatment and remained slightly increased 4 months after treatment in comparison with controls. Moreover, there was no significant change in PRL secretion (42, 134). Usually, all of these biochemical abnormalities are corrected after treatment. Table 1 summarizes the hormonal changes seen in female thyrotoxicosis.

**b. Menstrual disturbances.** Children born with neonatal GD have no defects in the reproductive system that could be related to the pathological entity. Hyperthyroidism occurring before puberty was reported to delay sexual maturation and onset of menses. However, other reports showed no significant effect of hyperthyroidism on the age of menarche, although in hyperthyroid girls the mean age of menarche was reported to be slightly in advance over that of their healthy controls (138).

Much confusion exists among physicians about the definition of different terms used to characterize menstrual abnormalities. It should be remembered that oligomenorrhea, polymenorrhea, and amenorrhea define the duration of the menstrual cycle, whereas hypomenorrhea, hypermenorrhea, and menorrhagia define the amount of menstrual flow. Thus, oligomenorrhea was identified when the interval between two periods was more than 35 d, polymenorrhea less than 21 d, and amenorrhea in women with previously normal periods when there was no menstruation for more than 3 months (139, 140). Hypomenorrhea was arbitrarily defined as more than 20% decrease in menstrual flow, hypermenorrhea as more than 20% increase in menstrual flow in comparison with the previous periods, and menorrhagia as heavy menstrual bleeding (8).

Amenorrhea is one of the earliest known clinical changes associated with hyperthyroidism and was already reported by von Basedow in 1840 (141). Since then, amenorrhea has been frequently reported, as well as a number of other menstrual cycle changes, including oligomenorrhea, hypomenorrhea, and anovulation. Biochemical and hormonal abnormalities, nutritional disturbances, and emotional upheavals that are commonly associated with hyperthyroidism may, individually or in combination, be the cause of the menstrual disturbances (16).

The frequency of menstrual abnormalities was not the same in more recent studies, compared with earlier series. Thus, in a study of 221 hyperthyroid patients, Benson and Dailey (142) found that 58% of the patients had oligomenorrhea or amenorrhea, and 5% had polymenorrhea. This is in general agreement with findings in older studies, such as those of Goldsmith *et al.* (143). Tanaka *et al.* (136) found that eight of 41 thyrotoxic patients had amenorrhea, and 15 had hypomenorrhea. More recently, Joshi *et al.* (144) in India found menstrual irregularities in 65% of hyperthyroid women, compared with 17% among healthy controls. These irregularities sometimes preceded the identification of thyroid dysfunction. Krassas *et al.* (7) found irregular cycles in only 46 of 214 (21.5%) thyrotoxic patients. Twenty-four of the patients had hypomenorrhea, 15 had polymenorrhea, five had oligomenorrhea, and two had hypermenorrhea; none had amenorrhea. In a similar number of normal controls, 18 (8.4%) had irregular periods, and of these 12 had oligomenorrhea. Although these findings indicate that menstrual disturbances are 2.5-fold more frequent in thyrotoxicosis than in the normal population, they are still lower than what had been described previously, and they support our current notion that, due to better medical care and public awareness, thyroid disturbances are diagnosed much earlier when the symptoms are still mild (Table 3).

The same authors found that smoking aggravates the development of menstrual disturbances in thyrotoxicosis. Fifty percent of the thyrotoxic patients with abnormal menstruation were smokers, compared with only 19% of the thyrotoxic patients with normal periods. Besides, patients with menstrual disturbances had higher total T<sub>4</sub> levels, and hormonal excess was higher in the smokers with abnormal periods. Thus, total T<sub>4</sub> levels appear to be an important factor related to the development of menstrual

**TABLE 3.** Menstrual disturbances associated with thyrotoxicosis and hypothyroidism

	Prevalence (%)	Ref.
Thyrotoxicosis		
Early studies		
Oligomenorrhea	58	142
Menstrual irregularities	65	144
Recent study		
Abnormal menses	22	7
Control subjects	8	
Hypothyroidism		
Early studies		
Menstrual disturbances	80	143
Menstrual irregularities	56	167
Menstrual irregularities	68	144
Recent study		
Irregular cycles	23	165
Control subjects	8	

abnormalities in thyrotoxicosis, in contrast with total  $T_3$ , for which no such correlation was found (7).

**c. Fertility in subclinical and overt hyperthyroidism.** Infertility is the inability to conceive after 1 yr of regular intercourse without contraception (145, 146). This definition was based on the study of 5574 women engaging in unprotected intercourse who ultimately conceived (1946–1956). Among these women, 50% conceived within 3 months, 72% within 6 months, and 85% within 12 months (147). Two more recent prospective, population-based studies have shown that 50% of healthy women became clinically pregnant during the first two cycles and 80–90% during the first 6 months (148, 149). The prevalence of infertility was estimated to range between 10 and 15% and remained stable over recent decades (147). Thirty-five percent of couples' inability to conceive is related to female causes, 30% to a male factor, 20% to both types of causes, and the remaining 15% is considered idiopathic, when the spermogram and female work-up are both normal (150, 151). Female causes of infertility comprise endometriosis, tubal occlusion, and ovulatory dysfunction (OD). Endometriosis, defined as the presence of uterine tissue outside its cavity, is deemed a cause of infertility when the disease exceeds stage 1, as defined by the American Society for Reproductive Medicine (152). Infertility associated with OD relates to a heterogeneous group of disorders, classified according to World Health Organization (WHO) criteria (WHO I, hypogonadotropic; WHO II, normogonadotropic; and WHO III, hypergonadotropic) (153).

Thyrotoxicosis in women has been linked with reduced fertility, although most thyrotoxic women remain ovulatory according to results of endometrial biopsies (143). Few studies have been conducted on this issue. Joshi *et al.* (144) found that three of 53 (5.8%) thyrotoxic women had primary or secondary infertility. Pontikides *et al.* (154) measured progesterone levels, a fertility parameter, in the middle of the luteal phase of the menstrual cycle in 74 women of reproductive age, 37 of whom had GD and 37 healthy controls matched for age and weight. All patients and control subjects had normal periods. When the authors measured progesterone levels at the same cycle phase after the patients had become euthyroid with ATD therapy, they observed that progesterone levels (decreased before treatment in comparison with controls) were not restored after 4 months of carbimazole (CMI) therapy. Final conclusions, however, could not be reached because endometrial biopsies were not performed.

The prevalence of hyperthyroidism in infertile women was studied prospectively by one of us (K.P.) (155). The prevalence of a suppressed serum TSH [both subclinical

hyperthyroidism (SCHT) and overt hyperthyroidism] was 2.1% (nine of 438 women of infertile couples), comparable to that in the fertile female control population (3% or three of 100). SCHT was present in seven of nine patients, and two had overt hyperthyroidism. Four of these nine patients with a suppressed serum TSH had positive TPO-Abs (the thyroid stimulating Ig were not measured in this study). When TPO-Abs were positive, a suppressed serum TSH was more frequent in all infertile women compared with that in women in the same groups without positive TPO-Ab (7 *vs.* 1%;  $P < 0.05$ ).

**d.  $R\text{-I}^{131}$  therapy for hyperthyroidism and reproduction.**  $R\text{-I}^{131}$  is widely used for treatment of hyperthyroidism and differentiated thyroid cancer. In hyperthyroidism, the average dose of  $R\text{-I}^{131}$  given is approximately 10 mCi (370 MBq), whereas for cancer the doses given are 10–20 times higher, exposing the gonads to a higher radiation dosage. In thyrotoxic women treated with 10 mCi of  $R\text{-I}^{131}$ , the genetic risk is negligible, and reproductive health of treated women as well as general health of progeny appear normal (53, 156). Therefore, the use of  $R\text{-I}^{131}$  for treatment of hyperthyroidism bears no significant detrimental effect on gonads, and it is customarily advised for prophylactic reasons to avoid conception until at least 6 months after the administration of  $R\text{-I}^{131}$  (8).

## **2B. Hypothyroidism in females**

**a. Hormonal changes.** Table 1 summarizes the main hormonal changes associated with female hypothyroidism. Hypothyroid women have decreased rates of metabolic clearance of androstenedione and estrone and exhibit an increase in peripheral aromatization (157, 158). The  $5\alpha/\beta$  ratio of androgen metabolites is also decreased in hypothyroid women, and there is an increase in excretion of 2-oxygenated estrogens (159). Plasma binding activity of SHBG is decreased, which results in decreased plasma concentrations of both total testosterone and  $E_2$ , but their unbound fractions are increased. Alterations in steroid metabolism disappear when a euthyroid state is restored (160). Gn levels are usually normal (161). However, blunted or delayed LH response to GnRH has been reported in some hypothyroid women (162, 163). When there is a delayed LH response, serum PRL concentration may be increased, and this may be due to hypothalamic TRH increasing both TSH and PRL secretion. Galactorrhea may also occur, but these disturbances disappear usually after  $T_4$  administration (164).

**b. Menstrual disturbances.** In women of fertile age, hypothyroidism results in changes in cycle length and amount of bleeding (*i.e.*, oligomenorrhea and amenorrhea, polymenorrhea, and menorrhagia). The latter is probably due to

estrogen breakthrough bleeding secondary to anovulation (165). Defects in hemostasis factors (such as decreased levels of factors VII, VIII, IX, and XI) that occur in hypothyroidism may also contribute to polymenorrhea and menorrhagia (166).

Goldsmith *et al.* (143) found that eight of 10 patients with primary myxedema had menstrual disturbances. More specifically, one patient had amenorrhea, five had clinical metrorrhagia (hemorrhage during the menstrual cycle), and two had menorrhagia. Benson and Dailey (142) investigated the menstrual pattern in 31 women who developed hypothyroidism after treatment for hyperthyroidism; menorrhagia, polymenorrhea, or both were noted in 59% of these women. Similarly, Scott and Mussey (167) observed that 56% of hypothyroid women presented menstrual irregularities, mainly metrorrhagia or menorrhagia alone or combined. Joshi *et al.* found that 68% of hypothyroid women had menstrual irregularities, compared with only 12% in controls (144). Of those, eight had oligomenorrhea, two amenorrhea, and five polymenorrhea and menorrhagia. One of us (G.E.K.) reported that among 171 hypothyroid women, 23% presented irregular cycles (compared with only 8% in controls); of those, 17 had oligomenorrhea, six hypomenorrhea, five amenorrhea, and 12 hypermenorrhea/menorrhagia (165).

Taken together, these findings indicate that the frequency of menstrual disturbances in hypothyroidism is approximately three times greater than in the normal population. The main menstrual irregularity observed in hypothyroid women was oligomenorrhea, at variance with the common belief that amenorrhea was the most frequent symptom. Although there was a tendency for women with more severe hypothyroidism to have more severe menstrual disturbances, the differences were not statistically significant. Finally, it is of interest to note that the presence of thyroid antibodies was not an important factor for development of menstrual abnormalities in hypothyroidism. The lower frequency of menstrual abnormalities reported in more recent studies, compared with the older ones, may be attributed to delayed diagnosis of hypothyroidism in the earlier studies, which would have resulted in a more severe clinical picture. Menstrual disturbances associated with thyrotoxicosis and hypothyroidism are presented in Table 3.

*c. Fertility in SCH and OH.* The association between SCH and infertility was evaluated in several studies, although most of these were retrospective and uncontrolled. In 1981, Bohnet *et al.* (168) performed TRH tests in 185 infertile women with an age range between 25 and 34 yr. Infertile women with an exaggerated TSH response to TRH (>20 mIU/liter) were considered to have SCH.

Twenty women (11%) were diagnosed with SCH, which was considered by the authors to represent an infertility factor. When treated with 50  $\mu\text{g/d}$   $T_4$ , 11 of 20 women normalized their midprogesterone secretion, and two infertile women became pregnant. In another small study, Bals-Pratsch *et al.* (169) investigated four women with SCH. The authors concluded that corpus luteum insufficiency in female infertility could not be explained by SCH and that such women should not be treated with  $T_4$  for fertility reasons. The study was criticized for its inappropriate design and the small number of patients investigated.

Gerhard *et al.* (170) showed a positive correlation between basal TSH, LH, and testosterone concentrations in the early follicular phase. Those women with an elevated TRH-stimulated TSH response had lower pregnancy rates than the women with normal TSH response. Of 185 infertile women, only one had an elevated serum TSH value, corresponding to SCH (170). Shalev *et al.* (171) examined retrospectively the prevalence of SCH in 444 infertile women in whom thyroid function was evaluated: only three of 444 women (0.2%) had increased TSH levels, and all three presented OD.

Grassi *et al.* (172) investigated 129 women from infertile couples with OD, male and idiopathic infertility: six women (4.6%) had serum TSH levels above 4.5 mIU/liter, and five of these had AITD. Mean duration of infertility was significantly longer in patients with thyroid abnormalities compared with controls (3.8 *vs.* 2.6 yr;  $P = 0.005$ ). Note that in this study, women patients with tubal or pelvic factors, including endometriosis (13.4% of the original cohort), were excluded, and this may explain the higher prevalence of SCH compared with other studies. Another uncontrolled retrospective study, carried out by Arojoki *et al.* (173), revealed an elevated serum TSH level in 12 of 299 women (4%) with infertility. In three of 12 cases, hypothyroidism had been diagnosed previously, but they were using an inadequate  $T_4$  dosage. The prevalence of increased serum TSH values was highest in the group with OD and lowest in the group with tubal damage (6.3 *vs.* 2.6%; difference not statistically significant).

One of us (K.P.) undertook a controlled prospective study in 438 women with various causes of infertility, with the aim to assess the prevalence of AITD and undisclosed alterations of thyroid function (155). Overall, median TSH was significantly higher in patients with female infertility, compared with the controls. Supranormal serum TSH values were not more prevalent in infertile women than controls. Only one patient in the OD group and one in the idiopathic infertility group had SCH, yielding an overall prevalence of 0.5%. Both patients had positive thyroid antibodies. There were also two patients with OH

and positive TPO-Ab. In 100 control women, the prevalence of SCH was 1%, *i.e.*, comparable to the data reported by Arojoki *et al.* (173).

The impact of SCH treatment has only been evaluated in one prospective study in women with infertility. Raber *et al.* (174) investigated prospectively a group of 283 women referred for infertility. All patients underwent a TRH test, and SCH was defined as a serum TSH response above 15 mIU/liter. Women with a diagnosis of SCH were treated with T<sub>4</sub> and followed over a 5-yr period. Of the referred women, 34% had SCH, an unusually high prevalence reflecting a bias due to the specific referral pattern. Among the women who became pregnant during the follow-up period, over 25% still had SCH at conception. Furthermore, these women who never achieved a basal serum TSH less than 2.5 mIU/liter or a TRH-stimulated TSH less than 20 mIU/liter became pregnant less frequently than those who did. Finally, more frequent miscarriages were observed in these women with a higher basal serum TSH, irrespective of the presence of AITD.

Abalovich *et al.* (175) investigated retrospectively 244 women consulting for infertility and 155 healthy women with confirmed fertility. TSH and TPO-Ab were measured in all patients, and a TRH test was performed in 71 patients to diagnose SCH. SCH was diagnosed in 14% of infertile women and 4% of controls ( $P < 0.002$ ). Patients with precocious ovarian failure, tubal disturbances, and OD presented significantly higher SCH rates than controls (40, 18, and 15%, respectively). There was no significant difference in the prevalence of AITD between infertile women and controls. Under LT<sub>4</sub> treatment, women with SCH achieved a pregnancy success rate of 44%. A synopsis of all studies published so far concerning the association between SCH and infertility is given in Table 4. As shown in Table 4, the design of the studies differed as well as definitions used for SCH, and therefore, direct comparison is hampered between these different results (176).

Studies that examined the incidence of infertility in hypothyroid patients are scarce. Ideally, this question should be evaluated prospectively by determining the incidence of infertility in hypothyroid patients compared with a matched control group. However, such data are not available, and most studies deal with the prevalence of infertility in a cross-sectional design of hypothyroid patients or the evaluation of the prevalence of hypothyroidism in selected (and therefore biased) populations presenting at specialized infertility clinics (91, 177).

Goldsmith *et al.* (143) reported that seven of 10 patients with myxedema had no evidence of ovulation, and one demonstrated inadequate corpus luteum. All seven patients had menstrual irregularities, and anovulation was reflected in the frequent finding of a proliferative endometrium on biopsy. Joshi *et al.* (144) detected primary and secondary infertility in one (*i.e.*, 6.2%) of 16 overtly hypothyroid women, a frequency comparable to that found in normal control women. Note that the number of patients was small, thyroid antibody status was unknown, and the control population was not clearly defined (144).

Lincoln *et al.* (178) determined serum TSH levels in 704 infertile women without previous thyroid disorders. Among those, 2.3% had increased serum TSH (with both OH and SCH). The frequency was comparable to that found in the general female population of reproductive age (although no control population was included in the study). The authors concluded that women with OD should be screened for hypothyroidism (178). In 2000, Arojoki *et al.* (173) investigated retrospectively the prevalence of hypothyroidism in 299 women with different causes of infertility. Overall, 4% of them had an increased serum TSH, and 3.3% had OH. The highest percentage with increased TSH was found in the group with OD (6.3%) compared with 4.8% in the idiopathic group, 2.6% in the tubal infertility group, and none in the endometriosis group. No statistical differences were obtained

**TABLE 4.** Prevalence of SCH in infertile women

First author (Ref.)	Prevalence of SCH in patients	Prevalence of SCH in controls	SCH was defined as	Type of study
Bohnet (168)	11% (20/185)	No controls	Basal TSH >3 mIU/liter or peak TSH <sup>c</sup> >15 mIU/liter	P
Gerhard (170)	43% (80/185) <sup>a</sup>	No controls	Peak TSH <sup>c</sup> >20 mIU/liter	P
Shalev (171)	0.7% (3/444)	No controls	Basal TSH >4.5 mIU/liter	R
Grassi (172)	4.6% (6/129)	No controls	Basal TSH >4.5 mIU/liter	P
Arojoki (173)	1.3% (4/299)	2–3% <sup>b</sup>	Basal TSH >5.5 mIU/liter	R
Poppe (155)	0.9% (4/438)	<1%	Basal TSH >4.2 mIU/liter	P
Raber (174)	34% (96/283)	No controls	Basal TSH >4 mIU/liter or peak TSH <sup>c</sup> >15 mIU/liter	P
Abalovich (175)	13.9% (34/244)	3.9% (6/155)	Basal TSH >4.22 mIU/liter, stimulating TSH >26.6 mIU/liter	R

P, Prospective; R, retrospective. [Reproduced from K. Poppe *et al.*, The role of thyroid autoimmunity in fertility and pregnancy. *Nat Clin Pract Endocrinol Metab* 4:394–405, 2008 (176), with permission. © 2008, Macmillan Publishers Ltd.]

<sup>a</sup> One in 185 patients had a basal serum TSH >6 mIU/liter (0.5%).

<sup>b</sup> Prevalence in the Finnish population.

<sup>c</sup> Peak serum TSH after TRH-stimulation test.

when comparing the frequency of hypothyroidism between different groups of women with infertility (173). Because of the low incidence of OH, it is generally accepted that screening for hypothyroidism is not warranted (179). However, it is difficult to draw a clear interpretation from available data. Patients with overt thyroid failure are probably detected before referral to infertility clinics, thereby introducing a bias in the estimated prevalence of infertility disorders. Given the potential implication of hypothyroidism on OD, screening is certainly justified in the presence of OD (145, 177).

