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Thyroid autoimmunity and hypothyroidism before and during pregnancy

Kris Poppe[1] and Daniel Glinoer[2,3]

[1]Academisch Ziekenhuis, Department of Endocrinology, Laarbeeklaan, Brussels and [2]University Hospital Saint-Pierre, Department of Internal Medicine; Thyroid Investigation Clinic, Brussels, Belgium

[3]To whom correspondence should be addressed at: University Hospital Saint-Pierre, Department of Internal Medicine; Thyroid Investigation Clinic, Rue Haute, 322, B-1000 Brussels, Belgium. E-mail: dglinoer@ulb.ac.be

In the present review, an attempt was made to describe current knowledge and concepts concerning the complex relationships that link thyroid autoimmunity (TAI) and hypothyroidism with female and male infertility, as well as abnormalities occurring during pregnancy, such as pregnancy loss and maternal and fetal repercussions associated with hypothyroidism. In the case of infertility, although the clinical relevance of TAI is somewhat controversial, when all available information is considered the results strongly suggest that when infertility is due to well-defined female causes, autoimmunity is involved and TAI constitutes a useful marker of the underlying immune abnormality, independently of thyroid function disorders. In the case of pregnancy loss, the vast majority of available studies clearly establish that TAI (even with no overt thyroid dysfunction) is associated with a significant increase in miscarriage risk. To find an association, however, does not imply a causal relationship, and the aetiology of increased pregnancy loss associated with TAI remains presently not completely understood. With regard to maternal repercussions during gestation, the main risk associated with TAI is the occurrence of hypothyroidism and obstetric complications (premature birth, pre-eclampsia, etc.). Thus, systematic screening of TAI and hypothyroidism during early pregnancy, monitoring of thyroid function with/without L-thyroxine treatment and follow-up during post-partum have proved helpful and important in order to manage these patients adequately. Finally, with regard to potential repercussions affecting the offspring, recent evidence suggests that thyroid maternal underfunction, even when considered mild (or subclinical), may be associated with an impairment of fetal brain development. When present only during the first half of gestation, maternal hypothyroxinaemia is a risk factor for impaired fetal brain development, due to insufficient transfer of maternal thyroid hormones to the feto-placental unit. When hypothyroidism is not restricted to the first trimester and worsens as gestation progresses (as in untreated hypothyroidism), the fetus may also be deprived of adequate amounts of thyroid hormones during later neurological maturation and development, leading to poorer school performance and lower IQ.

Key words: hypothyroidism/infertility/pregnancy and pregnancy loss (miscarriage)/systematic screening/thyroid autoimmunity or autoimmune thyroid disorders

Introduction

Infertility and pregnancy loss may be caused by many factors, including anatomical, hormonal, thrombotic, autoimmune, genetic, infectious or unknown causes. Over the past decade, investigators have given increased attention to the possible role of thyroid autoimmunity (TAI) in the context of these disorders. The particularity of TAI is two-fold. First, it represents the most common autoimmune disorder in humans (affecting 5–10% of the female population of childbearing age). Furthermore, TAI is the most frequent underlying factor leading to, or associated with, thyroid underfunction (subclinical or overt hypothyroidism)—a condition which may remain latent, asymptomatic or even undiagnosed for many years. It is with this scope in mind that the present update was considered by the authors, in an attempt to describe and review present knowledge concerning the complex relationships associating infertility (male and female) with TAI and hypothyroidism, and pregnancy as well as pregnancy loss with maternal thyroid underfunction and autoimmunity (Bakimer *et al.*, 1994; Peterson, 1994; Fausett and Branch, 2002).

Before the onset of pregnancy

Infertility: definition and clinical epidemiology

Infertility is classically defined as the inability to conceive after one year of intercourse without contraception (Healy *et al.*, 1994;

Hoxsey and Rinehart, 1997). When expressed as a percentage in all married women, the prevalence of infertility has remained stable over the past few decades, with 13% in 1965 and 14% in 1988 (Mosher and Pratt, 1991). Main causes of infertility include female factors (in 35%), male factors (in 30%), a combination of both female and male factors (in 20%), and finally unexplained or 'idiopathic' infertility (in 15%). With regard to female infertility, the main well-defined causes are endometriosis, tubal disease and ovulatory dysfunction (Thonneau *et al.*, 1991). The increased medical demand for infertility treatment probably results from the modern tendency to delay childbearing, a better understanding of the pathological mechanisms causing infertility, effectiveness of assisted reproduction technology (ART), and increased awareness by the public of these treatments. Among the negative prognostic factors that may influence fertility, immunological factors probably play an important part in the reproductive processes of fertilization, implantation and placental development. Different investigations support the notion that there is an association between reproductive failure and the presence of abnormal immunological tests results, including anti-phospholipid and anti-nuclear antibodies, as well as organ-specific autoimmunity, including thyroid antibodies (Kaider *et al.*, 1999).