Altered peripheral estrogen metabolism, hyperprolactinemia, defects in hemostasis, and disturbances in GnRH secretion that result in an abnormal pulsatile release of LH are some of the main causes to explain the high frequency of infertility in hypothyroid women (180). Moreover, both Gn and  $T_4$  appear necessary to achieve maximum fertilization rates and blastocyst development. Cramer *et al.* (181) showed recently that serum TSH levels are a significant predictor of fertilization failure in women undergoing IVF. These data support the importance of the role of thyroid hormones (THs) in oocyte physiology. Treatment with  $LT_4$  is straightforward and has been shown to normalize PRL levels as well as normal LH responses to LHRH, reduce menstrual disturbances to prevalences comparable to euthyroid women, and finally increase the chances of spontaneous fertility (8, 157, 181).

**d. Thyroid autoimmunity and female infertility.** AITD, with a prevalence varying between 5 and 15%, represent the most common endocrine disorders in women of reproductive age. Not only is AITD 5- to 10-fold more common in women than men but, in addition, AITD is often undiagnosed because it may be present without overt thyroid dysfunction for several years (145, 182). Relationships between autoimmune abnormalities and reproductive failure have been investigated extensively, and numerous studies have focused on the association of AITD with female infertility. Nevertheless, interpretation of available data is difficult for a variety of reasons, among which are heterogeneity of women samples studied, uncontrolled and retrospective design of many studies, differences due to small sample sizes, differences due to the assays used to detect AITD, and finally, differences arising from ethnic origins as well as geographical locations, including the role of highly variable iodine nutrition levels in the populations investigated (182).

Taken together, however, most studies showed an increased prevalence of AITD among women attending infertility clinics (183, 184). Some outstanding features of these studies are summarized below. In 1975, Wilson *et al.* (185) investigated 77 infertile women and 77 postpartum controls

for the presence of thyroid autoantibodies (Th-Abs) and found no significant difference for organ-specific antibodies between the two groups. In 1996, Roussev *et al.* (186) published the first controlled study aiming at determining the frequency of abnormal immunological tests in women with reproductive failure. The authors investigated 108 patients (among them, 45 women with unexplained infertility) using a variety of immunological assessments, which included thyroglobulin (TG) and microsomal antibodies. In women with reproductive failure, at least one test was positive for AITD in 70 of 108 women, yielding an overall prevalence of 65% (*vs.* 7% only in the controls;  $P = 0.0001$ ). Geva *et al.* (187) reported a significant 4-fold increase in the incidence of AITD in women with unexplained and mechanical infertility. In 1999, Kutteh *et al.* (188) investigated the prevalence of TG-Ab/TPO-Ab in women undergoing ART. AITD was diagnosed in 19% of women undergoing ART, compared with 15% in control women. Close scrutiny of the data indicated, however, that the control subjects were not adequately recruited in the study, because most of the positive thyroid antibody tests were found in women under 30 yr of age, whereas women over 30 yr of age had AITD significantly less frequently than the ART group. The same year, Kaider *et al.* (189) investigated 122 patients undergoing IVF, 97 of whom had unexplained infertility. Among the infertility group, 81% had at least one abnormal immunological test (including TPO-Ab/TG-Ab), compared with only 10% in fertile controls, a highly significant statistical difference. Reimand *et al.* (190) investigated 108 females with different pathologies leading to sterility, including unexplained infertility, and 392 normal fertile controls. Common antibodies were assessed by indirect immunofluorescence techniques, including TPO-Ab and TG-Ab. Results showed that 41% of patients presented one or more common antibodies, compared with 15% of controls.

In 2002, Poppe *et al.* (155) investigated 438 couples presenting for the first time to the infertility clinic and 100 fertile control couples matched for age. In couples where infertility was due to female causes, there was an increased risk of associated AITD found in the female partner [relative risk, 2.25; confidence interval (CI), 1.02–5.12;  $P = 0.045$ ]. The risk was further increased when the identified cause of infertility was endometriosis (relative risk, 3.57; CI, 1.09–11.8;  $P = 0.036$ ). Overall, however, the prevalence of thyroid dysfunction in the study group was not higher than in the control population, whereas median serum TSH level was slightly, but significantly, higher in patients with infertility, compared with controls (1.30 *vs.* 1.10 mIU/liter;  $P < 0.006$ ).

In 2004, Janssen *et al.* (191) investigated the prevalence of AITD in patients with polycystic ovary syndrome (PCOS). The authors evaluated thyroid function and mor-

phology in 175 PCOS patients and 168 age-matched healthy control women. Thyroid function and thyroid-specific antibody tests revealed elevated TPO-Ab and TG-Ab in 47 of 175 patients with PCOS, compared with only 14 of 168 controls (27 *vs.* 8%;  $P < 0.001$ ). On thyroid ultrasound, 42% of PCOS patients had hypoechoic areas characteristic of AITD, compared with 6.5% in controls ( $P < 0.001$ ). Although TH levels were normal in all healthy subjects, patients with PCOS had a higher mean serum TSH ( $P < 0.001$ ) and higher frequency of abnormally elevated serum TSH levels (11% in PCOS *vs.* 2% in controls;  $P < 0.001$ ). The conclusion of the study was that the prevalence of AITD in patients with PCOS was 3-fold greater in patients with PCOS than controls. Finally, Abalovich *et al.* (175) investigated 244 infertile women and compared them with 155 healthy fertile controls and found no significant difference in AITD between both groups. Finally, in a recent Brazilian study aimed specifically at evaluating the association between AITD and endometriosis, no such association was found (192). It should, however, be mentioned that in this study, the prevalence of AITD in the controls was much higher (26.5%) compared with that in most other studies.

With a few remaining exceptions (some easily explained, whereas others were not), when pooling together all the studies reported on this topic, the overall conclusion favors a significantly increased incidence of AITD in women with infertility. The underlying pathogenic mechanisms remain largely speculative because the information gathered from animal models, as well as from *in vitro* data, is scarce. Although AITD represents an organ-specific autoimmune disorder, associations with other non-organ-specific autoimmune disease states have also been described and suggest a shared immunogenetic background. In this context, the increased prevalence of AITD in women with endometriosis reported by one of us (K.P.) is noteworthy because there is abundant evidence that endometriosis is associated with a variety of immunological changes (155, 193). It has also become clear that adequate levels of circulating TH are of primary importance for normal reproductive function.  $T_3$  modulates FSH and LH action on steroid biosynthesis, and multiple  $T_3$  binding sites have been identified in mammalian granulosa and stromal cells, and more recently in human oocytes (194–196). Any impairment of  $T_3$  concentrations available locally (as could be the case in women with AITD) may therefore represent a cause of disruption of the normal female reproductive function.

In our present state of knowledge, an important question arises. Is screening warranted and cost-effective? Cost-effectiveness of screening compares favorably with other generally accepted preventive practices. The arguments for screening populations over 35 yr of age are

based on three potential benefits: risk of progression to OH in women with SCH, morbidity-associated hypercholesterolemia frequently seen in such patients, and reversal of potentially unrecognized symptoms associated with mild TH deficiency (197). In a population of infertile women, the prevalence of overt and subclinical thyroid dysfunction is comparable to that of the control female population with normal fertility, and the efficacy of medical intervention on fertility rates in the presence of thyroid abnormalities in such a highly selected population has not yet been evaluated prospectively. However, treating thyroid dysfunction on surrogate endpoints (such as menstrual cycle, LH pulsatility, hyperprolactinemia) has been clearly reported (8). Small intervention studies in SCH indicated a positive effect on spontaneous pregnancy rate, but the results remain an open question because there were no controls. Poppe *et al.* (198) have proposed to screen systematically infertile women for thyroid dysfunction and autoimmunity, especially when endometriosis or OD is the cause of infertility.

## 2C. Summary

Hyper- and hypothyroidism are the main thyroid diseases that may have an adverse effect on female reproduction. Changes in SHBG and sex steroids are a consistent feature of thyroid abnormalities in the above-mentioned diseases. Also, hyper- and hypothyroidism are causing menstrual disturbances, mainly hypomenorrhea and polymenorrhea in thyrotoxicosis and oligomenorrhea in hypothyroidism. In the more recent studies, fewer menstrual abnormalities were recorded, most probably because of an earlier diagnosis of the disease. Thyrotoxicosis in women has been linked with reduced fertility. The same applies for SCH and OH. Finally, regarding AITD and infertility, an increased prevalence of AITD has been found among women attending referral infertility clinics.

## III. Thyroid Function and Assisted Reproduction Technology (ART)

### A. Background information on ART

TH are in continuous interaction with other, mainly sexual hormones to preserve a normal menstrual pattern (199). An optimal thyroid function is therefore necessary to obtain normal fertility although, despite normal thyroid function, 10 to 15% of women remain childless after 1 yr of unprotected intercourse. After the work-up of the various known causes of infertility, a proposal for treatment is given to the couple with realistic prognosis regarding the final outcome. ART is generally proposed only after attempts such as ovulation induction, endoscopic alleviation of tubal obstruction or endometriosis, and intra-



uterine insemination have failed. Two types of ART can be used: IVF or intracytoplasmic sperm injection. After one cycle of ART, the live birth rate among women aged 30–35 yr ranges from 25 to 30% (147, 151, 200, 201).

Preparation for ART is the so-called controlled ovarian hyperstimulation (COH). This procedure combines treatment to down-regulate the pituitary-gonadal axis (GnRH agonists or antagonists) and ovarian stimulation recombinant FSH to obtain multiple cumulus-oocyte complexes. When three or more large follicles are visualized on echography, GnRH and FSH injections are discontinued and 10,000 U of hCG are given to induce ovulation. Depending on the protocol used,  $E_2$  levels become very high and comparable to those found in the second trimester of spontaneous pregnancy (1470–2203 pmol/liter or 4000–6000 ng/liter). The marked rise in  $E_2$  levels induces an additional strain on the hypothalamic-pituitary-thyroid axis and can, therefore, impair considerably TH distribution and kinetics.  $E_2$  increase depends on the type and duration of COH. Elevated  $E_2$  levels induce a marked increase in serum  $T_4$ -binding globulin (TBG) concentrations. Because the majority of serum  $T_4$  and  $T_3$  is transported bound to TBG, transthyretin, and albumin, and because TBG has by far the highest binding affinity for  $T_4$ , TBG binds approximately 75% of circulating  $T_4$ , whereas transthyretin binds approximately 20% and albumin the remaining approximately 5%. During pregnancy, serum TBG levels double, and this doubling rapidly increases the number of circulating  $T_4$  binding sites (202). In healthy pregnant women with a sufficient iodine intake, the required increase in TH production during pregnancy can be met easily and thus will not lead to development of hypothyroidism. In the study of Alexander *et al.* (203), the need for a rapid increase (already after 4–6 wk gestation) in  $T_4$  was identified in hypothyroid-treated women to maintain euthyroidism. The timing of such increased requirement was even more rapid and pronounced when conception had been achieved after ART procedures, probably because of the higher  $E_2$  levels reached in this clinical setting (203).

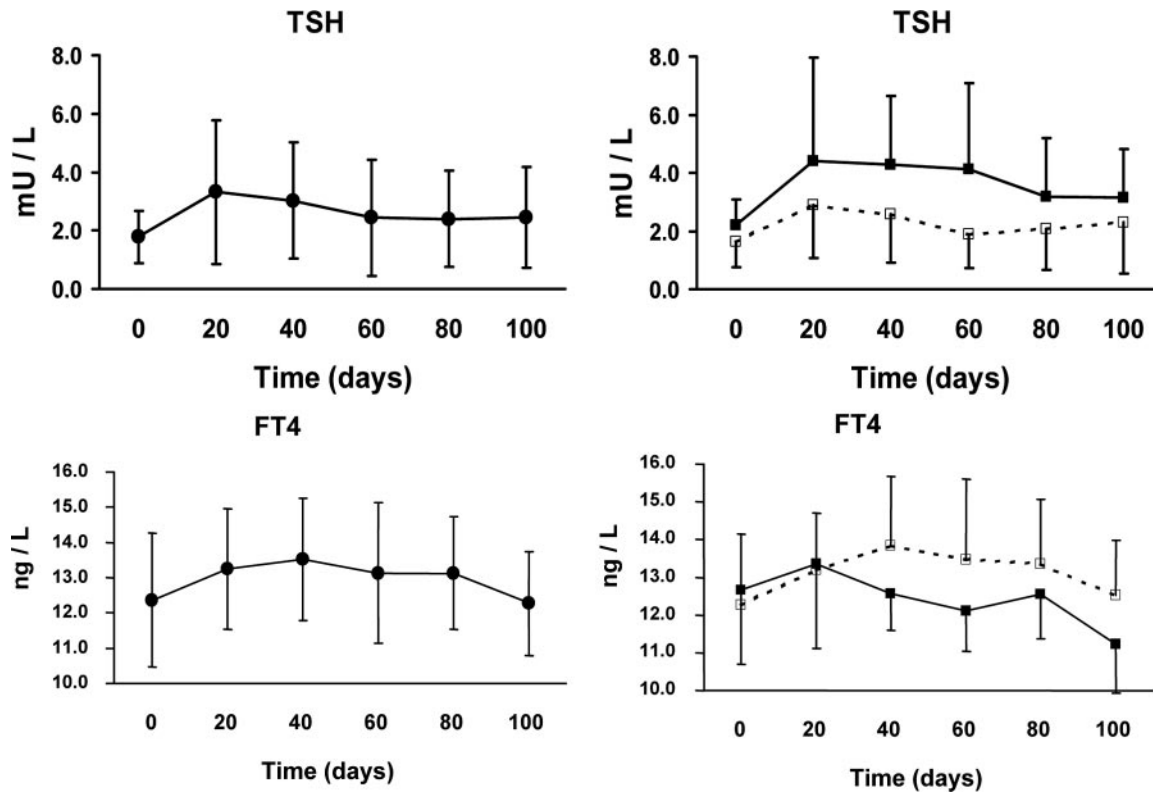
## B. Impact of ovarian hyperstimulation on thyroid function

### 1. In women with or without thyroid autoimmunity features

The optimal setting to investigate thyroid function in the very early gestational stages is accurately known in women who undergo COH in preparation for ART because the exact biochemical stage of the pregnancy is precisely determined. Muller *et al.* (204) were the first to perform a study to investigate thyroid function after COH. Compared with pre-COH values, their study showed that serum TSH increased significantly after COH

(3.0 *vs.* 2.3 mIU/liter;  $P < 0.0001$ ) and  $FT_4$  decreased (14.4 *vs.* 12.9 pmol/liter;  $P < 0.0001$ ). The authors confirmed that such changes in thyroid function were related to the rapid 10-fold  $E_2$  increase after COH (3492 *vs.* 359 pmol/liter;  $P < 0.0001$ ) which, in turn, led to an increase in serum TBG levels (34 *vs.* 25 mg/liter;  $P < 0.0001$ ). In this study, however, there was no long-term assessment of thyroid function after COH, nor did the authors mention the timing of TH measurements in relation to COH. Furthermore, it is not known whether some of these women may have had AITD, and the outcome of pregnancies was not reported. Following this pioneering study, one of us (K.P.) investigated the changes in thyroid function after COH until the end of first trimester in a study that allowed comparison of women with or without AITD (205). Thirty-five clinically proven pregnant women—including nine women with AITD (27%)—were evaluated prospectively after having benefited from the same COH procedure. Serum TSH,  $FT_4$ , and TPO-Abs were determined before COH and subsequently every 20 d after COH during the first trimester of pregnancy. The study confirmed a significant increase in both serum TSH and  $FT_4$  after COH, compared with baseline values (TSH, 3.3 *vs.* 1.8 mIU/liter;  $P < 0.0001$ ; and  $FT_4$ , 13.2 *vs.* 12.4 ng/liter;  $P = 0.005$ ). Among the AITD group, the area under the curve for serum TSH pattern of changes was significantly greater compared with women without AITD, and the opposite pattern was observed for serum  $FT_4$  ( $P = 0.02$ ) (Fig. 3). It should be noted that before COH, serum TSH levels were already slightly higher in those women with AITD, compared with controls (2.2 *vs.* 1.6 mIU/liter; difference was not significant).

The early pregnancy serum  $FT_4$  surge is partially mediated by increasing hCG levels after implantation and may therefore represent an example of control by the endocrine system. When thyroid function is impaired, steroid and cytokines actions may fail to sustain further early normal pregnancy. Due to the specific clinical settings in the two studies described above, it was not possible to determine whether thyroid autoimmunity status or low serum  $FT_4$  levels were the main determinants of pregnancy outcome after ART. In a subsequent study by Poppe *et al.*, 77 women, free of thyroid disorders, were investigated prospectively to assess changes in thyroid function before COH and during the first 6 wk after COH by comparing those women with ongoing pregnancy ( $n = 45$ ) or miscarriage ( $n = 32$ ) (206). Women considered to be without thyroid disorder were defined on the basis of not taking TH or ATD and without AITD. The pattern of changes in serum TSH and  $FT_4$  values after COH was as previously described. The areas under the curve for both serum TSH and  $FT_4$  values were similar, irrespective of pregnancy



**FIG. 3.** The graphs depict the patterns of time-related changes of serum TSH and FT<sub>4</sub> values (mean  $\pm$  SD), collected before COH (time 0) and 20, 40, 60, 80, and 100 d after successful ovulation induction. *Left panels*, There were significant changes among all patients over time for both serum TSH and FT<sub>4</sub> concentrations (TSH and FT<sub>4</sub>,  $P < 0.001$  and  $P = 0.005$ , respectively). *Right panels*, Patterns of serum TSH and FT<sub>4</sub> changes over time were different in TPO-Ab positive (■) and TPO-Ab negative (□) patients (TSH and FT<sub>4</sub>,  $P = 0.010$  and  $P = 0.020$ , respectively). [Adapted with permission from K. Poppe *et al.*, Impact of ovarian hyperstimulation on thyroid function in women with and without thyroid autoimmunity. *J Clin Endocrinol Metab* 89:3808–3812, 2004 (205), with permission. © 2005, The Endocrine Society.]

outcome. It is important to note that before and after ART, serum TSH levels remained below 2.5 mIU/liter in all women studied herein. The interest of this study was to provide an indirect indication (because all of these women were negative for AITD) that it was presumably the presence of AITD that led to TH changes after ART, thus potentially influencing pregnancy outcome. This conclusion is in line with the recent study by Männistö *et al.* (207) showing that first-trimester positive thyroid antibodies were a risk factor for perinatal death rather than the TH status *per se*. In another very recent study by Benhadi *et al.* (208), 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. AITD was found in 5.8% of all women, and none of them had a miscarriage. Child loss rate (after correction for other miscarriage risk factors) increased by 60% (odds ratio, 1.60; 95% CI, 1.04–2.47) for every serum TSH concentration doubling, which was not the case for changes in serum FT<sub>4</sub>. Note that in this study, median serum TSH was 1.17 mIU/liter in women without AITD compared with 2.16 mIU/liter in women with AITD ( $P < 0.001$ ).

## 2. According to the type of ovarian hyperstimulation

Because the use of ART and COH continues to grow steadily and also because there is increasing evidence of a negative impact of hypothyroidism on the outcome of pregnancy, it is important to delineate more precisely the effects on thyroid function of the different COH procedures that are commonly employed nowadays. The study by Davis *et al.* (209) is presently the only one that has investigated the impact of different types of COH procedures on thyroid function. On the basis of their findings, the authors concluded that women who would become pregnant after COH treatment with Gn stimulation or oral medications did not need additional LT<sub>4</sub>. They advised pregnant women who were already treated with LT<sub>4</sub> to increase their daily dosage by a mean 32% increment after treatment for infertility and a mean 30% increment in those who became pregnant spontaneously. Although in that study there was no significant difference in the need to increase LT<sub>4</sub> dosage between both groups of women, the postconception serum TSH levels were clearly higher after COH compared with spontaneous pregnancy (3.8 *vs.* 2.2 mIU/liter), and the lack of statistical significance might simply be due to the very small number of spontaneous pregnancies ( $n = 5$ ).