Infertility and TAI

The clinical relevance of TAI in infertility remains controversial. Several investigators have examined the potential association between TAI and infertility, by measuring microsomal (nowadays thyroperoxidase antibodies; TPO-Ab) and thyroglobulin antibodies (TG-Ab). The main results of these studies are listed in Table I. In the mid-1970s, one group (Wilson *et al.*, 1975) examined the presence of different organ-specific antibodies in infertile women with ovulatory dysfunction and found no difference in TAI positivity between infertile women and fertile controls. Some 20 years later, others (Roussev *et al.*, 1996) investigated the presence of abnormal immunological tests in women experiencing reproductive failure. TPO-Ab and TG-Ab were measured in women with a well-defined female cause of infertility: while 8% of them had TAI, compared with none in the controls, the difference did not reach statistical significance (Roussev *et al.*, 1996). Subsequently, another group (Geva *et al.*, 1997b) was the first to investigate the presence of thyroid antibodies in infertile but euthyroid women with idiopathic or tubal infertility: 19% of the infertile women had TAI, compared with only 5% in nulligravida controls. Although the relative risk to have TAI was increased, the difference was not significant (Geva *et al.*, 1997b). In 1999, an investigation was made retrospectively into the prevalence of TAI in women undergoing ART (Kutteh *et al.*, 1999). In this study, all causes of infertility were pooled: 19% of these women had TAI, a prevalence similar to the 15% observed in age-matched controls. In a later study by Roussev's group, the prevalence of several immunological factors was investigated again in women with infertility: 31% of them had TAI, compared with only 15% in fertile controls, the difference being highly significant (Kaider *et al.*, 1999). In 2001, another group (Reimand *et al.*, 2001) tested a panel of autoantibodies, including thyroid antibodies, in women with infertility caused by endometriosis or ovulatory dysfunction, or with idiopathic causes. The results showed there to be no difference in the prevalence of TAI, between the study group and controls. It should be mentioned, however, that the controls were 4 years older on average than the study group, potentially increasing artefactually the percentage of TAI (Reimand *et al.*, 2001). Finally in 2002, Poppe and colleagues investigated prospectively TPO-Ab positivity in 438 infertile women and 100 age-matched fertile controls. The infertile group was stratified into five categories based on infertility causes: endometriosis, ovulatory dysfunction, tubal disease, a male cause, or idiopathic infertility. When all the causes of infertility were pooled, no significant increase of TAI was evident in the infertile women. However, when the analysis was focused on the infertile

Table I. Risk of infertility associated with thyroid autoimmunity

Reference (country)	Year	Subjects	Thyroid Abs	RR (95% CI)	*P*
Wilson *et al.* (GB)	1975	Infertile	8/77	0.73	0.52 (NS)
		Controls	11/77	(0.28–1.92)	
Roussev *et al.* (USA)	1996	Infertile	5/63	1.19	0.80 (NS)
		Controls	0/15	(0.13–11.00)	
Geva *et al.* (Israel)	1997	Infertile	15/80	3.75	0.09 (NS)
		Controls	2/40	(0.81–17.30)	
Kutteh *et al.* (USA)	1999	Infertile	132/688	1.32	0.20 (NS)
		Controls	29/200	(0.85–2.05)	
Kaider *et al.* (USA)	1999	Infertile	51/167	2.08	0.02
		Controls	16/109	(1.11–3.88)	
Reimand *et al.* (Estonia)	2001	Infertile	2/108	0.48	0.34 (NS)
		Controls	15/392	(0.11–2.15)	
Poppe *et al.* (Belgium)	2002	Infertile	61/438	1.68	0.80 (NS)
		Controls	8/100	(0.78–3.65)	
[a]Poppe *et al.* (Belgium)	2002	Infertile	35/197	2.28	0.05
		Controls	8/100	(1.02–5.12)	
All studies pooled	–	Infertile	274/1621	1.95	< 0.0001
		Controls	81/933	(1.50–2.53)	

[a]Pertaining to the identifiable female causes of infertility.

group comprising only the three female well-defined causes, the relative risk associated with positive TAI became highly significant (Poppe *et al.*, 2002) (Table I).

What can be learned from these studies?

In most studies there was wide heterogeneity in the selection of both the study cases and the controls, as well as in the types of thyroid antibodies measured (TG-Ab, TPO-Ab and in the older studies microsomal antibodies). Also, most studies were retrospective, perhaps introducing biases in the observed results. Some studies examined only the association between TAI and one given cause of infertility, again introducing a bias related to the specificity of the disorder. Despite all these limitations, when the data from all studies are pooled, it becomes possible to calculate an 'average' relative risk clearly associating TAI with infertility, and this risk is highly significant (see Table I; lower section). Thus, these studies tend to show that in the case of infertility due to female causes, a yet-to-be-defined immune disorder is probably involved, whereas this is not the case with male or idiopathic infertility. Whether the presence of thyroid antibodies represents an epiphenomenon or is an actual marker of the underlying immune disorder cannot be determined, based on the studies available.

Female infertility and hypothyroidism

Thyroid autoimmunity is by far the most frequent cause of hypothyroidism in women of reproductive age (Vanderpump *et al.*, 1995; Hollowell *et al.*, 2002). Other causes include severe iodine deficiency, prior radical treatment for hyperthyroidism, post-partum thyroiditis, drug-induced hypothyroidism (e.g. antithyroid drugs, amiodarone, lithium). The prevalence of hypothyroidism in the general population of reproductive age is approximately 2% (Wang and Crapo, 1997; Bjoro *et al.*, 2000). The clinical implications of overt hypothyroidism in infertile women are easily understood, since thyroid hormones have direct effects on granulosa cells, luteal cells and oocytes, indicating a direct interference with normal ovarian function (Wakim *et al.*, 1993). In mild hypothyroidism, ovulation and conception can occur, but the resulting pregnancies are often associated with abortions, stillbirth or prematurity (Davis *et al.*, 1988). Severe hypothyroidism is commonly associated with ovulatory dysfunction and, thus, with infertility: for instance, 23% of hypothyroid women present menstrual irregularities, especially oligomenorrhoea. Thyroid underfunction can also interact more indirectly, for instance by altering the pituitary–ovarian axis, by decreasing the binding activity of sex hormome-binding globulin (SHBG) resulting in increased serum free testosterone and estradiol, by decreasing the metabolic clearance of androstenedione and estrone. Also, elevated thyrotrophin-releasing hormone (TRH) levels due to hypothyroidism are often associated with increased prolactin levels, and a delayed LH response to LH-releasing hormone (LHRH). Treatment of thyroid underfunction with L-thyroxine (L-T4) usually restores a normal menstrual pattern and alleviates these pathological mechanisms (Krassas *et al.*, 1999; see also the review by Krassas, 2000).

Studies on the prevalence of hypothyroidism in infertile women are limited in number. In 1993, one group (Joshi *et al.*, 1993) showed a 6% prevalence of primary and secondary infertility in a small group of women with overt hypothyroidism, but these figures were similar to the 5% prevalence observed in euthyroid controls presenting a goitre. Six years later, another group (Lincoln *et al.*, 1999) determined serum TSH levels in 704 infertile women without previously known thyroid disorder, and observed that 2% of them had overt hypothyroidism. The study, however, did not include a control population and the prevalence was not different from the general female population of reproductive age (Lincoln *et al.*, 1999). In 2000, Arojoki and colleagues investigated retrospectively the prevalence of hypothyroidism in 299 women with various causes of infertility (Arojoki *et al.*, 2000). Overall, 4% of the women had an increased serum thyroid-stimulating hormone (TSH) levels, with a majority presenting overt hypothyroidism. The highest frequency of increased serum TSH was observed among the women with ovulatory dysfunction (6.3%), but there was no statistical difference when elevated serum TSH levels were compared among the different causes of infertility (Arojoki *et al.*, 2000).

Subclinical hypothyroidism (SCH) is defined as a condition with supranormal serum TSH levels and normal free thyroid hormone concentrations (Huber *et al.*, 2002). In the early 1980s, one group (Bohnet *et al.*, 1981) investigated 185 infertile women aged 25–34 years, among whom 11% had SCH. Of these patients, 11 who had an inadequate mid-progesterone secretion reverted to normal after L-T4 treatment, and two actually became pregnant (Bohnet *et al.*, 1981). In 1986, it was reported that 35 of 54 women with a premenstrual syndrome had SCH; the symptoms were relieved in 34 of these women after treatment with L-T4 (Brayshaw and Brayshaw, 1986). In addition, in the study referred to earlier (Arojoki *et al.*, 2000), two out of four women with SCH became spontaneously pregnant after the onset of L-T4 treatment. All authors, however, do not agree with the possible impact of SCH on normal ovulatory cycles. For example one group (Bals-Pratch *et al.*, 1997), in a study of a small number of patients (and controls), observed no difference in the pulsatile secretion of prolactin, TSH, LH and cortisol between women with SCH and controls, nor secretion changes after L-T4 treatment.

How common is SCH among infertile women?

In 1994, a retrospective investigation was made into the overall prevalence of SCH in 444 women with infertility: of these women, 0.23% were found to have features of SCH, and 0.88% of those with ovulatory dysfunction presented with SCH (Shalev *et al.*, 1994). In another recent study (Grassi *et al.*, 2001), the authors reported that 4.6% of infertile women presented with SCH, though women with pelvic and tubal causes of infertility were excluded while those already receiving L-T4 were included. Such inclusion/exclusion criteria may clearly lead to unrealistic estimations of SCH (Grassi *et al.*, 2001). In a recent study, the prevalence of SCH was investigated among different groups of infertile women. Only one patient in the ovulatory dysfunction group and one in the idiopathic infertility group presented SCH, yielding an overall prevalence of 0.5%, which was not different from that in controls (Poppe *et al.*, 2002).

What can be learned from these studies?

Infertile women with overt hypothyroidism should be treated with an adequate dose of L-T4, especially before entering an ART programme. With regard to SCH and infertility, there is at present no mandatory evidence to advise prompt L-T4 treatment; rather, the

latter should be decided upon on an individual patient basis, in collaboration with the endocrinologist.

Male infertility and hypothyroidism

Thyroid disorders are seldom investigated in infertile males, because of the much lower prevalence of thyroid problems among males (Thonneau *et al.*, 1991; Vanderpump *et al.*, 1995). Primary hypothyroidism is known to cause a reduction in gonadotrophins that are essential to maintain normal spermatogenesis (Matsumoto and Bremner, 1987; Wortsman *et al.*, 1987). Two studies showed an increased incidence of organ-specific antibodies in men with sperm autoantibodies: compared with men without sperm antibodies, only thyroid autoantibodies were significantly increased in these patients. These studies demonstrated that TAI and other organ-specific antibodies are probably related to a common immune dysregulation (Baker *et al.*, 1985; Paschke *et al.*, 1994). In 1990, Corrales Hernandez showed, in a small number of post-pubertal men, that hypothyroidism during a 3-month period induced moderate sperm abnormalities such as decreased sperm volume and forward motility, insufficient to cause infertility (Corrales Hernandez *et al.*, 1990). In hypothyroid men, increased levels of SHBG, total testosterone and gonadotrophins have been reported, leading to oligospermia due to decreased free androgen levels. After treatment with L-T4, the sperm parameters tended to normalize (Clyde *et al.*, 1976). Others (Rojdmark *et al*., 1988) were able to confirm these findings in a study of the hypothalamic-pituitary-testicular axis in hypothyroid men. A recent prospective investigation in a large cohort of men with infertility included an analysis of the impact of thyroid dysfunction and autoimmunity on semen (Trummer *et al.*, 2001). TAI was found in 7.5% of these men, and elevated thyroid antibody titres were significantly correlated with pathozoospermia and asthenozoospermia. SCH was present in 3% of the cases, but there was no impact on semen density, motility or morphology (Trummer *et al.*, 2001).