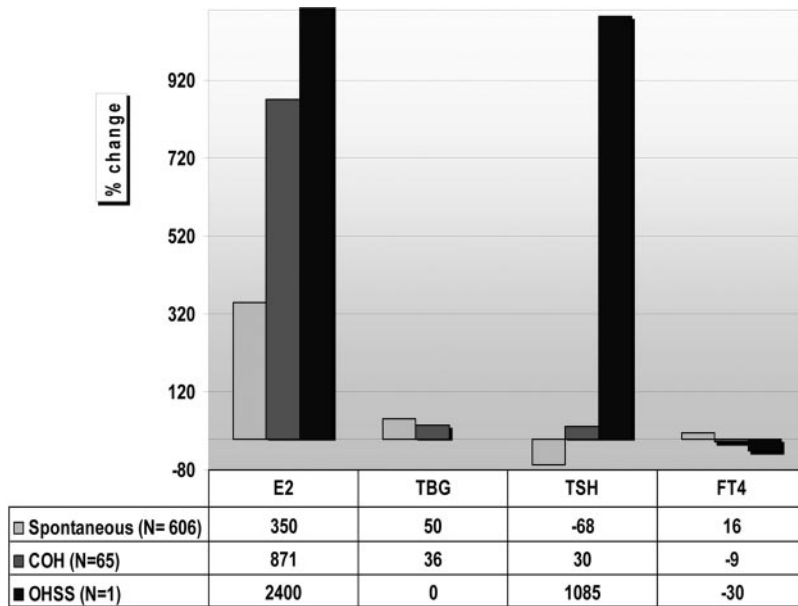
The most impressive clinical condition in which serum  $E_2$  levels increase sharply and markedly is the ovarian hyperstimulation syndrome (OHSS). OHSS is a potentially life-threatening complication of COH that is characterized by massive enlargement of the ovaries with simultaneous development of a large number of follicles and increased capillary permeability (210, 211). Clinical manifestations may vary from a slight increase in ovarian size with abdominal discomfort to more severe presentations such as ovarian enlargement with pleural effusions, ascitis, thromboembolic complications, and pulmonary edema. Such complications may lead to hypovolemic shock with multiple organ failure. The exact pathophysiology of OHSS remains unclear, but one striking feature is that extremely elevated serum  $E_2$  levels ( $\geq 5,000$  ng/liter) constitute a constant biological feature in the syndrome (212). OHSS occurs almost exclusively as a complication of COH for ART. A few cases of OHSS have also been described recently in spontaneous pregnancy and were associated with molar disease, PCOS, or activating FSH receptor mutations inducing a greater sensitivity to hCG (213, 214). Severe forms of OHSS complicate about 1% of ART cycles, with an early miscarriage risk reaching 30% (215, 216).

In the literature, data on OHSS impact on thyroid function are limited to a single case reported by one of us (K.P.) (217). This patient was a 37-yr-old woman with AITD treated with 125  $\mu\text{g}$  of  $LT_4$  daily who underwent COH for idiopathic infertility. Before COH, serum TSH and  $FT_4$  were 3.5 mIU/liter and 11.1 ng/liter, respectively (normal range for TSH, 0.27–4.2 mIU/liter; and for  $FT_4$ , 9.3–17.2 ng/liter). The patient decided to ignore the advice given to her to increase her daily  $LT_4$  dosage 4 wk before starting the COH procedure (consisting of 6 d of orgalutran, followed by 8 d of Menopur 1125 IU). Very soon after conception proved by a positive serum hCG of 300 IU/liter, she developed grade 2 OHSS (*i.e.*, moderate) associated with very high  $E_2$  levels (5,549 ng/liter). Thyroid function tests were performed and revealed severe, albeit asymptomatic, hypothyroidism (serum TSH, 42 mIU/liter;  $FT_4$ , 7.7 ng/liter).  $T_4$  dosage was increased to 200  $\mu\text{g}/\text{d}$ , and serum TSH decreased to 3.1 and 0.1 mIU/liter after 6 and 8 wk, respectively. At the time, her serum TSH was 0.1 mIU/liter, serum hCG level was 35,340 IU/liter, and  $E_2$  level had declined to 1,900 ng/liter. She eventually delivered a full-term healthy boy. A striking feature was that the increase in serum TSH was extremely pronounced in this patient, presumably because of the association between OHSS and AITD. However, whether the presence of AITD, development of OHSS, or both were the predominant factors leading to such severely altered thyroid function tests cannot be determined from this single report.

### C. Clinical management

Concerning screening for thyroid disorders, we outline a number of arguments that we consider to be in favor of systematic screening in the particular setting of infertility. The first argument is the increased prevalence of AITD among infertile women—especially those with endometriosis and ovarian dysfunction—in comparison to that in fertile women; increased AITD prevalence constitutes a risk factor for the development of hypothyroidism. The second argument is that  $LT_4$  therapy has been shown to have a beneficial effect on surrogate infertility endpoints (such as menstrual cycle, LH pulsatility, and hyperprolactinemia) in women with SCH. When hypothyroidism is treated and normal menses restored in infertile women, ART treatment could potentially be postponed, hence avoiding medical and psychological burden to the patient related to ART procedures (145). Data on the impact of  $LT_4$  administration on outcome of assisted pregnancies are limited to only one study that was not in favor of a beneficial impact in terms of miscarriage reduction (218). Figure 4 illustrates the differences in thyroid function and  $E_2$  levels occurring in spontaneous and assisted pregnancies and in the single personal case of a woman presenting OHSS. The data showed that COH and its major complication, OHSS, led to a markedly more pronounced  $E_2$  and TBG increased levels and, in turn, to more severe thyroid function changes than observed with spontaneous pregnancy. The conclusions drawn from the data illustrated in Fig. 4 are that in women who undergo a COH procedure, severe changes in serum TSH and  $FT_4$  may be expected to occur and, for this reason, thyroid function and thyroid antibodies should be measured before COH (217). In women with serum TSH levels between 2.5 and 4.0 mIU/liter, without AITD or prior thyroidectomy, we propose to monitor thyroid function tests after COH.  $LT_4$  administration should be initiated in case of a serum TSH above 2.5 mIU/liter and the presence of AITD. Also, an increase in the dose of  $LT_4$  should be considered in those women who are already on replacement therapy, with the aim to obtain a serum TSH level below 2.5 mIU/liter before COH because the latter procedure increases TH demands.

In summary, ovarian hyperstimulation in preparation for ART leads to an important increase in  $E_2$  levels. The  $E_2$  increase is dependent upon the COH procedure used, and  $E_2$  levels become excessively increased in OHSS. When AITD is present initially, the impact of COH on thyroid function is permanent (*i.e.*, TSH increases and  $FT_4$  decreases), and its magnitude depends on serum TSH and  $FT_4$  values before COH. In these instances, SCH may occur, which may alter pregnancy outcome. It is therefore advised to maintain serum TSH levels below 2.5 mIU/liter (as in patients who are on  $LT_4$  treatment) before starting



**FIG. 4.** Changes in thyroid function tests (serum TSH, FT<sub>4</sub>, TBG) and E<sub>2</sub> levels are shown as the comparison of percentage changes between prepregnancy and first trimester pregnancy data in spontaneous and assisted pregnancies. Incremental percentages were calculated from the actual serum concentrations of TSH, FT<sub>4</sub>, TBG, and E<sub>2</sub> as reported in the following original articles: spontaneous pregnancies, from D. Glinoer *et al.*: *J Clin Endocrinol Metab* 71:276–287, 1990 (219); COH, from A. F. Muller *et al.*: *J Clin Endocrinol Metab* 85:545–548, 2000 (204); and OHSS, from K. Poppe *et al.*: *Thyroid* 18:801–802, 2008 (217).

the COH procedure and to monitor thyroid function tests closely thereafter. Women with sufficient iodine intake and without primary thyroid disease are usually able to increase TH production in response to the additional strain induced by COH. Whether T<sub>4</sub> treatment in the specific instances of COH and ART, with serum TSH levels maintained below 2.5 mIU/liter, will in turn have a beneficial effect on the final outcome of pregnancy presently remains unclear.

## IV. Thyroid Function and Pregnancy

### A. Importance of thyroid function in the pregnant state

Numerous hormonal changes as well as alterations in metabolic demands occur during pregnancy, resulting in profound and complex effects on thyroid function. Because thyroid disorders are much more prevalent in women than men during the childbearing period, it is not surprising that common thyroid disorders such as chronic autoimmune thyroiditis, hypothyroidism, GD, *etc.*, are relatively frequently observed in pregnant women. To facilitate our understanding of the pathological processes that may affect thyroid function, it is important to delineate the normal physiological processes taking place in the pregnant state. Also, to ensure the best possible health status of both the mother and progeny, a better understanding of the complex maternal-fetal interrelationships related to the ongoing thyroid processes is important because the expecting mother is also the natural carrier of her future child.

Several complex physiological changes take place during pregnancy, which together tend to modify the economy of the thyroid and have a variable impact at different time points during gestation (2, 220). Among the main physiological thyroid economy changes is the marked increase in both serum TBG concentrations and extrathyroidal T<sub>4</sub> distribution space that take place during the first half of gestation (202). To maintain the homeostasis of T<sub>4</sub> concentrations, the thyroid machinery must produce more T<sub>4</sub> until a new steady state is reached around midgestation. Thus, the major change in thyroid function associated with the pregnant state is the requirement of an increased production of TH that, in turn, depends directly upon the adequate availability of dietary iodine and integrity of the thyroid gland. Therefore, any functional perturbation of normal thyroid function may have consequences for pregnancy outcome, and conversely, pregnancy by itself may affect

the presentation and course of most thyroid disorders.

Regarding the iodine nutrition status of pregnant women, several studies have clearly demonstrated the detrimental impact—both for the mother and progeny—of an insufficient iodine intake to ensure the physiological homeostasis of circulating TH levels (220–222). Iodine deficiency (ID) adds an important strain on the thyroid capacity to adapt to the required increase in hormone production, thus leading to hypothyroxinemia ((hypo-T<sub>4</sub>) with increased serum TSH levels and, in turn, frequent goiter formation. The WHO has endorsed recommendations to implement the iodine supplementation in pregnant women, taking into account the specific targets that need to be adapted to the natural iodine nutrition local conditions as well as the practical possibilities to provide adequate iodine supplements (223).

With regard to thyroid function assessment, it is important to recommend caution for a correct interpretation of thyroid function tests in pregnant women. The normal reference range of serum TSH is modified, implying the need to define trimester-specific normative TSH reference limits (224). Also, strong arguments exist to consider that serum FT<sub>4</sub> estimates, as measured by most—if not all—commonly available FT<sub>4</sub> assays, are flawed during pregnancy. The recent study by Lee *et al.* (10) concluded that FT<sub>4</sub> immunoassays in pregnant women yielded results that did not correspond to the actual FT<sub>4</sub> changes.

The overall clinical epidemiology of common thyroid disorders in pregnancy should also be mentioned briefly here. Thyroid dysfunction during pregnancy includes OH and SCH with relative incidences of approximately 0.4% for OH and approximately 3% for SCH, as well as overt and subclinical thyrotoxicosis, with relative incidences of approximately 0.2% for overt thyrotoxicosis and approximately 2.5% for subclinical thyrotoxicosis. Finally, concerning thyroid autoimmunity features in pregnancy, the prevalence of AITD was shown to range between 5 and 20%, with an average of 7.8%. AITD represents the main cause leading to hypothyroidism in pregnant women (see Section IV.B.3) (225).

## B. Hypothyroidism and pregnancy

### 1. Definitions of thyroid disorders applied to the pregnant state

Worldwide, ID remains the main cause of primary hypothyroidism, but in geographical regions where the iodine intake is sufficient, the most common cause of primary hypothyroidism is chronic autoimmune thyroiditis (226). Depending upon the duration and degree of severity of ID or of the autoimmune attack against the thyroid, a broad spectrum of clinical conditions may exist, and this explains the difficulties in interpreting published data on hypothyroidism in pregnancy and its potential repercussions on maternal health, pregnancy outcome, and fetal development (227). Such conditions are usually regrouped under the common term of hypothyroidism, maternal thyroid failure, or hypo-T<sub>4</sub> (228).

OH is defined as a low serum FT<sub>4</sub> with elevated serum TSH concentration. As alluded to above, it is important to take into account the modifications in serum TSH reference range in the context of pregnancy (224, 229, 230). Furthermore, whereas the solidity of assays used to measure serum TSH is not subject to particular caution, the validity of serum FT<sub>4</sub> measurements has been questioned and remains a matter of debate (10, 231–233). With regard to SCH in pregnancy, the upper normal limit of serum TSH values is shifted downward because of the indirect dampening effect of elevated serum hCG levels on TSH secretion, hCG acting as TSH-like agonist on the thyroid gland (231, 234, 235). Because of the physiological downward serum TSH shift, a significant proportion of pregnant women with only slight serum TSH elevations may not be diagnosed when using the upper normalcy limit recommended for nonpregnant individuals (236).

Besides the classical presentations of maternal thyroid failure as OH and SCH, another condition has been reported specifically in the context of pregnancy, namely isolated hypo-T<sub>4</sub>, which is defined as a lowering in serum FT<sub>4</sub> without concomitant serum TSH elevation. This bio-

chemical condition was first described in pregnant women residing in areas with mild to moderate ID where it was shown that the necessary rise in serum total T<sub>4</sub> accompanying the rapid physiological rise in TBG (that takes place during the first 10–16 wk of gestation) was not sufficient to maintain normal FT<sub>4</sub> levels, hence leading to a pattern of relative hypo-T<sub>4</sub> with normal serum TSH (219). This expression was extended progressively to various conditions wherein serum FT<sub>4</sub> levels are reduced near the lower serum FT<sub>4</sub> reference limit, or slightly below, in the context of pregnancy. In contrast with OH and SCH (primarily associated with AITD), isolated hypo-T<sub>4</sub> is invariably found in pregnant women without evidence of AITD. Its causes remain presently not well understood and even somewhat enigmatic. Recent studies in human fetuses have shown that in the first trimester of gestation, which is pivotal for the outcome of pregnancy, fetal tissues are exposed to FT<sub>4</sub> concentrations that are in the same range as those available in adult tissues. Therefore, any significant decrease in maternal serum FT<sub>4</sub>, irrespective of its causes, may potentially lead to detrimental effects on fetal neurodevelopment (237–241).

In summary, when analyzing published data on the repercussions of maternal hypothyroidism as well as isolated hypo-T<sub>4</sub> on the outcome of pregnancy, both in terms of maternal and fetal health, one needs to take into account the intricacies and specificities of the definitions of such conditions when applied to the specific condition that constitutes the pregnant state. It is not the elevation in serum TSH that is potentially detrimental *per se* for the outcome of pregnancy because the only known crucial impacting factor on the outcome is the lowering of TH levels. It is therefore imperative to assess how profound the lowering in serum FT<sub>4</sub> is, at what given time point during gestation it started, and how long it may have remained undiagnosed and hence untreated throughout the course of pregnancy. Although OH is a condition associated with hypometabolism and a clear-cut reduction in serum FT<sub>4</sub> concentrations, SCH is characterized by apparently low-normal serum FT<sub>4</sub>, although there are good reasons to consider that such values may already be too low to be strictly normal. Finally, isolated maternal hypo-T<sub>4</sub> probably represents a separate entity, not to be confounded with true hypothyroidism, and is characterized by a moderate degree of TH lowering with FT<sub>4</sub> values most frequently clustered around the lower limit of the normal (nonpregnant) range.

### 2. The incidence of maternal hypothyroidism and isolated hypo-T<sub>4</sub>

An attempt was made to evaluate relevant data available with regard to the actual frequency of maternal hypothyroidism in pregnancy and to analyze some of the

main clinical differences between OH, SCH, and isolated hypo-T<sub>4</sub>. Pregnant women presenting AITD with an apparently normal thyroid function in early gestation were also considered in this section because this autoimmune condition constitutes a preliminary state that often leads to maternal thyroid underfunction, especially as gestation progresses to term. The consequences of OH on maternal and fetal/offspring health that have been investigated in the past decade will also be outlined. Finally, we discuss shortly the issues related to management and screening for these conditions.

Table 5 lists relevant information colligated from 12 studies on hypothyroidism in pregnancy. In the 1970s, pregnancy in hypothyroid women was considered particularly rare, presumably because, at that time, standard textbooks of obstetrics indicated that hypothyroid women incurred a very high rate of anovulation and infertility, and when becoming pregnant, they had an elevated rate of fetal loss in the first trimester. The pioneering work of Evelyn Man and her colleagues (242), published in the late 1960s, never hit the front pages of endocrine and obstetrics textbooks, mainly because these studies were based on diagnoses made before the era of immunoassays for TH and TSH.

One of the first studies on pregnancy outcome in hypothyroid women was reported in 1981 (243). This study encompassed a small number of pregnancies with extremely severe hypothyroidism, as evidenced by markedly elevated mean serum TSH (>100 mIU/liter) and decreased total T<sub>4</sub> concentrations (2.3 μg/dl). Based on a case-study design, the main finding was that even women with severe hypothyroidism were able to conceive and sustain pregnancy, although most of them—after the diagnosis was made—received LT<sub>4</sub> treatment during gestation. This study also showed that the outcome of such pregnancies was successful, and offspring were apparently healthy. Later, the same group of investigators studied prospectively a larger group of pregnant women with less severe hypothyroidism (244). The aim was to evaluate pregnancy outcome in 68 hypothyroid patients, namely 23 women with OH already known before pregnancy onset and 45 women with SCH diagnosed during gestation. The main result was that pregnancy-induced hypertension was significantly more common in the hypothyroid population, especially when TSH remained abnormally elevated until delivery.

The first systematic study on the prevalence of thyroid deficiency in pregnancy was carried out in the United

**TABLE 5.** Hypothyroidism in pregnancy

Country (period of study)	Observed cases with hypothyroidism	Severity of hypothyroidism	TSH (mIU/liter)	Time of screening and/or diagnosis	First author (Ref.)
USA (1975–1979)	11 cases/51,245 deliveries (IR, NA)	Extremely severe OH	40–293 (mean, 105)	OH known before pregnancy; most women with LT <sub>4</sub> (Re)	Montoro (243)
USA (1981–1990)	68 cases (IR, NA)	1/3 of cases, OH; 2/3, SCH	TSH >5	First prenatal visit (Pro)	Leung (244)
Japan (1986–1990)	28 cases/9,453 deliveries	1/3 of cases, OH; 2/3, transient SCH	Not reported	First prenatal visit (Re)	Kamijo (253)
USA (after 1978)	49 cases/2,000 ♀ (IR, 2.5%)	SCH, 2.2% (43/49); OH, 0.3% (6/49)	TSH >6	15–18 wk (Re)	Klein (245)
Belgium (1990–1992)	41 cases/1,900 ♀ (IR, 2.2%)	Mostly SCH + a few ♀ with OH	TSH >4	First prenatal visit (Pro)	Glinoyer (246)
USA (1990–1992)	209 cases/9,403 ♀ (IR, 2.2%)	Mostly SCH + ♀ with moderate-severe OH	TSH >6	15–18 wk (Re)	Allan (247)
USA (2000–2003)	436 cases/16,125 ♀ (IR, 2.7%)	SCH, 2.5% (404/436); OH, 0.2% (32/436)	TSH >97.5th percentile	Before 20 wk (Pro)	Casey (250)
UK (2002–2003)	40 cases/1,560 ♀ (IR, 2.6%)	SCH, 1.6% (24/40); OH, 1.0% (16/40)	TSH >4.2	First prenatal visit (Pro) (median, 9 wk)	Vaidya (251)
USA (1999–2002)	273 cases/10,990 ♀ (IR, 2.5%)	SCH, 2.2% (240/273); OH, 0.3% (33/273)	TSH >4.29; TSH >3.94	First and second trimesters (Pro)	Cleary-Goldman (252)
Finland (1985–1986)	278 cases/5,805 ♀ (IR, 4.8%)	SCH, 3.9% (224/278); OH, 0.9% (54/278)	TSH >3.6	First trimester (Pro)	Mannisto (207)
India (not reported)	70 cases/633 deliveries (IR, 11.1%)	1/3 of cases, OH; 2/3, SCH	Not reported	Second trimester (Pro)	Sahu (255)
Netherlands (2003–2004)	11 cases/2,497 ♀ (IR, 0.44%)	Mostly SCH	TSH >5.6	First trimester (Pro)	Benhadi (208)

Studies were listed in chronological order of publication (1981 to 2009). The period of study (indicated in the first column) was sometimes unusually long (lasting several years) and did not always correspond directly to the final date of publication. Based on the information provided in the original articles, all figures were recalculated using (when listed) data referring to singleton pregnancies. IR, Incidence rate; NA, not appropriate; Re, retrospective survey; Pro, prospective study.