After the onset of pregnancy

Miscarriage and thyroid autoimmunity

Pregnancy loss is a common clinical problem, and the leading aetiologies associated with pregnancy loss include a variety of causes such as endocrine disorders, autoimmune diseases, anatomical abnormalities and infections (Coulam and Stern, 1994; Festin *et al.*, 1997; Geva *et al.*, 1997a). With regard to the thyroid, both hypothyroidism and hyperthyroidism have long been associated with increased fetal loss. Furthermore, such association is usually reversible after appropriate treatment of the underlying thyroid disease and normalization of thyroid function (Abramson and Stagnaro-Green, 2001).

With regard to the relationship between TAI and pregnancy loss, the main information from published studies is summarized in Table II. In 1990, Stagnaro-Green and colleagues were the first to report a doubling of the miscarriage rate in unselected euthyroid pregnant women with positive thyroid antibodies (Stagnaro-Green *et al*., 1990). In this study, the miscarriage rate was found to be unrelated to the titres of antibodies or to serum TSH levels. The authors mentioned however that serum TSH levels were abnormal in six out of 17 thyroid antibody-positive women with a miscarriage. In 1991, the results of a prospective investigation in 120 pregnant euthyroid women who presented various thyroid abnormalities, such as goitre, nodularity, past history of thyroid disorder, or TAI were reported (Glinoer *et al*., 1991). Compared with control pregnant women, the miscarriage rate was increased almost 4-fold in the TAI-positive group. In this study also, there was no significant difference in TSH levels between antibody-positive or negative aborters. Interestingly, it was noted that the age of women with TAI and an abortion was slightly (but significantly) higher than in controls (Glinoer *et al*., 1991). In a later study by the same group, it was shown that the majority of pregnancy losses occurred early—most typically in the first trimester of gestation—in TAI-positive women (Lejeune *et al*., 1993). In 1993, another group examined the prognostic value of positive thyroid antibodies in euthyroid women with a history of recurrent first-trimester abortions, on the risk of future pregnancy loss (Pratt *et al*., 1993). Among 42 such women, 30 successfully completed a new pregnancy and among them only five (17%) had thyroid antibodies. This was in sharp contrast with 12 of 42 women who aborted again during a subsequent pregnancy and among whom eight (67%) had thyroid antibodies (Pratt *et al*., 1993). In 1995, a report was made on the risk of miscarriage associated with TAI in 487 euthyroid women, successfully treated for infertility using ART (Singh *et al*., 1995). In this study, the outcome of pregnancy was that clinical miscarriages (those with a gestational sac visible on ultrasound) were twice as frequent in women with TAI compared with controls. Also in 1995, it was shown that the incidence of TAI was significantly increased in women with a history of recurrent spontaneous abortions, compared with control women who were either nulligravidae or multigravidae, but without endocrinopathy (Bussen and Steck, 1995). In 1997, the results of a comprehensive screening for seven autoantibodies in 1197 Japanese healthy women during the first trimester of pregnancy were reported (Iijima *et al*., 1997). In this prospective study, positive microsomal (thyroperoxidase) antibodies were detected in 10.6% of the cohort. Women with TAI miscarried twice as frequently as TAI-negative women. The study was of particular interest because among all the autoantibodies measured, only the thyroid and antinuclear antibodies were significantly associated—albeit independently of one another—with an increased rate of pregnancy loss (Iijima *et al*., 1997). In 1998, one group (Esplin *et al*., 1998) failed to find a significant association between positive thyroid antibodies and recurrent abortion in a group of 74/149 women from the Salt Lake City area. This study constitutes an exception, as it is still unclear today why this study yielded results that were at variance with almost all others. Referral biases and population differences may be a partial explanation for the negative findings. Also, the unusual and extremely high incidence of TAI-positive controls (>30%) may have impacted on the results of the study (Esplin *et al*., 1998). In 1999, Kutteh and colleagues compared the prevalence of TAI in 700 women with two or more consecutive spontaneous abortions to 200 non-pregnant healthy controls. In this study, the results showed a significantly higher TAI-positive rate in the study group compared with controls (Kutteh *et al*., 1999). The same year, Muller investigated prospectively a group of 173 women undergoing IVF procedures, and without a history of habitual abortion. In this study, 14% of the women presented TAI (Muller *et al*., 1999). Among those who became pregnant after IVF (31%), a

Table II. Miscarriages in women with positive thyroid antibodies

Reference	Country	No. of subjects	Positive thyroid Ab (%)	Miscarriage rate in			*P*	Characteristics of selection of the study groups
				Ab positive (%)		Ab negative (%)		
Stagnaro-Green *et al*. (1990)	USA	552	19.6	17.0	vs	8.4	0.011	Unselected population study
Glinoer *et al*. (1991)	Belgium	726	6.2	13.3	vs	3.3	< 0.005	Unselected population study
Lejeune *et al*. (1993)	Belgium	363	6.3	22.0	vs	5.0	< 0.005	Unselected population, before 14 weeks gestation
Pratt *et al*. (1993)	USA	42	31.0	67.0	vs	33.0	NA	Recurrent spontaneous abortions
Singh *et al*. (1995)	USA	487	22.0	32.0	vs	16.0	0.002	Pregnant with assisted reproductive techniques
Bussen and Steck (1995)	Germany	66	17.0	36.0	vs	7.0	< 0.03	Recurrent spontaneous abortions
Iijima *et al*. (1997)	Japan	1179	10.6	10.4	vs	5.5	< 0.05	Unselected population study
Esplin ety al. (1998)	USA	149	33.0	29.0	vs	37.0	> 0.05	Recurrent pregnancy loss
Kutteh *et al*. (1999)	USA	900	20.8	22.5	vs	14.5	0.01	Two or more consecutive abortions
Muller *et al*. (1999)	Netherlands	173	14.0	33.0	vs	19.0	0.29	Pregnant with assisted reproductive techniques
Bussen *et al*. (2000)	Germany	48	30.6	54.2	vs	8.3	0.002	Failure to conceive after three cycles of IVF
Dendrinos *et al*. (2000)	Greece	45	32.5	37.0	vs	13.0	< 0.05	Recurrent spontaneous abortions
Bagis *et al*. (2001)	Turkey	876	12.3	50.0	vs	14.1	< 0.0001	Unselected population study

miscarriage occurred more frequently in the TAI-positive women compared with TAI-negative women, but the association failed to reach statistical significance (Muller *et al*., 1999). In 2000, another group (Bussen *et al.*, 2000) published the results of a follow-up study on the association between thyroid antibodies and the outcome of IVF. The authors found a significantly increased incidence of TAI-positive euthyroid women with a history of three or more unsuccessful IVF attempts (compared with infertile controls), and concluded that thyroid autoimmunity adversely affected the outcome of IVF (Bussen *et al.*, 2000). Also in 2000, the results were reported of thyroid antibody determinations in 30 women with recurrent spontaneous abortions and 15 controls (Dendrinos *et al.*, 2000). In this study, TAI was seen 3-fold more frequently among the study cases, compared with controls. Finally in 2001, Bagis and colleagues investigated 876 consecutive pregnancies, among whom 12.3% tested positive for thyroid antibodies. In the TAI-positive group, 50% had had at least one spontaneous abortion, while in TAI-negative control women only 14% had experienced pregnancy loss (Bagis *et al.*, 2001).

What can be learned from these studies?

First, the information provided by the analysis of these 13 studies carried out over a decade only in three continents is impressive, with over 5500 women investigated, both as study cases and controls. Second, the studies are not easily comparable because of the different selection criteria employed for the specific aims pertaining to each study. Despite inherent heterogeneity, however, these studies cover a wide range of women of childbearing age, from healthy pregnancies to women with recurrent pregnancy loss and undergoing ART. Third, the incidence of positive thyroid antibodies varied widely, from 6% (Brussels) to as much as 33% (Salt Lake City), and an overall mean incidence of 15% (study cases and controls). The wide variability of antibody positivity constitutes an additional argument to indicate that the populations investigated differed, presumably depending upon local recruitment biases. Finally, no information could be gathered from an analysis of the published data with regard to the potential importance of the titres of positive thyroid antibodies, but it is likely that the intensity of autoimmune alterations was an important factor in relation to the risk of pregnancy loss. Given these limitations, and with the exception of only two studies, all the others concurred to establish that TAI—without overt thyroid dysfunction—is clearly associated with a significant increase in the miscarriage rate. Finding an association does not imply a causal relationship, and it should be stressed that the aetiology of increased pregnancy loss in women with TAI remains unknown. Three 'working' hypotheses have been proposed (Stuart, 1994; Glinoer, 1997; Matalon *et al.*, 2001). The first hypothesis holds that pregnancy loss is not directly related to the presence of circulating thyroid antibodies. In this view, antibodies only constitute a marker of an underlying (yet to be defined) more generalized autoimmune imbalance that, in turn, could explain a greater rejection rate of the fetal graft. The second hypothesis holds that despite apparent euthyroidism, the presence of TAI could be associated with a subtle deficiency in thyroid hormone concentrations or with a lesser ability of the thyroid gland to adapt adequately to the necessary changes associated with the pregnant state, because of the reduced functional reserve characteristic of chronic thyroiditis (Glinoer, 2000). To date, only one prospective study supports this hypothesis. In this study, the authors gave thyroid hormones prior to (and during) pregnancy to apparently euthyroid women with TAI and recurrent pregnancy loss, and were able to show a significant improvement in pregnancy outcome (Vaquero *et al.*, 2000). The third hypothesis holds that because TAI represents a risk factor for infertility, pregnancy could be delayed in such women. However, older age by itself could constitute an additional risk factor for increased pregnancy loss, since the absence of pregnancy is known to increase sharply after the age of 30–35 years, even in healthy married women

(Menken *et al.*, 1986; American Society for Reproductive Medicine Committee, 2002). These hypotheses are not in contradiction with one another, and it remains plausible that the increased risk of pregnancy loss associated with TAI is of multifactorial origin, eventually resulting from a combination of several independently deleterious factors.

Can medical intervention be proposed to help improve the pregnancy success rate?