States, and the authors reported an overall 2.5% incidence rate of hypothyroidism, consisting mainly of women with SCH (245). The pioneering aspect of this study was to demonstrate the relatively high frequency of undiagnosed hypothyroidism in a pregnant population and also that a majority of these women had AITD (58% with positive Th-Abs *vs.* 11% in controls). Its weakness was a retrospective design, with only one cross-sectional thyroid function measurement before midgestation, hence neglecting undetected hypothyroidism that would appear later during gestation. The first prospective evaluation of the occurrence of previously undiagnosed hypothyroidism was reported by one of us (D.G.) in a population study in Belgium. Among 1900 consecutive (and apparently healthy) pregnant women attending the antenatal clinic for the first time, 41 women presented an abnormally elevated serum TSH (range, 4 to 20 mIU/liter). They consisted mainly of women with SCH and a few with moderate OH. The two main causes identified were AITD and glandular hypotrophy at thyroid ultrasound examination (246).

The first large-scale population-based survey was carried out in the United States, as part of an investigation on Down's syndrome. Gestational hypothyroidism was diagnosed in 2.2% of the women, with SCH and OH prevalence rates that were almost identical to those found in the Belgian study. Thyroid antibodies were present in 55% of the women with SCH and in over 80% of the women with OH (247). Based on this population sample, the same group reported the first data to suggest the potentially detrimental impact of maternal hypothyroidism on subsequent neuropsychological development in offspring (248). Furthermore, serum FT<sub>4</sub> was decreased by more than 1 SD in 57% and more than 2 SD in 31% of these women (compared with a control pregnant population), a result that suggested strongly that a relative, but real decrement in free hormone concentrations was present even in women considered to present only SCH (249).

The first prospective analysis specifically dealing with SCH in pregnancy was reported in 2005 (250). Because of the uncertainties, alluded to above, of the upper normal serum TSH limit, the authors first developed a specific gestational-age dependent nomogram for the setting of the upper normal TSH value (236). Then, using this nomogram to diagnose SCH at any gestational stage, their study allowed for the identification of 436 hypothyroid women (32 OH, 404 SCH), yielding an overall incidence rate of 2.7%. This study also showed that placental abruption and preterm delivery were significantly increased in women with SCH.

The first study in which maternal hypothyroidism was diagnosed on the basis of a screening program was re-

ported in 2007 with the objective to assess the efficacy of a high-risk, case-finding approach for screening during gestation (251). One of the important conclusions of this study was to show that thyroid function testing, based on high-risk women alone, would have missed one third of pregnancies with hypothyroidism. In 2008, Cleary-Goldman *et al.* (252) reported data on a subset of the "FaSTER" Trial (First and Second Trimester Evaluation of Risk), a prospective multicenter investigation sponsored by the National Institutes of Health (NIH). The originality of this study was to compare the diagnoses of hypothyroidism (SCH and OH) made in both the first and second trimesters; the overall incidence rate of hypothyroidism was 2.5%.

A large cohort study was reported recently from Finland with incidence rates for hypothyroidism slightly higher than those found in many other studies (0.9% for OH, and 3.9% for SCH), thus yielding a global incidence of hypothyroidism that reached almost 5%. Although there is no clear explanation for this incidence discrepancy with most other studies, it is noteworthy that the Männistö *et al.* (207) study, although with a prospective design, was based on serum samples collected 14 yr before and kept frozen.

A few other studies are also mentioned here, although for reasons that remain unexplained to us, their results differ from mainstream data. For instance, in a study from Japan, only 10 women were found with OH and 18 women with a transient serum TSH elevation in the first trimester only (with spontaneous return to baseline values later on), thus yielding an overall low 0.3% rate of gestational hypothyroidism (253). In another study from Japan (these data are only available in a letter to the editor; see Ref. 254), thyroid function testing in over 70,000 pregnant women yielded a 0.14% incidence rate of hypothyroidism. No clear explanation can be provided for such low incidence rates in these Japanese studies, although it could be hypothesized that the marked differences in iodine nutrition, which is frequently elevated in the Japanese population, may perhaps provide a plausible explanation. To further emphasize some of our difficulties in analyzing reported data, two examples of studies published last year with strikingly different findings are included in Table 5. In a study from The Netherlands, the prevalence of SCH was only 0.44%, whereas another study from India yielded unusually high frequencies for both SCH and OH in pregnant women, yielding an overall incidence rate of gestational hypothyroidism exceeding 11% (208, 255).

Taken together, our detailed analysis of the studies listed in Table 5, carried out over the past 30 yr, yielded a 2.4% overall incidence of gestational hypothyroidism (1,425 cases identified among 60,366 pregnancies). It is

noteworthy that the incidence rates varied widely among the studies, from as low 0.4% to as high as 11.1%. Similarly, relative incidences of SCH and OH also showed wide variations, although on the whole SCH represented at least two thirds of all cases. This analysis serves to emphasize the differences in definitions of hypothyroidism used by these authors as well as marked differences in the timing of diagnosis in pregnancy. Another uncertainty factor was that women with a personal history of thyroid disorder or who were known to have AITD were or were not systematically excluded. Finally, women already diagnosed with hypothyroidism before conception and, therefore, often treated were or were not included.

In this section, we discuss information concerning maternal isolated hypo-T<sub>4</sub> associated with pregnancy. The main data from eight studies reported in the last decade are presented in Table 6. The first study dealing specifically with isolated hypo-T<sub>4</sub> was reported from The Netherlands (256). The authors screened thyroid function prospectively at 12 wk gestation in 220 healthy women in an area with iodine sufficiency and identified those women with the lowest “normal” serum FT<sub>4</sub> concentrations (1st to 10th centiles), namely 22 women whose serum FT<sub>4</sub> was below 10.4 pmol/liter (with normal serum TSH). Compared with the 198 control women with a serum FT<sub>4</sub> value between the 10th and 100th centiles, the study showed that a low maternal FT<sub>4</sub> during early gestation in apparently healthy women was associated with a significantly increased risk of impaired neurodevelopment in offspring. In a second study published a few years later, the same investigators extended their initial observations on a larger group of women with isolated hypo-T<sub>4</sub> with a more appropriate control group of matched pregnant women with normal FT<sub>4</sub> (257). Children’s development was evaluated during the first 3 yr of life, and the conclusion was that isolated hypo-T<sub>4</sub> in early gestation was an independent determinant of a delay in infant neuropsychomotor development, hence confirming their initial observations. However, and at variance with the authors’ own previous results, this second study showed that early isolated hypo-T<sub>4</sub> did not follow a homogeneous pattern of changes: only 14% of initially hypo-T<sub>4</sub> women remained hypothyroxinemic, whereas 26% recovered spontaneously normal serum FT<sub>4</sub> and 60% had a partial FT<sub>4</sub> recovery when thyroid function was evaluated again in the last trimester of gestation. Interestingly, the degree of neurodevelopmental impairment in infants was correlated with the women’s ability to recover normal serum FT<sub>4</sub> values during later gestational stages, indicating that early hypo-T<sub>4</sub> *per se* was not sufficient to affect adversely the infants’ development.

The CATS (Controlled Antenatal Thyroid Screening) study in the United Kingdom was initiated as a prospective interventional trial wherein women with low serum FT<sub>4</sub> or high serum TSH were randomized to no screening *vs.* thyroid testing followed by intervention (LT<sub>4</sub> administration). This cohort study will eventually encompass 22,000 pregnant women recruited before 16 wk of gestation and is presently still in progress with neurocognitive function in offspring as its major outcome endpoint (258–260). Until now, only partial results have been presented and, to the best of our knowledge, these preliminary results indicate that thyroid function abnormalities tend to cluster around two main subgroups, namely isolated hypo-T<sub>4</sub> identified in about half of the women with thyroid abnormalities and an equal percentage presenting SCH/OH.

The first systematic study aiming at evaluating the perinatal significance of isolated hypo-T<sub>4</sub> was reported in 2007 from the United States (261). Identified in the first half of gestation, the incidence of isolated hypo-T<sub>4</sub> was 1.3%, contrasting with a higher incidence (3.4%) of women diagnosed with SCH in the same cohort. There was no excess of adverse effects on pregnancy outcome in women with isolated hypo-T<sub>4</sub>, and the authors questioned the biological significance of isolated FT<sub>4</sub> lowering. In another recent study from the United States, the incidence of isolated hypo-T<sub>4</sub> was higher than reported by Cleary-Goldman *et al.* in the same country, namely 2.1 and 2.3% in the first and second trimesters, respectively, comparable to the 2.2% incidence of SCH (252).

Two other recent studies carried out in Europe deal with a particularly interesting aspect of isolated hypo-T<sub>4</sub>, namely its surprising high frequency found in areas with ID. Investigators from Sicily initially carried out a small study on 16 euthyroid pregnant women (before 20 wk gestation) and reported that maternal hypo-T<sub>4</sub> (defined as a borderline-low serum FT<sub>4</sub>) was present in six of 16 women, with serum TSH remaining within the normal range (262). Based on these initial data, the same group conducted a second prospective study on 220 consecutive women with the aim of identifying maternal hypo-T<sub>4</sub> throughout the entirety of gestation (263). The results were surprising because isolated hypo-T<sub>4</sub> was present in seven women identified in the first trimester already, in 28 additional women identified in second trimester, and in another 21 women identified in third trimester, eventually yielding a total of 56 of 220 diagnosed women with hypo-T<sub>4</sub>, *i.e.*, a staggering overall prevalence that exceeded 25%. By comparison, SCH in the three trimesters of pregnancy was found in only 26 of 220 women (*i.e.*, 12%). The authors elected to treat with LT<sub>4</sub> all women diagnosed with both SCH and hypo-T<sub>4</sub> and were therefore able to compile thyroid function abnormalities appearing suc-



**TABLE 6.** Isolated maternal hypothyroxinemia in pregnancy

Country (period of study)	Observed cases with isolated maternal hypo-T <sub>4</sub>	Some relevant clinical characteristics of the study	Reference ranges for serum FT <sub>4</sub> and definitions of hypo-T <sub>4</sub>	Time of screening	First author, publication year (Ref.)
Netherlands (1994)	22 cases/220 ♀ (IR, NA)	Iodine sufficient area P.S., consecutive ♀ Th-Abs similar to Cx Known TD excluded	Hypo-T <sub>4</sub> (1–10th centile), <10.4 pm/liter Controls (10–100th centile), mean (±SD), 13.1 ± 2.6 pm/liter FT <sub>4</sub> assay range, 8.8–18.0 pm/liter Hypo-T <sub>4</sub> (1–10th centile), between 8.4 and 12.0 pm/liter Controls (50–90th centile), between 15.4 and 19.0 pm/liter FT <sub>4</sub> assay range, 8.7–19.0 pm/liter Hypo-T <sub>4</sub> (<2.5th centile), mean FT <sub>4</sub> 10.2 pm/liter	≤12 wk	Pop, 1999 (256)
Netherlands (1994)	57 cases matched with 58 controls (IR, NA)	Known TD excluded Same conditions as in the study above	Controls (25–75th centile) between 12.8 and 15.0 pm/liter at 11 wk FT <sub>4</sub> assay range, lower limit of 10.8 pm/liter at 11–16 wk GA Hypo-T <sub>4</sub> (<2.5th centile), <11.2 pm/liter	≤12 wk	Pop, 2003 (257)
UK (presently ongoing study)	116 cases among 204 ♀ with abnormal TFTs (IR, NA)	A total of 22,000 ♀ will be recruited prospectively Among 204 ♀ with abnormal TFTs, hypo-T <sub>4</sub> represented 57%, SCH 39%, OH 4%	Controls (2.5–97.5th centile), 11.2–24.7 pm/liter FT <sub>4</sub> assay range, from lower 10.0–11.6 to upper 19.7–24.8 pm/liter, depending on GA at screening	<16 wk	Lazarus, 2004 and 2005 (258–260)
USA (2000–2003)	233 cases/17,298 ♀ (IR, 1.3%)	Retrospective study Th-Abs similar to Cx Comparison made with SCH women from the same cohort	Hypo-T <sub>4</sub> (<2.5th centile), <11.2 pm/liter	1st half of gestation	Casey, 2007 (261)
USA (1999–2002)	232 (1st trimester) and 247 (2nd trimester) cases/10,990 ♀ (IR, 2.3%)	P.S. in area of the FaSTER trial Comparison made with SCH women from the same cohort	Hypo-T <sub>4</sub> , <2.5th centile of Cx Controls (2.5–97.5th centile), 9.4–19.0 (1st trimester) and 17.1 pm/liter (2nd trimester) FT <sub>4</sub> assay range, NR	1st and 2nd trimesters	Cleary-Goldman, 2008 (252)
Italy (NR)	56 cases/220 ♀ (IR, 25.4%)	P.S. in area with ID Once hypo-T <sub>4</sub> diagnosis was made, women received LT <sub>4</sub> (1.65 µg/kg/d)	Controls, median of 15.7 pm/liter FT <sub>4</sub> assay range, 10.4–26.2 pm/liter	1st, 2nd, 3rd trimesters	Moleti, 2009 (263)

(Continued)

TABLE 6. Continued

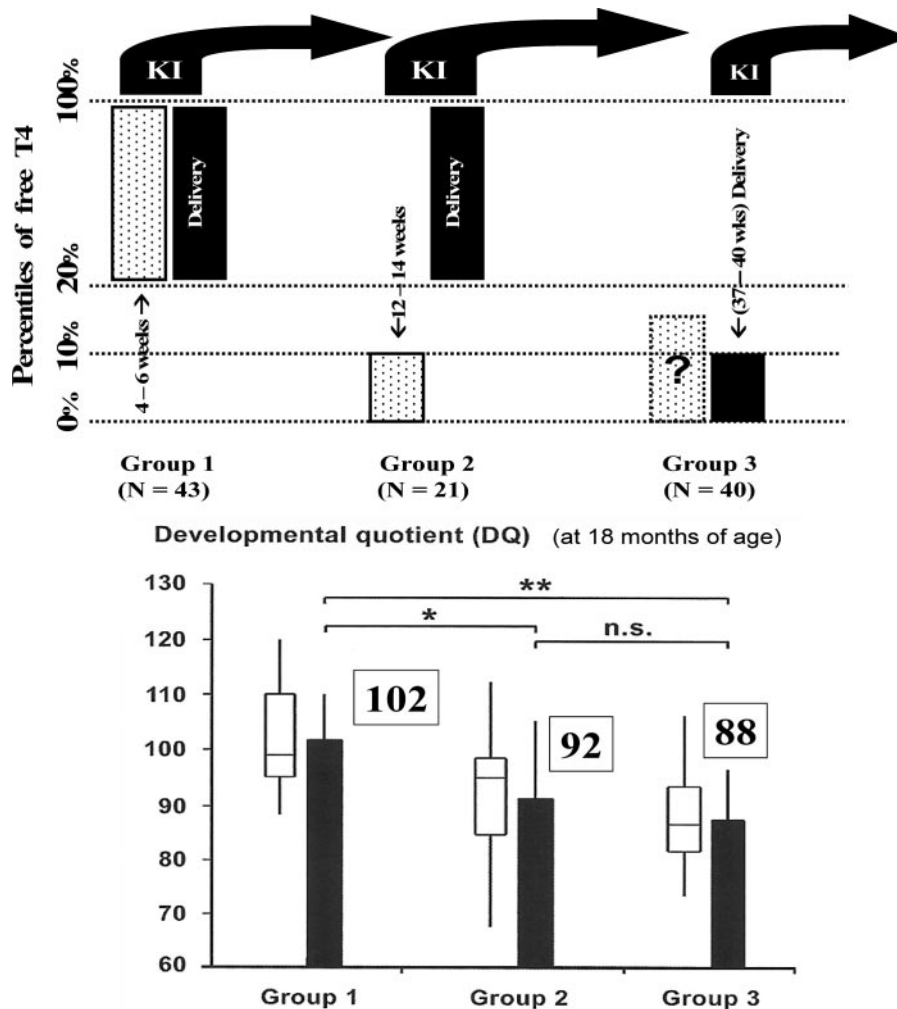
Country (period of study)	Observed cases with isolated maternal hypo-T <sub>4</sub>	Some relevant clinical characteristics of the study	Reference ranges for serum FT <sub>4</sub> and definitions of hypo-T <sub>4</sub>	Time of screening	First author, publication year (Ref.)
Spain (NR)	21 cases/102 ♀ (at 12–14 wk) and 40 cases/151 ♀ at term (IR, 24.1%)	P.S. in area with ID Once hypo-T <sub>4</sub> diagnosis was made, women received 200 µg KI	Hypo-T <sub>4</sub> (1–10th centile), <10.7 pmol/liter Controls (20–100th centile), 12.0–24.0 pmol/liter FT <sub>4</sub> assay range, 9.2–24.0 pmol/liter Hypo-T <sub>4</sub> , NR FT <sub>4</sub> assay range, 10.3–24.5 pmol/liter	1st, 2nd, 3rd trimesters	Berbel, 2009 (264)
China (2005–2008)	103 cases/4,800 ♀ (IR, 2.2%)	P.S. in area without ID Authors used two definitions for the upper TSH limit, based either on the assay reference ranges or on a gestation week-specific range		First half	Shan, 2009 (267)

The eight studies were listed in chronological order of publication, between 1999 and 2009. Note that the study period (listed in the first column) sometimes took place several years before the date of publication (listed in the last column). All figures were recalculated to the best of our ability, based on the information provided in the full articles: ID, Thyroid disorder; TFTs, thyroid function tests; GA, gestational age; Cx, control pregnant women; IR, incidence rate; NA, not appropriate; P.S., prospective study.

cessively throughout the three trimesters of gestation because, once treated, these women were excluded from further analysis. Thyroid function abnormalities were attributed to ID, although the authors were unable to provide an explanation for the elevated frequency of isolated hypo-T<sub>4</sub> as well as for the possible reasons to explain the absence of serum TSH increase in these women. In their conclusions, the authors insisted on the necessity to fortify dietary iodine intake in early gestation and indicated that screening carried out in the first trimester alone would have missed a large proportion of women with later thyroid underfunction. The second study originates from Spain, where a group of investigators carried out an extensive study to assess the influence of isolated maternal hypo-T<sub>4</sub> on subsequent development in offspring (264). Three groups of pregnant women were compared, subdivided on the basis of the absence of hypo-T<sub>4</sub> both in early gestation and at term (group 1, controls); the presence of hypo-T<sub>4</sub> at the end of first trimester but not at term (group 2, transient early hypo-T<sub>4</sub>); and finally, the presence of hypo-T<sub>4</sub> at delivery (group 3, late and/or prolonged hypo-T<sub>4</sub>) (Fig. 5). Because of the potential importance of this study, the results were recently discussed in detail by Glinner and Rovet in an editorial in the journal *Thyroid* (265). In brief, despite inherent weaknesses as well as a complicated study design that led to eliminating over 85% of the children born to the women initially enrolled in the study, this work had the merit of showing significant differences in infants' outcome associated with early and transient isolated hypo-T<sub>4</sub> in the presence of normal serum TSH levels in an area with mild ID, thereby strongly reinforcing the recommendation to fortify dietary iodine intake as early as possible in pregnancy (266).