If increased pregnancy loss is due to an underlying generalized immune dysregulation, and if thyroid antibodies merely represent an indirect marker of the immune condition, then there is no proven medical intervention that can presently be proposed. It is worth mentioning that in a few isolated cases, short-term steroid administration or injections of immunoglobulins have been employed, with variable success, to modulate the immune response in women with recurrent abortions. Also, if mild thyroid underfunction does play a significant role, then this would constitute a good argument for systematically screening women (either before conception, when they express a desire of being pregnant or as soon as a pregnancy is ongoing) for the presence of TAI and/or mild thyroid insufficiency, in order to give these patients the potential benefit of L-T4 treatment. Finally, if delayed conception plays a significant role to decrease fertility in women with TAI, then this would constitute an argument for systematically screening infertile women, particularly when seeking medical advice for ART. In theory, women with TAI could be advised to plan for a pregnancy at a younger age, but such type of medical advice is more easily said than applicable in practice. In summary, a fascinating novel area of clinical research has recently arisen on the association between asymptomatic chronic autoimmune thyroiditis and the risk of pregnancy loss. Further research is needed to clarify the causal relationship (if any?) between TAI and recurrent abortion, to explore the mechanisms of pregnancy loss in women with TAI, and finally to evaluate whether therapeutic intervention trials, using thyroid hormones, could prove effective to help reduce pregnancy loss (Glinoer, 2002a).

Hypothyroidism during pregnancy: maternal aspects

Clinical epidemiology

The most common cause of primary hypothyroidism in women in reproductive age is chronic autoimmune thyroiditis. This occurs in both the goitrous and atrophic forms of the disease. Between 1 and 2% of women who become pregnant already receive L-T4 for hypothyroidism (Lazarus and Othman, 1991; Mestman *et al.*, 1995). In two population-based studies, the prevalence of elevated serum TSH concentrations was investigated systematically in the early part of gestation, in women without known hypothyroidism: overall, 2.5% of apparently healthy unselected pregnant women had elevated TSH levels. In one retrospective study (Klein *et al.*, 1991), serum TSH, free T4 and TPO-Ab were measured in 2000 pregnant women. Among these women, 49 had an elevated TSH (2.5% of the cohort) and six also a low free T4, hence yielding a prevalence of undisclosed overt hypothyroidism of 0.3%. Some 58% of the women with an elevated TSH tested positive for thyroid antibodies, compared with only 11% in euthyroid pregnant controls. The design of this study did not permit the investigators to determine whether women with an elevated TSH had a known thyroid disease (in which case they could have been taking an inappropriately low L-T4 dose or, alternatively, excessive doses of antithyroid drugs). In a more recent prospective population study (Glinoer *et al.*, 1994), systematic screening of a cohort of 1660 apparently healthy pregnant women showed that 2.2% of them had an elevated TSH during early gestation. In this study, all cases with known thyroid disease had been excluded. Thus, similar prevalences of undisclosed SCH were found, during the first half of gestation, in a retrospective American study (Klein *et al.*, 1991) and a prospective European study (Glinoer *et al.*, 1994).

Fetal microchimerism

A fascinating new topic in the field of autoimmunity and pregnancy is that of 'fetal microchimerism'; that is, the migration of fetal cells into maternal blood during pregnancy and the prolonged engraftment of fetal progenitor cells into maternal tissues. Recent studies have confirmed that microchimerism occurs within the thyroid gland in women with Hashimoto's and Graves' diseases. Although the functional consequences of persisting fetal microchimerism are not yet known and are only beginning to be explored, fetal cells engrafted into maternal tissues may possibly play a role in the aetiology of autoimmune thyroid diseases, and perhaps also in the modulation of autoimmunity during pregnancy (Klintschar *et al.*, 2001; Ando *et al.*, 2002; Imaizumi *et al.*, 2002).

Hypothyroidism and obstetric complications

As already alluded to, hypothyroidism has until recently been—wrongly—considered to be relatively rare during pregnancy, presumably because of the increased infertility and miscarriage rates associated with hypothyroidism (Thomas and Reid, 1987). Nowadays, this view has changed. Several studies have shown that when hypothyroid women become pregnant and maintain the pregnancy, they carry an increased risk for obstetric and fetal complications. The main obstetric complications that have been described in association with hypothyroidism are listed in Table III. Both maternal and fetal complications occur more frequently, and they are more severe when pregnant women present overt hypothyroidism, compared with SCH. In one recent study (Abalovich *et al.*, 2002), the authors showed that it was not so much the diagnosis of overt versus subclinical hypothyroidism that mattered in relation with the obstetrical complications, but rather the adequacy of L-T4 treatment given during pregnancy. Clearly, many data concerning obstetric repercussions refer to times when the correct diagnosis of hypothyroidism was perhaps not always correctly made before conception, or when L-T4 was given only during late gestational stages, or when thyroid function was not sufficiently monitored, or finally when the required adaptation of L-T4 doses was not systematically implemented (Lowe and Cunningham, 1991; Mestman *et al.*, 1995). In addition, these studies frequently mention the association with other deleterious conditions (hypertension or diabetes), which may also have increased the overall obstetric risks (Jovanovic-Peterson and Peterson, 1988). Even though relatively few reports have been made on pregnancy outcome in hypothyroid pregnant women left untreated, the available information shows that adequate L-T4 treatment greatly improves—but does not entirely suppress—the frequency of obstetric complications (Montoro *et al.*, 1981; Davis *et al.*, 1988; Liu *et al.*, 1994). In one study (Abalovich *et al.*, 2002), the authors showed that when hypothyroid patients were not rendered euthyroid, their pregnancy either ended in

Table III. Obstetric complications associated with hypothyroidism during pregnancy