A last study related to hypo-T<sub>4</sub> is mentioned here because it originated from China, where very few data have been reported on thyroid abnormalities associated with pregnancy (267). Using a specific gestational-age reference range to define the upper serum TSH limit in the first half of gestation, the authors compared the frequencies of SCH and isolated hypo-T<sub>4</sub> among 4,800 pregnancies and found incidences of 2.2% for isolated hypo-T<sub>4</sub> and 5.4% for SCH. It should be noted, however, that when they used a nonpregnant reference range for serum TSH, the incidence of isolated maternal hypo-T<sub>4</sub> declined to only 0.4%.

In summary, scrutinizing the literature of the last decade allowed us to analyze eight studies related to maternal isolated hypo-T<sub>4</sub>, yielding an overall incidence of hypo-T<sub>4</sub> of approximately 2% in unselected pregnancies. In the two recent publications from the southern part of Europe, carried out in areas known to be moderately iodine deficient, the incidence of isolated maternal hypo-T<sub>4</sub> was, however, markedly higher, reaching ap-



**FIG. 5.** The *upper panel* depicts schematically the design of the study. Pregnant women were divided into three groups: group 1, control women with serum FT<sub>4</sub> above the 20th centile initially and at delivery; group 2, women with transient hypo-T<sub>4</sub> (FT<sub>4</sub> between 0 and 10th centiles) in early gestation and normal FT<sub>4</sub> (FT<sub>4</sub> >20th centile) at delivery; and group 3, women with hypo-T<sub>4</sub> (FT<sub>4</sub> between 0 and 10th centile) at delivery, without available information on serum FT<sub>4</sub> before that time. All women received KI supplements (200 μg/d), initiated early in the first trimester (group 1), in the second trimester (group 2), and from delivery onward (group 3). Iodine supplements were maintained throughout pregnancy and the breastfeeding period (for 6 months). The *lower panel* shows the results of developmental quotients (DQ) measured at 18 months in offspring of the three groups. The *white boxes* show the median ± interquartile ranges for DQ; *black boxes* show the mean DQ (±SD) in children of the three groups of women. \*,  $P < 0.05$ ; \*\*,  $P < 0.001$ ; n.s., not significant. [Lower panel Adapted from P. Berbel *et al.*, Delayed neurobehavioral development in children born to pregnant women with mild hypothyroxinemia during the first month of gestation: the importance of early iodine supplementation. *Thyroid* 19:511–519, 2009 (264), with permission. © 2009, Mary Ann Liebert, Inc.]

proximately 25%. In none of the studies listed in Table 6 was there a plausible explanation for the presence of isolated hypo-T<sub>4</sub>, which therefore remains somewhat of an enigma. As alluded to above, caution is recommended in interpreting data based on FT<sub>4</sub> estimates in pregnancy, because of possible major flaws associated with free hormone determinations in this particular context. However, in view of the potentially detrimental associations that seem to exist between isolated hypo-T<sub>4</sub> and fetal neurodevelopment, our opinion is to maintain an open mind and await further developments in this field, which should hopefully become available in the near future.

### 3. Causes of maternal hypothyroidism

It is beyond the scope of the present review to discuss in detail all causes of hypothyroidism that can be associated with pregnancy. Although major progress has been made over the past several decades to eradicate ID in the world, ID still affects over 2 billion individuals today and constitutes, therefore, the most widespread cause of thyroid insufficiency in women of childbearing age (124, 221–223, 227, 268, 269). However, when the iodine nutrition status is adequate, AITD represent the main cause of maternal primary hypothyroidism (2, 15, 225). A wide range of clinical situations as well as causal factors that may potentially restrain the functional reserve of the thyroid

gland and impair TH production ought to be considered in the differential diagnosis of maternal thyroid failure (prior thyroidectomy, R-I<sup>131</sup> administration, ATD therapy). Several other, albeit less frequent, clinical situations also causing hypothyroidism include subacute (or silent) thyroiditis, CH or resistance to TH in women who contemplate a pregnancy, drug-induced hypothyroidism (amiodarone, iodine excess, lithium, *etc.*), prior neck irradiation (for Hodgkin's disease, *etc.*), pituitary or hypothalamic disease (lymphocytic hypophysitis, for instance), and finally, the presence of TSH-receptor binding Ig with blocking activity. Confronted with a suspicion of maternal hypothyroidism, other personal or familial risk factors should also be considered, such as the notion of a family history of AITD, a personal history of type 1 diabetes, and finally those women diagnosed with hypothyroidism before pregnancy and who receive LT<sub>4</sub> replacement (270). Such additional causes remain quite exceptional in a majority of endocrine practices in general hospitals. However, it is worth mentioning that, in highly specialized tertiary reference centers, the prevalence of maternal hypothyroidism due to previous thyroid surgery and R-I<sup>131</sup> administration may exceed that of AITD. For instance, in a recent retrospective study reported by Loh *et al.* (271), 38 hypothyroid women (45 pregnancies) were evaluated to assess the extent of T<sub>4</sub> adjustment during gestation. Hypothyroidism resulting from the cure of GD after thyroidectomy or R-I<sup>131</sup> administration represented 21% of the cases, whereas hypothyroidism resulting from thyroidectomy for cancer with or without R-I<sup>131</sup> remnant ablation represented 47% of the cases, thus with primary hypothyroidism (presumably of autoimmune origin) representing only 32% of all cases (271). Finally, given the well-documented requirement to increase LT<sub>4</sub> dosage in pregnancy, it is not unusual that in women with established hypothyroidism (irrespective of its causes) who are already under TH replacement before conception, a high percentage among these can be found to have abnormally elevated serum TSH values in early pregnancy because of insufficient or late dosage adaptation (203, 272).

As already mentioned, AITD is the major cause of hypothyroidism in pregnancy in the absence of ID. Because positive Th-Abs constitute the most frequent prerequisite leading to progressive development of hypothyroidism, the presence of positive antibodies in unselected pregnancies has been reviewed recently by one of us (D.G.). After scrutinizing 18 studies originating from 10 countries and published over the past three decades, an analysis of the data reported (encompassing a total of over 42,000 pregnant women) showed that thyroid autoimmunity features were present in 5–20% of women, with an overall 7.8% prevalence of AITD (225). The results of nine epidemio-

logical studies in which the prevalence of Th-Abs was compared between hypothyroid and control pregnant women are presented in Table 7. In control women (*i.e.*, euthyroid pregnant women from the same cohort), the prevalence of positive Th-Abs ranged between 4 and 11%, with a mean of 8.8%. In contrast, the prevalence of Th-Abs in pregnant women with a diagnosis of hypothyroidism was much higher, between 25 and 77% with a mean prevalence of 48%, hence confirming that AITD is 5.7-fold more prevalent in pregnant women with a diagnosis of hypothyroidism.

Because AITD is the predominant causal factor predisposing women to the development of gestational hypothyroidism, it is important to note that the pattern of positive Th-Ab titers is modified during gestation, with an overall 50% decrement in Th-Ab titers between early gestation and term, in relation with the relative immunosuppression state associated with pregnancy (273–275). This marked fall in antibody titers is important for several reasons. Although it does indicate an amelioration of the immune aspect of AITD, such theoretical improvement is paradoxical in view of the progressive deterioration of normal thyroid function in women with AITD who, although often euthyroid in early gestation, tend to become hypothyroid as gestation progresses to term. Th-Abs may also become negative in many women with the progression of gestation, and this may have an impact on the timing of screening programs. Finally, women with AITD incur a 50% risk of developing thyroid dysfunction during the postpartum period. It has been shown that the more drastic the pregnancy-associated decline in Th-Abs is, the more striking its rebound in the months after delivery (276, 277). The apparent paradox between the antibody fall and increased risk of hypothyroidism can be explained. The risk is ascribed to the diminished functional reserve of the maternal thyroid machinery because women with AITD have a less than adequate capacity of the thyroid to adapt to the necessary changes in thyroidal economy associated with the pregnant state; namely, the increased requirements in TH production are not counterbalanced by the decrease in thyroid antibody titers (273, 278, 279).

#### **4. Consequences of hypothyroidism on pregnancy outcome**

Several obstetrical complications have been described in relation to maternal hypothyroidism. In Fig. 6, an attempt was made to illustrate together the main results from 18 studies (spanning four decades) in which the relationship was analyzed between pregnancy outcome and maternal hypothyroidism, defined as OH, SCH, or isolated hypo-T<sub>4</sub>. For each pregnancy-associated complication that was analyzed, a major and inescapable difficulty

**TABLE 7.** Thyroid autoimmunity in pregnant women with a diagnosis of hypothyroidism (OH and SCH)

Country where study was performed (no. of hypothyroid women/total no. of pregnancies)	Prevalence of thyroid antibodies in hypothyroid women (%)	Prevalence of thyroid antibodies in controls (%)	Ratio of positive antibodies in hypothyroid vs. Controls	Type of antibody measured (timing of screening)	First author, publication year (Ref.)
USA (49/2,000)	58.0	11.0	5.3	TPO-Ab (15–18 wk)	Klein, 1991 (245)
Belgium (41/1,900)	40.0	6.4	6.3	TPO-Ab and TG-Ab (first P.V.)	Glinoer, 1995 (246)
USA (62/2,000)	77.0	14.0	5.5	TPO-Ab (17 wk)	Haddow, 1999 (248)
USA (209/9,403)	60.0	9.0	6.7	TPO-Ab and TG-Ab (15–18 wk)	Allan, 2000 (247)
USA (62/186)	57.0	10.0	5.7	TG-Ab (17 wk)	Mitchell, 2003 (249)
USA (16/248)	25.0	11.0	2.3	TPO-Ab and TG-Ab (15 wk)	Stagnaro-Green, 2005 (280)
USA (598/17,298)	31.0	4.0	7.8	TPO-Ab (<20 wk)	Casey, 2007 (261)
UK (126/1,560)	50.0	8.1	6.2	TPO-Ab and TG-Ab (first P.V.)	Vaidya, 2007 (251)
USA (389/9,562)	30.1	5.7	5.3	TPO-Ab and TG-Ab (first and second trimester)	McClain, 2008 (281)

Studies were listed according to their chronological order of publication (last column). The third column (Prevalence of thyroid antibodies in controls) refers to the prevalence of positive Th-Abs determined in pregnant women with a euthyroid status from the same study. All numbers and percentages were recalculated (to the best of our ability) from the information provided in the articles. P.V., Prenatal visit. [Derived from D. Glinoer: *The Thyroid and Reproduction*, Georg Thieme Verlag, New York, 2009 (225).].

arose; unless specifically mentioned in the original articles, it was not always clear whether the hypothyroid pregnant women were under LT<sub>4</sub> treatment or not. Thus, the impact of thyroid dysfunction on pregnancy outcome was likely to be influenced, depending on whether a diagnosis of hypothyroidism was made already before conception or only during pregnancy, and depending also on whether and when T<sub>4</sub> treatment was initiated and monitored thereafter, with (in)adequate adjustment of LT<sub>4</sub> dosage throughout gestation. These factors could, by themselves, explain some of the discrepancies reported in literature.

The risk of spontaneous abortion during early gestation is known to be significantly increased in women with OH and SCH. For instance, the recent study by Benhadi *et al.* (208) showed a positive linear relationship between fetal/child loss and serum TSH, which extended from abnormally elevated TSH values down into the normal TSH range. Normal thyroid function's pivotal role was also demonstrated in the study of Abalovich *et al.* (282), 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 LT<sub>4</sub> administration. Similarly, Negro *et al.* (279) carried out a prospective study in a group of euthyroid women with positive Th-Abs and showed that when such women were left untreated, with a likely progression to hypothyroidism later in pregnancy, the miscarriage rate was high (14%), whereas the rate remained normal (2%) in these women with AITD who received LT<sub>4</sub> during the first weeks of gestation. In contrast with those findings, no association was found between OH/SCH/hypo-T<sub>4</sub> and the risk of spontaneous miscarriage in two other recent studies, and the reasons for such discrepancy remain unclear (207, 252). With regard to anemia, this complication was only assessed in two relatively older studies; an association with OH was found in one (but not in the second), and no association was found with SCH (283, 284).

Gestation-induced hypertension (and/or preeclampsia) was assessed in five studies, yielding discrepant results. Although the older studies by Davis *et al.* (283) and Leung *et al.* (244) showed an association between OH/SCH and gestational hypertension, no such association was evident in two more recent large-scale population studies by Allan *et al.* (247) and Cleary-Goldman *et al.* (252). The study by Tan *et al.* (285) is of interest in this discussion because these authors evaluated specifically a group of hypothyroid women correctly treated in early pregnancy and showed no increase in risks of maternal or neonatal morbidity, thus confirming that adequate LT<sub>4</sub> replacement helped to improve drastically (and perhaps even normal-

Author (year) (reference)	Number of women with thyroid dysfunction in the study	Early fetal loss (spontaneous abortion)	Anemia	Gestation-induced hypertension and pre-eclampsia	Placental abruption	Congenital anomalies	Preterm Delivery and/or Low Birth Weight	Fetal distress in labour	Stillbirths/Perinatal Death	Postpartum Hemorrhage	Increased frequency of Caesarian section
Jones & Man (1969) (242)	33 (OH)	●				●	●		●		
Niswander (1972) (288)	244 (OH)								●		
Montoro (1981) (243)	11 (OH)						○		○		
Davis (1988) (283)	28 (OH: 16; SCH: 12)		●□	●■	●□		●		●	●■	
Leung (1993) (244)	68 (OH: 23; SCH: 45)			●■		●	●■		●	■	
Wasserstrum (1995) (284)	42 (OH: 9; SCH: 33)		○□				○□	●■			●
Allan (2000) (247)	209 (OH: 37; SCH: 172)	●■		○□	○□		○□		●		○□
Abalovich (2002) (282)	51 (OH: 16; SCH: 35)	●■				●	●■		●		
Blazer (2003) (289)	259 (treated HO)					●	●				
Pop (2004) (287)	135 (hypo-T <sub>4</sub> )										▲
Casey (2005) (250)	404 (SCH)				■	□	■	■			□
Idris (2005) (290)	40 (OH)						●				●
Tan (2006) (285)	419 (treated HO)			○	○		○				○
Matalon (2006) (291)	1.102 (treated HO)				○		○			○	●
Casey (2007) (261)	831 (SCH: 598; Hypo-T <sub>4</sub> : 233)				■△		■△				
Cleary-Goldman (2008) (252)	490 (SCH: 247; Hypo-T <sub>4</sub> : 243)	○△		□	□▲		□▲	□	□		
Mannisto (2009) (207)	278 (OH: 54; SCH: 224)	○□				○□	○□	○□	●■		
Benhadi (2009) (208)	11 (SCH)	■							■		

**FIG. 6.** The figure depicts in tabular presentation the results of 18 studies published over the last four decades in which the outcome of pregnancy was analyzed in women with hypothyroidism (OH, SCH, and treated OH) and isolated hypo-T<sub>4</sub>. The *three black symbols* represent the positive associations found between thyroid dysfunction and pregnancy complications, whereas the *three open symbols* indicate the absence of such association. For OH, ●, association; ○, no association. For SCH, ■, association; □, no association. For maternal isolated hypo-T<sub>4</sub>, ▲, association; △, no association. [The figure was derived based on Fig. 1 in S. H. LaFranchi *et al.*: *Thyroid* 15:60–71, 2005 (292); and on Table 3 in A. Stagnaro-Green: *Clin Thyroidol* 21:3–6, 2009 (286).]

ize) the outcome of pregnancy in women with a diagnosis of hypothyroidism.

Risk of placental abruption was increased in one study on women with OH, an association that was not confirmed in two other studies (but one of the latter dealt with adequately treated hypothyroid women). No association was found in any of three studies that examined the possible relationship between placental abruption and SCH. Surprisingly, however, in the study by Cleary-Goldman *et al.* (252), the rate of placental abruption was double (1.8 *vs.* 0.9%) in women with isolated hypo-T<sub>4</sub>, although the odds ratio did not reach statistical significance, perhaps because of the low frequency of this obstetrical complication. An increased rate of congenital anomalies (including CH) was found in some studies in women presenting OH, SCH, and even hypo-T<sub>4</sub>, but was not confirmed in an equal number of other studies.

Nine studies have examined the possible association of thyroid dysfunction with the risk of preterm delivery

(and/or low birth weight) and 11 studies with the risk of fetal distress in labor. Together, these complications probably represent the most frequently reported positive associations with OH, SCH, and hypo-T<sub>4</sub>. Although positive data were not found uniformly, the results certainly strike us as one of the most telling features in all studies examined (286). A higher rate of stillbirth and/or perinatal death occurrences was found in four of six studies in association with OH and in one of three studies with SCH. An increased frequency of postpartum hemorrhage was also shown associated in four of four studies with OH and in four of five studies with SCH. Finally, an association of increased frequency of cesarean sections was reported in three of five studies in women with OH (but not in women with SCH) and in one study with isolated maternal hypo-T<sub>4</sub> (287).

In summary, although there is little doubt that associations do exist between various degrees of thyroid dysfunction and obstetrical/neonatal morbidity complicating

pregnancy outcome, a review of available data also indicates that these associations are far from univocal, leaving many questions unanswered. Are discrepancies observed between these studies solely due to the duration and severity of thyroid dysfunction? What is the precise role of  $LT_4$  replacement therapy to drastically minimize the rate of obstetrical complications when given early and correctly monitored during gestation? Are there other factors to consider, such as the cause of thyroid dysfunction? For instance, the presence of thyroid autoimmunity features as the main OH/SCH cause should certainly be regarded as a potentially important additional factor to explain some of the differences in risks observed in these clinical studies. Finally, the role of high-risk antenatal clinics, taking care of women with a suspicion or a diagnosis of thyroid dysfunction, may also have a major positive impact on favorably limiting the occurrence of obstetrical complications. We are in general agreement with Stagnaro-Green (286) who wrote recently that “the relationship between thyroid dysfunction and fetal demise remains murky. Overt hypothyroidism appears to be linked to fetal demise, but whether or not a similar relationship exists with subclinical hypothyroidism is unclear.” The detailed analysis of a large number of older and more recent studies (as illustrated in Fig. 6) provides some support to the notion that an association between thyroid dysfunction and pregnancy complications exists, although the features are probably obscured by some of the unanswered questions alluded to above (288–291).

### 5. Management of maternal hypothyroidism

Readers are referred to detailed publications concerning therapy and monitoring of hypothyroidism in pregnancy as well as to the recent consensus guidelines for management of hypothyroidism in pregnancy endorsed by major international endocrine and thyroid societies (15, 278, 293–297).

$T_4$  is the drug of choice for the treatment of hypothyroidism. In women who contemplate pregnancy, in whom a diagnosis of hypothyroidism is already made, and who therefore receive  $LT_4$ , the recommendation is to adjust the preconception  $LT_4$  dosage to reach a serum TSH level not higher than 2.5 mIU/liter. During pregnancy, there is a need to increase daily  $LT_4$  doses by 30–50% on the average, as a result of the increased requirements of TH production that characterize the pregnant state. On a body weight basis, this increment corresponds to a full replacement dose that increases from 1.6–2.0  $\mu\text{g}/\text{kg}$  body weight/d (before pregnancy) to 2.0–2.4  $\mu\text{g}/\text{kg}$  body weight/d (during gestation) (293, 298). The need to increase preconception  $LT_4$  doses becomes manifest as early as after 4–8 wk gestation, and the magnitude of final hormone requirement changes must be tailored individu-

ally because they are extremely variable between one patient and another (203). An alternative that has sometimes been recommended is to anticipate the expected increases in serum TSH by raising  $LT_4$  dosage before conception, a strategy that has not proved to be beneficial but would certainly help to reduce the frequency of women who are still hypothyroid at their first antenatal visit (272, 290, 299).

The magnitude of  $LT_4$  changes in pregnancy depends primarily on the etiology of hypothyroidism, namely the presence or absence of residual functional thyroid tissue. Women without residual tissue require a greater dosage increment than those with Hashimoto's disease, who usually have some residual functional tissue. It is also important to take into account the preconception  $LT_4$  dose adjustment. For instance, in the recent study by Loh *et al.* (271), where a majority of women were hypothyroid after thyroid ablation for cancer, the necessary increment remained minimal because the daily dose had been purposely adjusted to reach a low serum TSH level before conception. Finally, although the need to increase  $LT_4$  occurs generally in early pregnancy, it is important to remember that about a quarter of hypothyroid women who maintain a normal serum TSH in the first trimester and about a third of those with a normal serum TSH in the second trimester will nevertheless require an increase in  $LT_4$  later on (295, 298).

For all hypothyroid  $LT_4$ -treated women, serum TSH levels should be monitored every 6–8 wk unless an increase in dosage is needed, in which case, serum TSH should be rechecked after 4 wk to ensure that the therapeutic serum TSH target value has been reached. Concerning this target specifically, the recommendation is to reach and maintain thereafter a serum TSH level not higher than 2.5 mIU/liter in the first trimester and not higher than 3.0 mIU/liter in the second and third trimesters. Close monitoring of thyroid function in  $LT_4$ -treated hypothyroid pregnant women is of utmost importance. A recent study has examined how closely the management of hypothyroidism in the general pregnancy population satisfies recently issued international guidelines (281). This observational retrospective study concerned 389 women (at five recruitment centers in the United States), and the results showed that 43% of serum TSH levels were at or above the recommended upper limit of 2.5 mIU/liter when measured in the first trimester, and 33% of serum TSH measurements were still at or above the recommended upper limit of 3.0 mIU/liter when measured in the second trimester. Even when the authors used a less restrictive upper limit, defined as serum TSH above the 98th centile of normalcy, the data showed that 20% of serum TSH values in the first trimester and 23% in the second trimester

ter were above the upper normal limit. The obvious inference of such data is that future strategies should focus more effectively on monitoring LT<sub>4</sub> administration during pregnancy.

In women in whom hypothyroidism is diagnosed during pregnancy, LT<sub>4</sub> treatment should be initiated immediately (with a dose of 100–150 µg/d) or titrated according to body weight. When hypothyroidism is severe initially, therapy may be initiated by giving for the first few days a LT<sub>4</sub> dose corresponding to two or three times the estimated final replacement daily dose to more rapidly normalize the body's extrathyroidal T<sub>4</sub> pool.

Finally, after parturition, most hypothyroid women need to decrease the LT<sub>4</sub> dose received during pregnancy, usually over a period of approximately 4 wk in the postpartum. It should be remembered that women with evidence of AITD are also at risk of developing postpartum thyroiditis, a syndrome that may justify differences between the pre- and postpregnancy LT<sub>4</sub> doses, and it is therefore important to continue monitoring thyroid function tests in the mother for at least the first 6 months after delivery (300, 301).

### **6. Some issues related to screening for maternal hypothyroidism**

A controversy persists today between endocrinologists and obstetricians regarding whether thyroid function should be screened in all pregnant women (296). Many major scientific societies have considered this issue. The AACE (American Association of Clinical Endocrinologists) has recommended routine TSH measurements during the first trimester (or before a pregnancy) in all women (302). The American Endocrine Society and all four world thyroid associations [American Thyroid Association (ATA), European Thyroid Association, Asia and Oceania Thyroid Association, and Latino American Thyroid Association] have endorsed the international guidelines recommending screening of pregnant women, especially those in high-risk groups (15). The “middle-way” position taken by the endocrine and thyroid societies resulted from a compromise within the *ad hoc* committee that prepared the guidelines, mainly to satisfy the opposite views held by our Ob-Gyn colleagues. In the end, the ACOG (American College of Obstetricians and Gynecologists) did not endorse the guidelines, considering that routine screening of thyroid function in pregnant women could not be recommended because of the lack of studies showing a proven benefit, even if asymptomatic women with SCH were identified and treated (303). It is beyond the scope of the present review to discuss all the arguments pro and con justifying these opposite attitudes. Suffice it to mention here that, in our opinion, the prevalence of maternal thyroid failure is sufficiently elevated, and the potential con-

sequences on maternal and fetal health are sufficiently alarming to justify screening. Taken together, the data discussed above yielded an overall 2.8% incidence for gestational hypothyroidism (1.6–2.5% for SCH and 0.2–1.0% for OH). If, to these figures, one adds the 5–20% of women with asymptomatic AITD, a condition that is recognized to constitute a major immunological risk factor leading to development of hypothyroidism during pregnancy, and also the 2% of women with isolated hypo-T<sub>4</sub>, there is at least sufficient quantitative evidence to justify screening, based on the epidemiology of these medical conditions.

Targeted case finding has been recommended as the least population-invasive screening method, although it is worth noticing that in many centers, both in the United States and abroad, and irrespective of official positions taken by scientific bodies, systematic screening is already largely performed, even in obstetrical practices (11). In The Endocrine Society guidelines, high-risk categories of women justifying targeted screening included those with a personal or family history of thyroid disease, symptoms of thyroid dysfunction, history of other autoimmune diseases, infertility, type I diabetes, history of head and neck irradiation, and obviously also women with positive Th-Abs (15). Note also that the last item presents an inherent contradiction because the presence of thyroid antibodies usually results from its detection by thyroid function screening, rather than constituting the reason to request screening. The study from Vaidya *et al.* (251) has shown that targeting high-risk groups is not a panacea because in the experience of these authors, targeted screening would still have missed about one third of all pregnant women with hypothyroidism.

Two large population-based studies are presently under way (in the United States and the United Kingdom), and the results of a third study (in southern Italy) have been recently published (305). As mentioned before, CATS is a cohort study that will eventually encompass 22,000 pregnant women recruited before 16 wk gestation, with the neurocognitive function of offspring as the major outcome endpoint (258–260). When completed, that study may be pivotal for a better understanding of the potential repercussions of isolated maternal hypo-T<sub>4</sub>, and the final results are scheduled to be presented at the 14th International Thyroid Congress (Paris, September 2010). A second study is presently in progress, under the auspices of the NIH. Pregnancy screening was initiated in October 2006, and study completion is scheduled for 2015. That study will eventually comprise a total of 120,000 pregnant women, recruited among the obstetrical U.S. network including 14 institutions. To the best of our knowledge, no results have been available so far, but the protocol



overview presented at the ATA's 2009 Spring meeting (Washington, D.C.) indicated that women with SCH or isolated hypo-T<sub>4</sub> would be randomized to placebo treatment *vs.* LT<sub>4</sub> administration to normalize serum TSH in women with SCH or to normalize serum FT<sub>4</sub> in women with isolated hypo-T<sub>4</sub> (304). Finally, the study by Negro *et al.* (305) was published very recently. The aims were to compare the ability of universal screening *vs.* case finding in detecting thyroid dysfunction and to determine whether treatment of thyroid dysfunction in pregnancy modifies the outcome of adverse obstetrical events. A total of 4,562 pregnant women were randomized to case finding or universal screening, and the main results were to show that although the occurrence of adverse obstetrical events was not different between the case-finding and universal-screening groups, the treatment of thyroid dysfunction was associated with a lower rate of adverse obstetrical outcomes, even in those women identified by screening and considered to belong to the low-risk category.

Thus, this issue is clearly far from settled, and if it is perhaps still premature to recommend universal screening, an acceptable position would be to recommend that clinicians remain fully aware of the pros and cons of screening thyroid disorders in pregnancy, try to establish the closest possible links with Ob-Gyn colleagues in our respective institutions to improve dialog and interchange, and finally disseminate the well-needed knowledge about these questions in the general population and also among the many—and highly diverse—medical care providers (general practitioners, midwives, *etc.*) who are involved in the management of pregnant women (296, 306).

## 7. Summary

Most of the women with OH are usually known and are on LT<sub>4</sub> treatment. With SCH (and SCH is by far more prevalent than OH), most patients have not yet been diagnosed and will not be diagnosed easily unless a screening procedure is set in place. Among all known risk factors investigated to date (when the dietary iodine supply is adequate), AITD represents the single predominant causal factor to explain at least one half of all women affected by thyroid deficiency during gestation. Thus, this autoimmune condition is a major prerequisite for development of hypothyroidism and is present as asymptomatic chronic thyroiditis in 5–20% of unselected pregnant women. Finally, several reports in recent years have outlined the nonnegligible frequency (probably ~2%) of pregnant women who have isolated hypo-T<sub>4</sub>. Although the causes leading to this situation remain unclear, its role should not be overlooked because several reports have indicated a potential detrimental link with pregnancy outcome.

The consequences of maternal thyroid underfunction on the outcome of pregnancy are diverse and not universally acknowledged. OH has been recognized as a cause for increased rates of spontaneous abortion, premature delivery and/or low birth weight, fetal distress in labor, and perhaps also gestation-induced hypertension and placental abruption. Well-designed, large-scale, prospective studies (some of which are presently in progress) are needed to help elucidate some of the discrepancies reported in literature and discussed in the present review. Based on their anticipated results, we hope to gain a better insight as to whether early diagnosis followed by treatment may help reduce the rate of obstetrical and neonatal complications. This concept is at the basis of any reasoning in favor of screening pregnant women. In the meantime, sound individual judgment remains the best rational basis as to the necessity of setting up screening programs in our respective institutions.

## C. Thyrotoxicosis and pregnancy

### 1. Clinical epidemiology

Clinical hyperthyroidism in pregnancy is much less common than hypothyroidism, and its prevalence has been estimated to range between 0.1 and 1% (0.4% clinical, and 0.6% subclinical) (307–310). The causes of hyperthyroidism include those evident in the general population, as well as others that occur only in pregnancy. The most common cause is GD because this etiology accounts for over 85% of overt hyperthyroidism in pregnant women. A second common etiology is gestational transient thyrotoxicosis (GTT), *i.e.*, nonautoimmune hyperthyroidism. GTT results from the direct stimulatory effects of hCG on the thyroid and is most often present as SCHT observed transiently in the first half of gestation. It is usually clinically much less severe and, therefore, often remains unnoticed. Because GD differs fundamentally from GTT, the clinical challenge is to distinguish these two entities since their respective courses, associated risks for fetal health, management, and follow-up are entirely different (311–313).

Concerning other etiologies, clinical entities such as toxic adenoma and multinodular toxic goiter are rare, representing less than 5% of all cases in pregnancy. Molar disease should always be considered in the differential diagnosis and can potentially lead to severe thyrotoxicosis (314, 315). Uncomplicated hydatidiform mole, however, is nowadays most often diagnosed in early gestation and therefore rarely leads to severe hyperthyroidism (316). Finally, other etiologies such as subacute or silent thyroiditis, iodide-induced thyrotoxicosis, thyrotoxicosis factitia, hyperplacentosis, struma ovarii, *etc.*, are extremely uncommon during pregnancy (317, 318).

The historical clues and physical findings of hyperthyroidism in pregnant women are the same as those found in nonpregnant patients. However, their recognition is sometimes more difficult because of similarities between symptoms frequently observed in normal pregnancy with those more specific of thyrotoxicosis. For instance, fatigue, palpitations, anxiety, heat intolerance, and excess sweating are all symptoms that can be observed in pregnant women without thyrotoxicosis (15, 319). A useful symptom is when, instead of the customary gain weight, women report weight loss or, perhaps even more frequently, the absence of weight gain despite increased appetite in the first weeks of gestation (unless excessive vomiting is associated with this situation).

## 2. Significance of low serum TSH

In clinical practice, the suspicion of thyroid hyperfunction in pregnancy arises most of the time from the finding of an abnormally low serum TSH. Therefore, the significance of low serum TSH values ought to be assessed in the context of the physiopathological changes that take place in pregnancy. Secretion of hCG begins very early, and peak hCG values are reached by 8–10 wk gestation (320). Peak hCG levels vary widely among individuals, and they usually range between 30,000 and 100,000 IU/liter. The peak lasts for only a few days, and thereafter, serum hCG decreases gradually to concentrations in the range of 5,000 to 20,000 IU/liter around midgestation (321). Peak hCG levels are significantly greater and prolonged in the case of twin pregnancy (322). In normal pregnancy, serum TSH levels fall to a nadir and present a mirror image with peak hCG values near the end of the first trimester (219). The accepted explanation is that hCG, via its relative TSH-like activity, directly stimulates TH secretion by thyrocytes, and this effect becomes manifest when hCG levels exceed 75,000–100,000 IU/liter for a certain period of time. Thus, peak hCG induces a physiological blunting of the pituitary-thyroid axis that leads to transiently reduced or suppressed serum TSH concentrations. In a systematic study of pregnant women during the first trimester, it was shown that approximately one fifth of unselected pregnancies presented partial or total serum TSH suppression that, in approximately 5% of the women, could still extend into the second trimester (234). Furthermore, the inverse correlation observed between peak hCG and TSH suppression is consistent with the positive correlation that exists between peak hCG values and increasing serum FT<sub>4</sub> concentrations. In a recent study by Lockwood *et al.* (323), it was shown that when serum hCG levels reached (or exceeded) 200,000 IU/liter, serum TSH was suppressed in 67% of the sera collected, and when hCG levels reached (or exceeded) 400,000 IU/liter, serum TSH was invariably and consistently totally suppressed. It is noteworthy, how-

ever, that such elevations in serum hCG are uncommon in normal pregnancy and are more frequently associated with gestational trophoblastic disease (324).

The inference of these effects of hCG on the thyroid is double. Women with abnormally elevated and sustained hCG concentrations during an unusually long time are at risk of developing GTT (see *Section IV.C.3*). Furthermore, hCG levels influence the pattern of serum TSH values in pregnancy, inducing a downward shift of the TSH reference range. One of the subsequent implications of such changes is that in the first trimester, but also to a lesser degree during later gestational stages, a normal pregnant woman may be misdiagnosed as having SCHT when using classical, nonpregnant serum TSH reference ranges (0.4–4.0 mIU/liter) (325). For these reasons, several authors have proposed to use trimester-specific reference norms for serum TSH, and an illustration of such pregnancy-adapted specific serum TSH reference ranges is shown in Fig. 7. Globally and notwithstanding some discrepancy between different studies on normative serum TSH reference limits, such adjustments lead to a lower normal TSH limit of approximately 0.03–0.08 mIU/liter in the first trimester, approximately 0.10–0.20 mIU/liter in the second trimester, and approximately 0.20–0.30 mIU/liter in the third trimester (224, 231, 236, 326). It is important to note that it is not only the lower serum TSH limit that will be affected, but also the entire normal TSH range; the downward shift of the TSH reference range also modifies the upper limit of normal TSH values.

## 3. GTT

The prevalence of GTT varies widely among different studies and regions. Although its prevalence was 2.4% in a cohort of unselected pregnancies in Belgium, prevalence rates as low as 0.1% in Japan and as high as 11% in Hong Kong have been reported (13, 219, 327, 328). Reasons for such geographical (or perhaps ethnic) differences remain unknown. Because of the transient nature of the syndrome, clinical manifestations are not always apparent in women with GTT. Furthermore, in most instances, GTT presents only as SCHT and does not seem linked to increased morbidity (329). In a minority of cases, the clinical presentation of GTT may be much more impressive, and in those circumstances, GTT presents classically in association with more elevated and sustained hCG concentrations, as well as higher FT<sub>4</sub> levels. There is good evidence of a direct correlation between the biochemical severity of GTT and the intensity of morning sickness and excessive vomiting (311).

In its severe clinical presentation, GTT is often associated with the syndrome of hyperemesis gravidarum (HG), known to occur in 0.05–1% of unselected pregnancies and characterized by weight loss (>5% of body weight), de-

hydration, abnormal liver tests, and ketonuria (330). This situation can cause severe morbidity, with symptoms and signs that are sufficiently alarming to require hospitalization and treatment. Regarding the association between HG and GTT, it has been estimated that 30–60% of patients with HG have elevations in serum FT<sub>4</sub> concentrations, along with a suppressed serum TSH (15, 320, 331). GTT is always transient and, as gestation progresses and serum hCG levels progressively fall, elevated serum FT<sub>4</sub> concentrations revert gradually to normal in parallel with the decrease in serum hCG levels. It is also noteworthy that serum TSH values may often remain totally or partially suppressed for several weeks after serum FT<sub>4</sub> returns to normal, *i.e.*, until after midgestation. By coincidence, GTT may also occur in women with underlying thyroid disorders, and when such an association exists, it has been claimed that it may often lead to more severe presentations of thyrotoxicosis. The exacerbation of thyrotoxicosis due to GD, frequently encountered during the first trimester, may be explained (in some women, at least) by the additional thyroid stimulatory action of elevated serum hCG levels (332).

Based on the marked structural homology between hCG and TSH molecules, GTT is considered to result from the thyrotropic activity of abnormally elevated circulating levels of hCG in normal pregnancy or from abnormal molecular hCG variants in trophoblastic disease (333). An interesting isolated exception was reported a decade ago in a woman with recurrent gestational hyperthyroidism (334). This patient had overt hyperthyroidism in early pregnancy (requiring treatment with PTU) and experienced a relapse of hyperthyroidism during a subsequent pregnancy. The patient's mother had also been diagnosed with hyperthyroidism in two pregnancies and was mistakenly thought to be GD. A study of the TSH receptor in this patient disclosed a single mutation in the extracellular TSH receptor domain (K183R) rendering this mutant receptor highly sensitive to hCG and accounting for recurrent thyrotoxicosis in the presence of normal hCG levels. So far, only this case has been reported with a substantially increased sensitivity of the TSH receptor to stimulatory effects of hCG in humans.