	Frequency	%[a]	Hypo-thyroidism	Reference
Mother				
Anaemia	Increased	31	OH	Davis *et al.* (1988)
Post-partum haemorrhage	Increased	4	SCH	Leung *et al.* (1993)
	Increased	19	OH	Davis *et al.* (1988)
Cardiac dysfunction	Increased	NA	OH	Davis *et al.* (1988)
Pre-eclampsia	Increased	15	SCH	Leung *et al.* (1993)
	Increased	22	OH	Leung *et al.* (1993)
	Increased	44	OH	Davis *et al.* (1988)
	Increased	NA	OH	Mizgala *et al.* (1991)
Placental abruption	Increased	19	OH	Davis *et al.* (1988)
Fetus				
Fetal distress in labour	Increased	14	OH	Wasserstrum and Anania (1995)
Prematurity/low birth weight	Increased	31	OH	Davis *et al.* (1988)
	Increased	9	SCH	Leung *et al.* (1993)
	Increased	22	OH	Leung *et al.* (1993)
	Increased	13	OH	Abalovich *et al.* (2002)
Congenital malformations	Increased	4	OH	Leung *et al.* (1993)
	Increased	6	OH	Abalovich *et al.* (2002)
Fetal death	Increased	4	OH	Leung *et al.* (1993)
	Increased	12	OH	Davis *et al.* (1988)
	Increased	3	OH	Abalovich *et al.* (2002)
	Increased	8	OH	Allan *et al.* (2000)
Perinatal death	Increased	9–20	OH	Montoro *et al.* (1981)
	Increased	3	OH	Allan *et al.* (2000)

Percentages listed were taken (or recalculated) from the studies shown as References.
NA = non-appropriate; OH = overt hypothyroidism; SCH = subclinical hypothyroidism.

spontaneous abortion (in over 60% of cases) or led to an increased prevalence of preterm deliveries. Conversely, in pregnant hypothyroid women with adequate treatment, the frequency of abortions was minimal and, in general, the pregnancies were carried to term without complications (Abalovich *et al.*, 2002) (Figure 1).

Thyroid function in pregnant women with 'asymptomatic' TAI

A decade ago, a prospective longitudinal study was carried out in 1660 consecutive healthy pregnancies to evaluate the changes in thyroid function occurring in pregnant women who had thyroid autoantibodies, but were euthyroid during early gestation (Glinoer *et al.*, 1994). Among these women, 87 (5.2% of the cohort) were shown to have TAI with normal thyroid function tests at initial screening. Closely monitored during gestation and without administration of thyroid treatment or iodine supplements, the study showed that despite the expected decrease in thyroid antibody titres during gestation (Figure 2, left graph), thyroid function showed a gradual deterioration toward subclinical hypothyroidism in a significant fraction of TAI-positive women. Already in the first trimester, serum TSH (albeit within the normal range) was significantly shifted to higher values than in TAI-negative pregnant controls. Thereafter, serum TSH remained higher throughout gestation and, at parturition, 40% of TAI-positive women had a serum TSH >3 mU/l, with almost one-half of them exceeding 4 mU/l (Figure 2, upper right graph). Thus, TAI-positive women were able to maintain a normal thyroid function in the early stages of gestation, due to sustained thyrotrophic stimulation. At delivery, however, their serum free T4 was significantly lower than that in the antibody-negative controls, and their mean serum free T4 was at the lower limit of the normal range. The 30% average reduction in serum free T4 indicated that almost one-half of TAI-positive women had free T4 values below normal at the end of the pregnancy, hence confirming that these women had a reduced functional reserve associated with TAI (Figure 2, lower right graph). At the individual level, it was possible to predict the risk of progression to hypothyroidism, based on serum TSH levels and TPO-Ab titres: when serum TSH was >2.0 mU/l and/or TPO-Ab titre >1250 U/ml before 20 weeks, these markers were indicative of the propensity to develop hypothyroidism before the end of pregnancy. These observations are important, since they provide clinicians with simple tools to identify, during early gestational stages, those women who carry the highest risk. As a consequence, thyroid function can be closely monitored and preventive treatment with L-T4 administered, to avoid potential deleterious effects of hypothyroxinaemia on both maternal and fetal outcomes.

Therapeutic considerations

In a newly diagnosed hypothyroid pregnant patient, a full replacement L-T4 dose should be instituted immediately, assuming that there are no abnormalities in cardiac function. In order to normalize the extrathyroidal thyroxine pool more rapidly, therapy may be initiated by giving for 2–3 days a L-T4 dose which is two to three times the estimated final replacement daily dose; this will allow