With regard to GTT treatment, no study is available today to delineate which patients should be treated with ATD. Because GTT is mainly associated with SCHT, most patients do not present signs of thyrotoxicosis, and the syndrome is always transient with spontaneous recovery after a few weeks. The administration of  $\beta$ -blocking agents has been advocated, with beneficial effects on hyperemesis. In women with severe GTT, ATD may be administered with caution and with close monitoring of thyroid function tests; ATD therapy can often be discontinued after a few weeks before midgestation. In a pro-

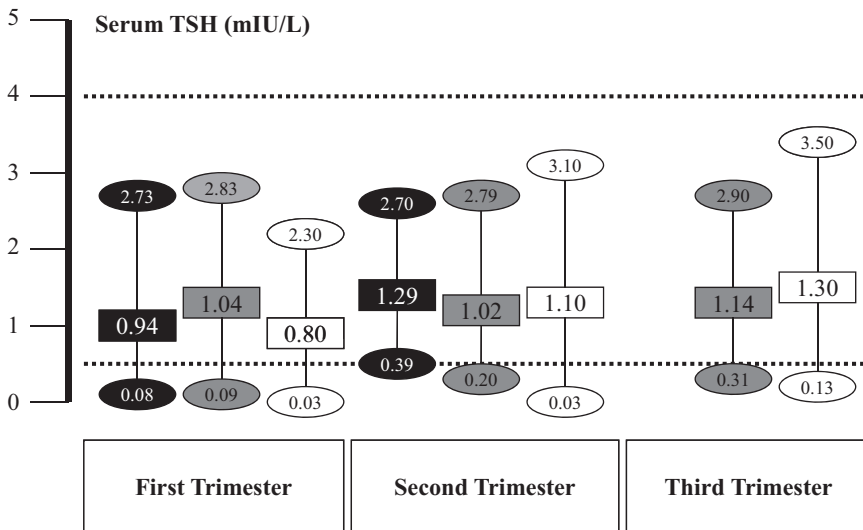
spective observational study by Tan *et al.* (335) of 39 women (35 singleton and four twin pregnancies) with severe GTT and HG who required hospitalization for rehydration, the authors followed the course of serum FT<sub>4</sub> levels without ATD administration. Starting with a mean serum FT<sub>4</sub> value of 40 pmol/liter at 8–9 wk gestation, FT<sub>4</sub> levels were normalized by 14–15 wk, whereas serum TSH values remained suppressed until 19 wk in most cases. Concerning pregnancy outcome, there was no premature delivery, and birth weight was normal. The authors observed a small difference (albeit not significant) in birth weights between women who experienced significant weight loss and those who did not (respectively, 2.9 *vs.* 3.1 kg;  $P = 0.09$ ). In another prospective observational study by Deruelle *et al.* (336) on 33 women admitted to hospital for HG, 22 of them (*i.e.*, two thirds) presented GTT. The patients did not present clinical signs of thyrotoxicosis and received no specific antithyroid treatment, but it was noted that HG severity correlated directly with the degree of thyrotoxicosis, namely, the elevations in both serum FT<sub>4</sub> and FT<sub>3</sub>, as well as TSH suppression.

In summary, ATD administration should probably be reserved for a minority of patients with extremely severe GTT. Treatment of SCHT in the context of GTT has not been found to improve pregnancy outcome and may risk unnecessary fetal exposure to potential side effects of ATD (15, 278, 329).

#### 4. GD: maternal and fetal/neonatal aspects

**a. Clinical presentation and diagnosis.** Various clinical presentations ought to be considered in women with past or present history of GD in the specific context of pregnancy, including: 1) women with active GD diagnosed before the onset of pregnancy who are under ATD treatment; 2) women known to have had GD but who are in remission after prior ATD treatment; 3) women with a previous history of GD who have been cured by thyroid ablation (surgery or R-I<sup>131</sup> administration); 4) women with hyperthyroidism due to GD who are diagnosed for the first time in pregnancy; and 5) women with a history of previous birth of a child with neonatal thyroid dysfunction (337). All pregnant women with a suspicion of hyperthyroidism require confirmation by measuring serum TSH, T<sub>4</sub>, and T<sub>3</sub> levels, Th-Abs (TG-Ab and TPO-Ab), and TSH-receptor antibodies (TR-Ab). Most GD patients have detectable TR-Ab, and TR-Ab measurement is useful to help distinguish GD from GTT. TR-Ab production tends to undergo immunological remission during the second half of gestation, and therefore, detection of positive TR-Ab may depend upon gestation time at measurement (225, 338, 339).

**b. Pregnancy outcome and control of thyrotoxicosis.** Multiple retrospective studies have shown that the outcome of preg-



**FIG. 7.** The figure illustrates the downward shift of the TSH reference range, according to trimesters of pregnancy. The graph shows the median TSH values (boxes) and the upper and lower reference limits of normal (ovals). The black set of symbols was recalculated from J. E. Haddow et al.: *J Med Screen* 11:170–174, 2004 (235); the upper and lower limits show the 5th and 95th centiles. The grey set of symbols was recalculated from R. Stricker et al.: *Eur J Endocrinol* 157:509–514, 2007 (326); the upper and lower limits show the 2.5th and 97.5th centiles. The white set of symbols was recalculated from N. S. Panesar et al.: *Ann Clin Biochem* 38:329–332, 2001 (231); the upper and lower limits show the 5th and 95th centiles. The horizontal dotted lines show the nonpregnant serum TSH reference range (0.40–4.0 mIU/liter).

nancy, namely risks of maternal and fetal/neonatal complications, was directly related to the duration and inadequate control of maternal thyrotoxicosis (310, 313, 337, 340–343). Poor control of thyrotoxicosis is associated with a risk of spontaneous abortion, congestive heart failure, thyrotoxic storm, preeclampsia, preterm delivery,

low birth weight, and stillbirth (Table 8). In a study from Australia by Smith et al. (344), the outcome of pregnancy was evaluated in women with undiagnosed GD. Results showed severe prematurity (mean delivery time, 30 wk) associated with very low birth weight (<2 kg) and neonatal hyperthyroidism requiring ATD treatment. In contrast, pregnancy outcome was excellent for women with GD in whom diagnosis was made early and ATD treatment was started promptly (344). The detrimental role of elevated TH levels on pregnancy outcome was also demonstrated in an elegant study of women with a diagnosis of resistance to TH (i.e., syndrome of genetic resistance to TH). Although these patients were euthyroid, they experienced a significantly increased miscarriage rate compared with normal women, and the explanation proposed by the authors was that elevated maternal serum T<sub>4</sub> levels, characteristic of this syndrome, caused fetal hyperthyroidism in the offspring not carrying the mutated RTH gene (345). In another report by Vaidya et al. (346), premature delivery and low birth weight were consistently associated with an unusual cause of thyrotoxicosis, namely a family with non-autoimmune hyper-

**TABLE 8.** Pregnancy outcome and control of maternal thyrotoxicosis due to GD

Pregnancy complications	Late or poor control of thyrotoxicosis (%)	Adequate control of thyrotoxicosis (%)	No. of pregnant women with GD evaluated in the study	First author, year of publication (Ref.)
Spontaneous abortion	26	13	N.R.	Momotani, 1991 (348)
Congestive heart failure	25	3	60	Davis, 1989 (340)
Thyroid storm	21	<2	60	Davis, 1989 (340)
Preeclampsia	21	6	60	Davis, 1989 (340)
	11	2	223	Millar, 1994 (341)
Premature delivery	15	10	Not reported	Momotani, 1991 (348)
	18	3	223	Millar, 1994 (341)
Low birth weight	23	10 (P = 0.04)	188	Phoojaroenchanachai, 2001 (342)
	27	6	223	Millar, 1994 (341)
Stillbirth	25	0	60	Davis, 1989 (340)

In the study by Davis et al. (340), 60 pregnant women with GD were evaluated during the period 1974–1985. There were 120,000 deliveries during the same period, yielding a prevalence of GD in pregnancy of approximately 0.2%. Among the 60 patients, 36 women were euthyroid with adequate ATD therapy, whereas 16 women remained thyrotoxic during a large part of the pregnancy, and another 18 women were left untreated.

In the study by Millar et al. (341), 181 pregnant women with GD were evaluated during the period 1974–1990. There were 241,000 deliveries during the same period, yielding a prevalence of GD in pregnancy of approximately 0.1%. Among the 181 patients, 34 women were euthyroid with adequate ATD therapy, whereas 147 women remained either thyrotoxic during a large part of pregnancy (n = 90) or uncontrolled for thyrotoxicosis (n = 57).

In the study by Phoojaroenchanachai et al. (342), 188 records of 181 pregnant women with GD were evaluated during the period 1982–1996. The number of deliveries during the same period was not provided by the authors. Among these 188 patient records, 153 women were euthyroid with adequate ATD therapy, whereas 35 women had biochemical hyperthyroidism during the third trimester of gestation.

The data from the study of Momotani et al. (348) were taken from a review article by Mestman (337) published in 2004.

thyroidism due to an activating TSH-receptor gene mutation. Finally, in a study of 230 pregnant women with GD in Japan, it was shown that there was no adverse impact on pregnancy outcome in women who were adequately treated for thyrotoxicosis (347).

*c. Importance of TSH-receptor autoantibody determination.*

GD is an autoimmune disorder due to circulating TR-Ab. TR-Abs are capable of stimulating growth and function of both maternal and fetal thyroid glands, at least when the fetal gland has sufficiently differentiated *in utero* in the second half of gestation. As is the case for other autoimmune disorders, the activity level of GD fluctuates with gestation time. Exacerbation is frequently observed during the first trimester, as well as gradual improvement during later gestation stages, with many pregnant women with GD entering spontaneous remission in late gestation (337, 338, 349). Early pregnancy-related exacerbation of thyrotoxicosis in GD women may be related to the coincidental additional thyroid stimulatory action of elevated hCG levels, as recently shown to occur in perhaps as many as one quarter of GD pregnant women (332). Concerning the spontaneous improvement usually observed in pregnant women with GD, three main independent reasons have been advocated: 1) pregnancy is associated with partial immunosuppression with a progressive decrease in TR-Ab; 2) the rapid and marked rise in serum TBG in the first trimester induces a significantly increased serum hormone binding capacity for both  $T_4$  and  $T_3$  that tends to decrease free hormone fractions and hence,  $FT_4$  and  $FT_3$  concentrations; and 3) the increased obligatory iodine losses associated with the pregnant state also tend to reduce iodine availability for the maternal thyroid gland and, paradoxically, this physiological mechanism may constitute an advantage for women with GD (316).

It is recommended to determine TR-Ab titers in pregnant women suspected to have GD. During early gestation, the measurement of TR-Ab will help clinicians to assess the immunological activity of the disease, and this is particularly important in view of the various clinical presentations of GD summarized above. Women with *de novo* GD usually have TR-Ab titers that are significantly higher than women with a prior diagnosis of GD who are already under ATD therapy. Conversely, GD women who have been cured by prior surgical treatment or R-I<sup>131</sup> administration and who are euthyroid or under  $LT_4$  replacement may still maintain persistent TR-Ab elevation (350, 351). During late gestation, the measurement of TR-Ab will help clinicians to assess the risk of fetal/neonatal thyrotoxicosis due to maternal GD (352). There is an ongoing debate on when, in whom, and how TR-Ab should be measured in pregnancy. In the International Guidelines

published in 2007, the consensus reached was that TR-Ab should be measured at least once—by the end of the second trimester—to assess the risk of abnormal fetal thyroid gland stimulation in mothers with current GD or with a history of GD treated by surgery or R-I<sup>131</sup> administration before pregnancy or in women with a previous neonate with GD (15). In the European guidelines for TSH-receptor antibody measurement in pregnancy, different clinical situations were distinguished (352). First, in euthyroid women who do not receive medication and who have previously been treated with ATD, the risk of maternal recurrence of GD was considered to be very low and that of fetal/neonatal hyperthyroidism negligible; the recommendation was, therefore, that thyroid function be assessed (as part of normal pregnancy care), but not necessarily systematic measurement of TR-Ab. Second, in women with active GD and who received ATD therapy since before pregnancy onset, the recommendation was to measure TR-Ab in the last trimester because the risk of neonatal thyrotoxicosis was directly related to elevated levels of maternal TR-Ab. Third and finally, in women who were euthyroid after a prior cure of GD by surgery or R-I<sup>131</sup>, the risk of fetal/neonatal thyrotoxicosis depended upon maternal TR-Ab titers. The recommendation was to measure maternal TR-Ab in the first trimester; if negative, no further evaluation was required because the risks were negligible. If high TR-Ab titers were still present, close fetal monitoring was recommended, and TR-Ab would be measured again in the last trimester to assess the risk of neonatal thyrotoxicosis.

When maternal TR-Ab is present, these autoantibodies may have different actions on the TSH receptor: stimulation, blocking activity, and even neutral-type activity (353). With regard to the question of how to measure TR-Ab, different assays are available for maternal TR-Ab determination. The most commonly used methodology is the TSH-binding inhibitory Ig (TBII) assay, *i.e.*, radio-receptor assay of TSH-binding inhibitory Ig (354). Such assays measure the displacement of a ligand (radiolabeled TSH) from its receptor on thyroid membranes by specific autoantibodies present in maternal serum. In patients with GD, it is assumed that such antibodies stimulate receptor activity and, hence, thyroid function. However, albeit highly sensitive and specific, TBII assays do not discriminate between *in vivo* stimulating antibodies (responsible for GD), blocking-type antibodies (found rarely in women with Hashimoto's disease), or neutral antibodies (355). Currently available bioassays are the thyroid-stimulating antibodies (TS-Ab) assays. These assays measure the capacity to stimulate cAMP generation in thyroid membranes or intact cells [Chinese hamster ovary (CHO) cells], expressing (by transfection) the human TSH receptor

when incubated in the presence of serum from GD patients (356). In the context of pregnancy with GD suspicion, there is presently no strong evidence to indicate that one assay type (*i.e.*, TS-Ab) is clinically more useful than the other (*i.e.*, TBII), although, at least in theory, arguments do exist in favor of TS-Ab determination. TS-Ab determinations allow differentiation between stimulating and blocking-type antibody activity, and this may be useful in the management of pregnant women with GD because the presence of maternal blocking-type autoantibodies may cause hypothyroidism in both mother and fetus (357, 358). One of the practical difficulties is that, whereas TBII assays are commercially available and therefore easy surrogates for TSH receptor stimulation, TS-Ab assays are usually restricted to specialized institutions or research settings (359).

**d. Management of GD in pregnancy.** The overall goal of therapy is to control maternal thyrotoxicosis as early as possible. With the use of ATD, which constitute the first-line therapy option for GD in pregnancy, women should be maintained at a high euthyroid or borderline hyperthyroid level (15, 337, 359). Because all ATD cross the placenta, it is recommended to use the smallest possible ATD dose that will allow for controlling maternal thyrotoxicosis without the risk of hurting the fetus because ATDs also inhibit fetal thyroid function. Combined administration of ATD and  $LT_4$  to the mother should be avoided because the transplacental passage of ATD is high, whereas it is negligible for THs; hence, addition of  $LT_4$  will not protect the fetus from ATD-induced hypothyroidism.

ATDs belong to the thionamide drug family, and these compounds are prescribed as PTU, MMI, or CMI, the pharmacological precursor of MMI (348, 359, 360). These medications act by blocking TH synthesis via inhibition of iodide organification and iodotyrosine coupling. Pregnancy does not appear to alter significantly ATD pharmacokinetics; PTU, MMI, and CMI have all been used extensively in pregnancy and are equally effective (361). PTU was historically preferred over MMI (especially in the United States), with the rationale that the former was more water soluble and more extensively bound to albumin than MMI at physiological pH, thus limiting hypothetically more transplacental passage of ATD (362–364). Because from today's available information, differential placental transfer of PTU and MMI is unlikely, it does not support the preferential use of PTU. Furthermore, it is important to note that PTU is not available in many European countries as well as Japan, for instance, countries where MMI (or CMI) is commonly used in pregnancy without particular problem (365).

With regard to MMI, there have been multiple reports of two distinct teratogenic patterns associated with fetal

exposure to MMI, although it should be noted that no prospective study has been published clearly establishing causality (359). These congenital anomalies are part of the so-called “MMI embryopathy” and include aplasia cutis and choanal or esophageal atresia (366–368). Aplasia cutis is the absence of skin and accessory structures over the scalp, and it has so far not been reported in mothers exposed to PTU. Skin defects are estimated to occur in one of approximately 4,000 to approximately 10,000 pregnancies, and from the scarce data available, it is considered that this incidence is not above background in pregnant women who have received MMI (369). Choanal or esophageal atresia is a severe congenital anomaly requiring major surgery to repair and is considered to have a higher incidence than expected in fetuses exposed to MMI in the first trimester (370). The relative risk of choanal atresia in pregnant women receiving MMI was estimated to be approximately 17-fold greater than in the general population, although it should be noted that such congenital birth defects could also be attributed to thyrotoxicosis *per se* rather than to the administration of MMI (371).

With regard to PTU, a controversy has recently come to light after the alarming report that the use of PTU for treatment of pediatric GD was associated with a significant and therefore unacceptable risk of liver failure (372–374). Soon thereafter, The Endocrine Society alerted its members about the risk of hepatotoxicity and recommended that PTU use be stopped in the pediatric population (375). An additional concern is that liver failure related to PTU administration is idiosyncratic, and therefore, no biomarkers can be used to predict liver toxicity (376). In the specific context of the first trimester of pregnancy, however, PTU remains the drug of choice because of the potential adverse effects of MMI on the fetus, described above (377, 378). Although there have been a few isolated reports of maternal liver injury associated with the use of PTU in pregnancy, there are presently no clear data that would allow to us evaluate the relative risks of MMI-induced fetal anomalies *vs.* PTU-associated liver failure. A possible modification of presently available recommendations could be to limit the use of PTU to the first trimester of gestation—during which time completion of organogenesis takes place—and possibly to switch women with active GD to MMI treatment thereafter. Finally, pregnant women under PTU should report any new symptom (such as anorexia, nausea, *etc.*) to their physician, and although liver toxicity may appear abruptly, it seems reasonable to propose to monitor liver function tests.

Overall guidelines for GD treatment in pregnancy are summarized in Table 9. The goal is to administer the lowest ATD dose required to control maternal thyrotoxicosis. Maintaining a mild degree of hyperthyroidism is accept-

**TABLE 9.** Guidelines for the medical treatment of GD in pregnancy

1	Monitor clinical signs (heart rate, weight gain, thyroid size, etc.) and serum FT <sub>4</sub> and FT <sub>3</sub> , TSH every 2–4 wk.
2	Use the lowest dose of ATD to maintain the patient in a euthyroid or mildly hyperthyroid state. ATD dosage can usually be lowered after the first trimester and often discontinued during the last trimester. To avoid fetal hypothyroidism, it is advised to maintain maternal serum FT <sub>4</sub> concentrations at or slightly above (<10%) the upper limit of the normal nonpregnant reference range (~1.9 ng/dl or ~24.5 pmol/liter).
3	Do not attempt to normalize serum TSH. Serum TSH concentrations between 0.1 and 0.4 mIU/liter are appropriate. Lower or undetectable TSH levels are acceptable if the patient's clinical condition remains satisfactory.
4	Concerning the choice of ATD, the use of PTU is preferable during the first trimester (remember the potential risk of liver injury).
5	With PTU (or its equivalent dosage for MMI/CMI), doses as little as 100–200 mg/d may still affect fetal thyroid function. However, there are many reports of PTU dosages as high as 400 mg/d in literature (without serious side effects).
6	Communicate regularly with obstetric care providers, especially with regard to the risk of fetal hyperthyroidism in the second half of gestation. Useful tools to this aim are fetal ultrasonographic features and maternal TR-Ab measurements.
7	$\beta$ -Blocking agents and iodines may be used pre- or perioperatively to control thyrotoxicosis.
8	Consider thyroidectomy (in second trimester) if patient is noncompliant or cannot tolerate the administration of ATD, or when persistently elevated doses of ATD are required (PTU >600 mg/d or MMI >40 mg/d).
9	When ATD have been withdrawn in the last weeks of gestation, keep in mind that a rebound of thyrotoxicosis may occur in early postpartum with the need to reinstitute (or increase) ATD dosage after delivery.

The table reflects the current opinions of the authors and was derived from D. Gliener: Werner's and Ingbar's the Thyroid: A Fundamental and Clinical Text, Chap 80, Lippincott Williams & Wilkins, Philadelphia, 2008 (220).

able, as long as the patient tolerates this situation and pregnancy progresses satisfactorily (379). Patients should be monitored closely (weight gain, heart rate, etc.) with monthly thyroid function tests. A typical starting dose is 50–100 mg PTU twice daily (or its equivalent dose for MMI/CMI). After control of thyrotoxicosis, it is often possible to reduce the ATD dosage in the second half of gestation, and it should be remembered that ATD therapy can be withdrawn in approximately 30% of women in the last trimester (15, 220, 359).

Propranolol may be used transiently to control symptoms of thyrotoxicosis and also for preoperative preparation because there is no significant teratogenic effect of propranolol reported in humans or animals. If a patient

should require long-term propranolol administration, careful monitoring of fetal growth is advised because of a possible association with intrauterine growth restriction (380, 381).

Although potassium iodide (KI) can be used temporarily in preparation for thyroidectomy, iodides should not be used as a first-line therapy in pregnancy because the use of high-dose iodine confers a significant risk for fetal hypothyroidism. One study investigating the use of KI (6–40 mg/d) administered to selected hyperthyroid pregnant patients showed improved maternal function with a normal neonatal outcome (382).

Thyroidectomy during pregnancy should be reserved as a second-line therapy in specific situations: persistent high ATD doses required to control maternal thyrotoxicosis; patients with serious side effects to ATD (allergy, intolerance, liver tests abnormalities, etc.); noncompliant patients; and rare cases with upper respiratory compressive symptoms due to goiter size. Pregnant women should be prepared for surgery by using  $\beta$ -blocking agents and a 10- to 14-d course of supersaturated KI solution (50–100 mg/d) to reduce thyroid vascularity. Surgery in pregnancy is deemed safest if undertaken in the second trimester when organogenesis is complete, the fetus is at minimal risk for teratogenic effects of medications, and the uterus relatively resistant to contraction-stimulating events (383).

R-I<sup>131</sup> administration is obviously contraindicated during pregnancy. In case of inadvertent R-I<sup>131</sup> administration, the fetus is exposed to radiation from mother's blood (approximately 0.5–1.0 Rad per mCi administered). Because fetal thyroid uptake of R-I<sup>131</sup> commences after the 12th week, exposure to maternal R-I<sup>131</sup> before this time is not associated with fetal thyroid dysfunction. However, treatment with R-I<sup>131</sup> after 12 wk leads to significant radiation effects on the fetal thyroid. Multiple incidents of inadvertent exposure to R-I<sup>131</sup> have been reported, causing fetal thyroid destruction, *in utero* hypothyroidism, and subsequent neural damage (384–386).

Finally, concerning hyperthyroidism in the postpartum period, two presentations are frequently observed, resulting from the rebound of GD or postpartum thyroid dysfunction (PPTD). Both entities have in common serum TSH suppression with elevated serum FT<sub>4</sub> and FT<sub>3</sub>, the appearance of thyroid dysfunction shortly after the delivery, thyroid gland enlargement, and elevated TPO-Ab titers. From an epidemiological standpoint, the most likely etiology of postpartum hyperthyroidism is PPTD because its prevalence is much greater than that of GD (4.1 vs. 0.2%) (313, 387–390). For the differential diagnosis between these entities, an extremely useful parameter is that TR-Ab is usually elevated in GD, whereas it is negative in PPTD. Furthermore, a thyroid scan may also prove clin-

ically useful because women with PPTD display marked reduction of thyroïdal tracer uptake, contrasting with increased tracer uptake typical of GD. In those women who present only mild hyperthyroidism during the postpartum period, it is reasonable to repeat thyroid function tests 4 to 6 wk after the initial suspicion (hence, before thyroid scanning), because a gradual resolution of hyperthyroidism is more consistent with the transient hyperthyroid phase that characterizes PPTD, thus avoiding additional thyroid scanning (391). Finally, it is important to remember that GD has a tendency to recur during postpartum and that a clinically significant number of women may develop *de novo* GD after childbirth (392–394).

*e. Fetal aspects related to management of maternal GD.* One of the challenges facing clinicians for the management of pregnant women with thyrotoxicosis due to GD is that the treatment (or the absence of treatment) may also affect fetal thyroid function. The fetal thyroid becomes gradually functional between 12 and 20 wk gestation. Before midgestation, the fetal thyroid starts producing T<sub>4</sub> and is, therefore, susceptible to iodine trapping (which is negatively affected by ATD given to the mother) as well as to regulation by TSH (or maternal TR-Ab). Fetal/neonatal thyrotoxicosis constitutes a real risk when maternal TR-Ab production with thyroid-stimulating activity remains elevated in the second half of gestation (395–397). Due to transplacental passage of maternal stimulating TR-Ab, 1 to 5% of infants born to mothers with GD may present fetal/neonatal thyrotoxicosis. The overall incidence remains relatively low because of maternal ATD treatment and perhaps also because of the balance between stimulatory and inhibitory autoantibodies (352, 359). In a study by Mitsuda *et al.* (347), for instance, the incidence of neonatal thyroid dysfunction reached 67% when maternal TR-Ab was above 130% and 83% when TR-Ab was above 150%, compared with only 11% when maternal TR-Ab was below 130% of normal (normal TR-Ab in this study was <115%).

Major progress was achieved recently in studies by Polak and his group in Paris (398, 399). These authors reported their experience on 72 mothers with past or present GD, who were investigated using clinical evaluation, maternal TR-Ab determination (by TS-Ab measurements), and ultrasound evaluation of the fetal thyroid. In 31 pregnant women, TR-Ab was undetectable, and ATD treatment was not required; without exception, all newborns had normal thyroid function at birth. Among the remaining 41 pregnancies, 30 women were positive for TR-Ab and/or required ATD treatment. In them, fetal thyroid ultrasound carried out at 32 wk gestation was normal, and there was no evidence of neonatal thyroid dysfunction

(with one exception). Finally, the remaining 11 mothers had fetuses that presented an enlarged thyroid size, with seven infants shown to be hypothyroid and four hyperthyroid at birth. Neonatal hypothyroidism was associated with low maternal TR-Ab titers and high (presumably too high) ATD dosage given to the expecting mothers, whereas conversely, neonatal hyperthyroidism was associated with high maternal TR-Ab titers and low (presumably too low) ATD dosage given to the expecting mothers. Based on these observations, the authors recommended that TR-Ab measurements be carried out in all women with current or past GD at the beginning of the pregnancy, with close monitoring of those pregnancies with elevated TR-Ab titers or requiring ATD treatment. The other major feature was to show the usefulness of fetal thyroid ultrasonography. The authors proposed to perform fetal thyroid ultrasonography on a monthly basis after 20 wk gestation. In summary, fetal goiter may result directly from placental transfer of thyroid growth-stimulating effects of elevated maternal TR-Ab as well as from the inhibitory effects of ATD (given to the mothers) on the fetal thyroid, thereby inducing fetal hypothyroidism and goiter formation.

Finally, there have been a few reports of infants born to mothers with uncontrolled thyrotoxicosis due to GD who presented CH of central origin (337, 400, 401). The explanation was based on the notion that high maternal serum T<sub>4</sub> levels during a prolonged period of time crossed the placental barrier and, in turn, suppressed fetal TSH by pituitary feedback. In most cases, the diagnosis was made at birth or shortly thereafter on the basis of a low neonatal serum total T<sub>4</sub> contrasting with an inappropriately low serum TSH. In a majority, euthyroidism was restored within a few weeks or months. However, a recent publication suggests that in children born to mothers with inadequately treated GD during pregnancy, there may also be a risk of thyroid “disintegration” (*i.e.*, abnormal ultrasound patterns found during childhood), possibly as a result of prolonged central hypothyroidism (402).

## 5. Summary

The two main causes of thyrotoxicosis in pregnancy include GD (relatively uncommon, but potentially pregnancy threatening) and GTT gestational nonautoimmune transient hyperthyroidism (relatively more common, but usually mild). The natural history of GD is altered in pregnancy, with a tendency for exacerbation in the first trimester, spontaneous improvement in the second and third trimesters, and a risk of rebound during the postpartum period. When treating thyrotoxic patients with ATD, it should be kept in mind that all ATD cross the placenta and affect fetal thyroid function. Fetal/neonatal hyperthyroidism is due to transplacental transfer of maternal



stimulating TR-Ab, and its diagnosis is usually based on fetal tachycardia, accelerated bone age, and intrauterine growth retardation. It may occur in infants born to women with active GD, but also to women who had a prior definitive cure of their disease (by surgery or R-I<sup>131</sup>) who maintained elevated TR-Ab titers.

Quoting proposals recently made by Chan and Mandel (359), there are several areas for future research that need to be elucidated. One area is the determination of assay-specific norms for serum FT<sub>4</sub> concentrations and gestation-specific norms for serum TSH to aid in the diagnosis of thyroid dysfunction in pregnancy. We and others have witnessed several cases of women who received ATD unduly during gestation, sometimes on the basis of a single serum TSH measurement showing a blunted value during early gestation. Another area is to delineate more precisely the targets to reach (and maintain thereafter) for maternal serum FT<sub>4</sub> levels in women with active GD who require ATD therapy in order to establish optimal ATD titration. Another important area of recent concern is the choice of the ATD type to use in pregnancy, especially after the recent report that PTU may cause fatal liver damage. Further work is needed to assess validity of recommendations made by endocrine and thyroid societies in the United States to minimize potential teratogenic and side effects of the use of such drugs. Finally, exploring new noninvasive detection methods to assess fetal thyroid dysfunction (such as fetal ultrasonography) will require skillful training of the different medical care providers directly involved in the management of pregnant women with hyperthyroidism.

#### D. Postpartum thyroiditis

Although not related directly to reproductive health *stricto sensu*, postpartum thyroiditis is one of the most common endocrine disorders experienced by women and is, therefore, a critical topic that ought to be mentioned within the overall scope of the present review. PPTD is a syndrome of thyroid dysfunction occurring in women during the first year after parturition (391, 403). Reported incidence rates of PPTD have been highly variable through geographic differences as well as differences in diagnostic criteria and study design such as, for instance, timing of screening (during *vs.* after pregnancy) and frequency of TSH measurements. It is generally agreed that PPTD occurs in 5–9% of unselected postpartum women and is almost invariably associated with positive TPO-Ab detected in early pregnancy (403, 404). In a large quantitative review that included 21 published articles encompassing a total of over 8000 women, the pooled prevalence of PPTD was 8.1% (405). The prevalence rate of PPTD is also known to be significantly higher in women with type 1 diabetes mellitus, reaching almost 20% (391, 405, 406). Besides positive thyroid antibodies or diabetes as risk fac-

tors, PPTD has a high recurrence rate; 70% of women with a prior episode of PPTD develop a recurrence during the subsequent pregnancy. In contrast, women with positive TPO-Ab but who did not develop PPTD during an initial pregnancy have only a 25% risk of having PPTD after the next pregnancy, and women with neither positive thyroid antibodies nor PPTD during an initial pregnancy do not develop PPTD in future pregnancies (300, 390, 407).

PPTD is a destructive thyroiditis that is etiologically regarded as an exacerbation of an underlying autoimmune thyroiditis (408). As an organ-specific autoimmune disorder, PPTD develops during the postpartum period as a consequence of the immunological rebound that follows the partial immunosuppression characteristic of the pregnant state (387, 388, 409). Women expressing human leukocyte antigen haplotypes DR-3, DR-4, and DR-5 have an increased risk for PPTD, and histologically, the thyroid reveals either lymphocytic infiltrate or diffuse destruction, *i.e.*, changes that are similar to those observed in both Hashimoto's disease and silent thyroiditis (391, 403, 409, 410).

Clinically, PPTD is typically characterized by a biphasic syndrome with an episode of early transient hyperthyroidism occurring between 3 and 4 months postpartum, followed by transient hypothyroidism between 3 and 8 months, eventually with a return to a euthyroid state by 1 yr postpartum; in this classical presentation, hyperthyroidism always predates hypothyroidism (411). Other presentations of PPTD include an episode of transient hyperthyroidism alone with resolution to euthyroidism within a couple of months, and similarly, the lone presentation of PPTD may be transient hypothyroidism. Taken together, the biphasic presentation of PPTD occurs in 25–35% of all cases, lone transient hyperthyroidism in 20–30%, and lone transient hypothyroidism in 40–50% (390, 403, 412). It is important to note that PPTD can also occur in hypothyroid women who already received LT<sub>4</sub> treatment before and during pregnancy because this led to modifications in the T<sub>4</sub> dosage required by such women after pregnancy, compared with before (301). As already alluded to, the majority of women with PPTD return to a euthyroid state by the end of the first year postpartum. However, several long-term follow-up studies in women with PPTD have shown that approximately 30–50% of them will develop permanent primary hypothyroidism within the next 10 yr, hence indicating that women with PPTD should be monitored carefully after LT<sub>4</sub> withdrawal and also checked annually for thyroid function. Progression to permanent hypothyroidism was more common in those women with higher serum TSH levels and higher TPO-Ab titers in the hypothyroid phase of PPTD (390, 413–415). The development of permanent hypothyroid-

ism in this context provides further evidence that PPTD truly represents a clinical presentation of preexisting Hashimoto's thyroiditis (390).

Hypothyroidism occurring in the postpartum period in women with positive thyroid autoantibodies is virtually pathognomonic for PPTD. With regard to the diagnostic aspects of hyperthyroidism, it is important to differentiate between the thyrotoxic phase of PPTD and GD recurring or developing *de novo* during the postpartum period (15, 416). Although GD often recurs during the postpartum period, there are data to suggest that a clinically significant number of women may also develop GD *de novo* after childbirth, although the strength of this association remains uncertain and debatable (394, 417). Moreover, from an epidemiological perspective, the thyrotoxic phase of PPTD is 20 times more common than postpartum GD (390). Symptoms during the thyrotoxic phase of PPTD tend to be milder than during thyrotoxicosis due to GD. Furthermore, whereas 95% of women with GD test positive for the presence of TSHR-Ab, such autoantibodies are not found in PPTD (unless there is, exceptionally, coexisting GD). Also, in contrast to GD with its typical high R-I<sup>131</sup> tracer uptake, PPTD is characterized by a very low tracer uptake due to its intrinsic destructive nature. Differential diagnosis between these two entities is important because the management of both conditions is strikingly different; ATD are not indicated in women with PPTD, whereas ATD therapy (or other more radical approaches) is the treatment of choice for thyrotoxicosis due to GD (15).

With regard to treatment, because the typical hyperthyroid phase in PPTD is limited in time and remains relatively mild, the majority of women do not require therapy. If, nevertheless, treatment of thyrotoxic symptoms is required (for instance, to alleviate palpitations, nervousness, irritability, *etc.*), a short course with  $\beta$ -blocking agents may be used because these agents are not contraindicated during lactation (390). As already mentioned, ATD should not be used. Concerning the treatment of hypothyroidism, Stagnaro-Green (390) showed in a 2002 review article that 13 to 73% (mean, 34%) of women with PPTD received LT<sub>4</sub>. Once instituted and adjusted to normalize serum TSH, it is advisable to maintain the treatment for a period of 1 yr because it is not known initially whether the patient will or will not develop permanent hypothyroidism (404). Finally, a study by Negro *et al.* (418) provided an interesting development for the possible prevention of PPTD by the administration of selenium during pregnancy and the postpartum period. The study was based on the notion that selenium may act as an anti-inflammatory agent in autoimmune thyroiditis. In this prospective, randomized, placebo-controlled trial, the au-

thors showed that the incidence of both PPTD and permanent hypothyroidism was significantly reduced (28.6 *vs.* 48.6% for PPTD; 11.7% *vs.* 20.3% for hypothyroidism, respectively, in the selenium-treated group compared with the placebo-treated group) in women with positive TPO-Abs who received selenomethionine (200  $\mu$ g/d) from 12 wk gestation onward until 1 yr postpartum. Further investigation remains warranted to evaluate whether these beneficial effects of selenium administration are maintained for the long term in patients with AITD.

## V. Conclusions

Since 1905, when Kendle reported the development of precocious puberty in a young girl with severe hypothyroidism for the first time, it has been realized that normal thyroid function is important to maintaining normal reproduction via its interaction in several pathways. In the last decade, tremendous progress has been made on this issue, and many important papers have been published regarding thyroid function and infertility in males and females and thyroid function and pregnancy. With the expanding use of ART in recent years, new information has arisen regarding the important role that the thyroid machinery is playing in the successful outcome of this procedure.

Hyper- and hypothyroidism are the main diseases that may adversely affect male reproduction. Changes in SHBG and sex steroids are a consistent feature of these disorders and have been reported many years ago. Thyrotoxicosis produces abnormalities in seminal parameters, mainly sperm motility, whereas hypothyroidism has abnormalities in sperm morphology. These abnormalities improve or normalize when euthyroidism is restored. It is of note that many patients with ED display thyroid abnormalities and, here again, normalization of thyroid function with treatment restores normal erectile function.

Changes in SHBG and sex steroids are also a consistent feature of thyroid abnormalities in female patients. Moreover, hyper- and hypothyroidism are causing menstrual disturbances, mainly hypomenorrhea and polymenorrhea in thyrotoxicosis and oligomenorrhea in hypothyroidism. In more recent studies, fewer menstrual abnormalities were recorded, most probably because of an earlier diagnosis of the disease. Thyrotoxicosis, SCH, and OH in females have been linked with reduced fertility.

Finally, an increased prevalence of AITD has been found among females attending referral infertility clinics, a finding that may prove to be extremely important if the negative impact of AITD on infertility will be confirmed in future studies.

Regarding ART, new data have been accumulated in the last few years. COH procedure is leading to an important

increase in the E<sub>2</sub> levels. This increase is dependent on the type of COH and is excessively high in the case of hyperstimulation syndrome. When AITD is present, the impact of COH on the thyroid function is more severe and depends on the pre-COH serum TSH and FT<sub>4</sub> values. In cases where SCH or OH is present during pregnancy, the pregnancy outcome may be altered. It is therefore advised to maintain the serum TSH levels below 2.5 mIU/liter before starting a COH procedure and to monitor them closely after COH.

As far as hypothyroidism in pregnancy is concerned, among all known risk factors investigated today (with sufficient iodine intake), AITD is the most common causal factor. Asymptomatic chronic thyroiditis is present in 5–20% of unselected pregnant women. Around 2% of pregnant women have isolated hypo-T<sub>4</sub>, the cause of which is unclear. OH has been recognized as a cause for increased rates of spontaneous abortion, premature delivery and/or low birth weight, fetal distress in labor, and perhaps also gestation-induced hypertension and placental abruption. Screening programs have been advertised, and the authors of this review are in favor of this notion in pregnant women, at least in those with thyroid-positive family history and a history of thyroid diseases.

Clinical hyperthyroidism in pregnancy is much less common than hypothyroidism. Its prevalence has been reported to range between 0.1 and 1%; 85% of all cases are caused by GD.

GTT is the second common etiology. The latter results from direct stimulatory effects of hCG on the thyroid gland and is most often present as SCHAT occurring transiently in the first half of gestation.

Physical findings are more or less the same as those occurring in nonpregnant patients. Because most of the symptoms are similar to those of normal pregnancy, the diagnosis is sometimes difficult. The natural history of GD is altered in pregnancy, with a tendency for exacerbation in the first trimester, spontaneous improvement in the second and third trimesters, and a risk of rebound during the postpartum period. It should be remembered that all ATD cross the placenta and may therefore affect fetal thyroid function. Fetal/neonatal hyperthyroidism is due to transplacental transfer of maternal stimulating TSH-receptor antibodies. Diagnosis of the latter is usually made on the basis of fetal tachycardia, accelerated bone age, and intrauterine growth retardation.

An area of important recent concern is related to the choice of the ATD type to be used in pregnancy, especially after the recent report that PTU may cause fatal liver damage. Further work is needed before we reach final conclusions on this issue.

Finally, postpartum thyroiditis, although not directly related to reproductive health, is one of the most common

endocrine disorders experienced by women and is discussed here within the overall scope of the present review.

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