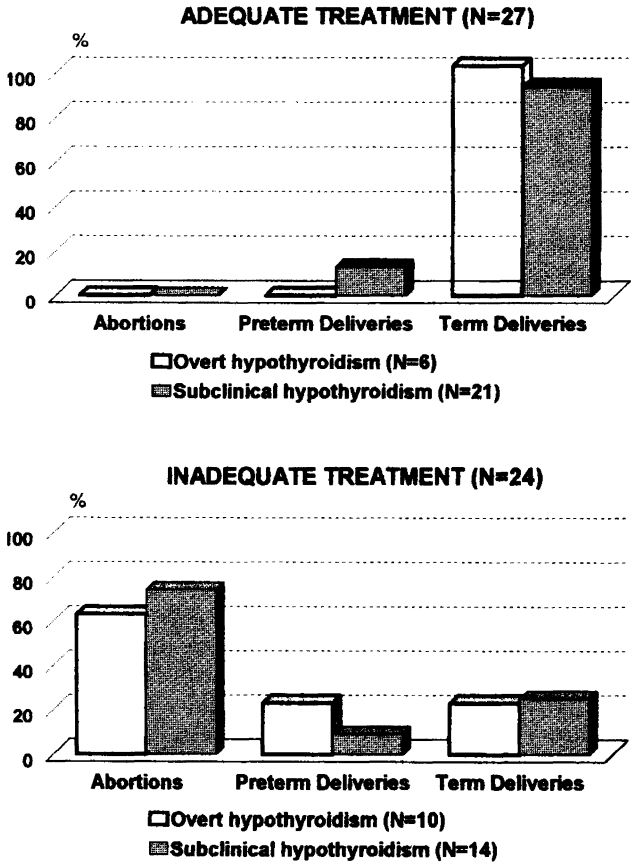

Figure 1. Pregnancy outcome (abortion, preterm and full-term deliveries) in relation with adequate (upper graph) versus inadequate (lower graph) treatment with L-thyroxine in pregnant women with known hypothyroidism, according to thyroid function at the time of conception. (Reproduced from Abalovich *et al.*, 2002; with permission of the authors and editor.)

more rapid normalization of circulating T4 levels and a more rapid return to the euthyroid state.

Several studies have now confirmed that L-T4 requirements in most—if not all—women with pre-existing hypothyroidism increase significantly during pregnancy (mean increment of ~50%). Several physiological reasons explain the increased hormone requirements. They include the estrogen-induced increase in thyroxine-binding globulin (TBG) concentrations, the increased volume of distribution of thyroid hormones (hepatic, feto-placental unit) and the increased placental T4 transport and degradation (Glinoer, 1997; 2002b). The adjustment of L-T4 doses should be implemented early, preferably within the first trimester of pregnancy. If the pregnancy is planned, the patient should have thyroid function tests soon after the missed menstrual period. If serum TSH is not increased at that time, tests should be repeated at 8–12 weeks and 20 weeks, as the increase in hormone requirements may not become apparent until later during gestation (Costante *et al.*, 1987; Tamaki *et al.*, 1990).

The magnitude of the increment in L-T4 doses (above preconception) depends in part upon the aetiology of hypothyroidism. Women with a history of radioiodine ablation for hyperthyroidism or thyroid surgery for cancer (i.e. without residual thyroid tissue) require a mean L-T4 increment of ~50%, whereas women with Hashimoto's disease (i.e. with residual functional thyroid tissue) require a smaller increment, of ~25%. It is important to remember also that 25% of women with a normal serum TSH in the first trimester, and 35% of those with a normal serum TSH in the second trimester, will later require an increase in L-T4 dose (Kaplan, 1992). Finally, the need to adapt L-T4 doses is extremely variable among hypothyroid patients. Therefore, treatment monitoring should be tailored individually, although the general guidelines given above remain valid (McDougall and Maclin, 1995; Roti *et al.*, 1996). Finally, women with SCH, who already take small L-T4 doses before pregnancy, may not systematically require an increase during gestation (even though they frequently do), if their functional reserve is sufficient. After delivery, L-T4 doses should be reduced progressively to pregestational doses and serum TSH rechecked during the post-partum period (Mandel *et al.*, 1990; 1993).

Hypothyroidism during pregnancy: fetal aspects

In general, infants born to hypothyroid mothers appear healthy and without evidence of thyroid dysfunction, provided that there was no severe iodine deficiency *in utero*. Clearly, maternal hypothyroidism during pregnancy raises a serious concern about long-lasting psychoneurological consequences for the progeny, due to the risk of an insufficient placental transfer of maternal thyroid hormones to the developing fetus during the first half of gestation; that is, before the fetal thyroid becomes functional. Because of the importance of such potential consequences, this topic has been extensively reviewed and is only summarized here (see reviews by Porterfield and Hendrich, 1993; Glinoer and Delange, 2000; Morreale de Escobar *et al.*, 2000; Smallridge and Ladenson, 2001).

Since the fetal thyroid gland becomes operational only after mid-gestation, thyroid hormones transferred transplacentally from mother to fetus are important, both before and after the onset of fetal thyroid function (Contempré *et al.*, 1993; Calvo *et al.*, 2002). It is presently considered that 30% of serum T4 levels measured at birth in cord blood are still of maternal origin (Vulsma *et al.*, 1989). Development of the fetal brain (with neuronal multiplication, migration and architectural organization) during the second trimester corresponds to a phase during which the supply of thyroid hormones to the growing fetus is almost exclusively of maternal origin. During later phases of fetal brain development (with glial cell multiplication, migration and myelinization), from the third trimester onwards, the supply of thyroid hormones to the fetus is essentially of fetal origin. Therefore, while severe maternal hypothyroidism during the second trimester will result in irreversible neurological deficits, maternal hypothyroxinaemia occurring at later stages will result in less severe, and also partially reversible, fetal brain damage.

In disease, three sets of clinical disorders ought to be considered, and are illustrated schematically in Figure 3. For infants with a defect of thyroid gland ontogeny leading to congenital hypothyroidism, the participation of maternal hormones to the fetal circulating T4 environment remains unaffected, and therefore the risk of brain damage results exclusively from insufficient fetal thyroid hormone production. In contrast, when only the maternal thyroid gland is deficient, such as in women with TAI, it is both the severity and temporal occurrence of maternal hypothyroidism that drive the resulting consequences for fetal neuronal development. Finally in iodine deficiency, both maternal and fetal thyroid functions are affected, and it is the

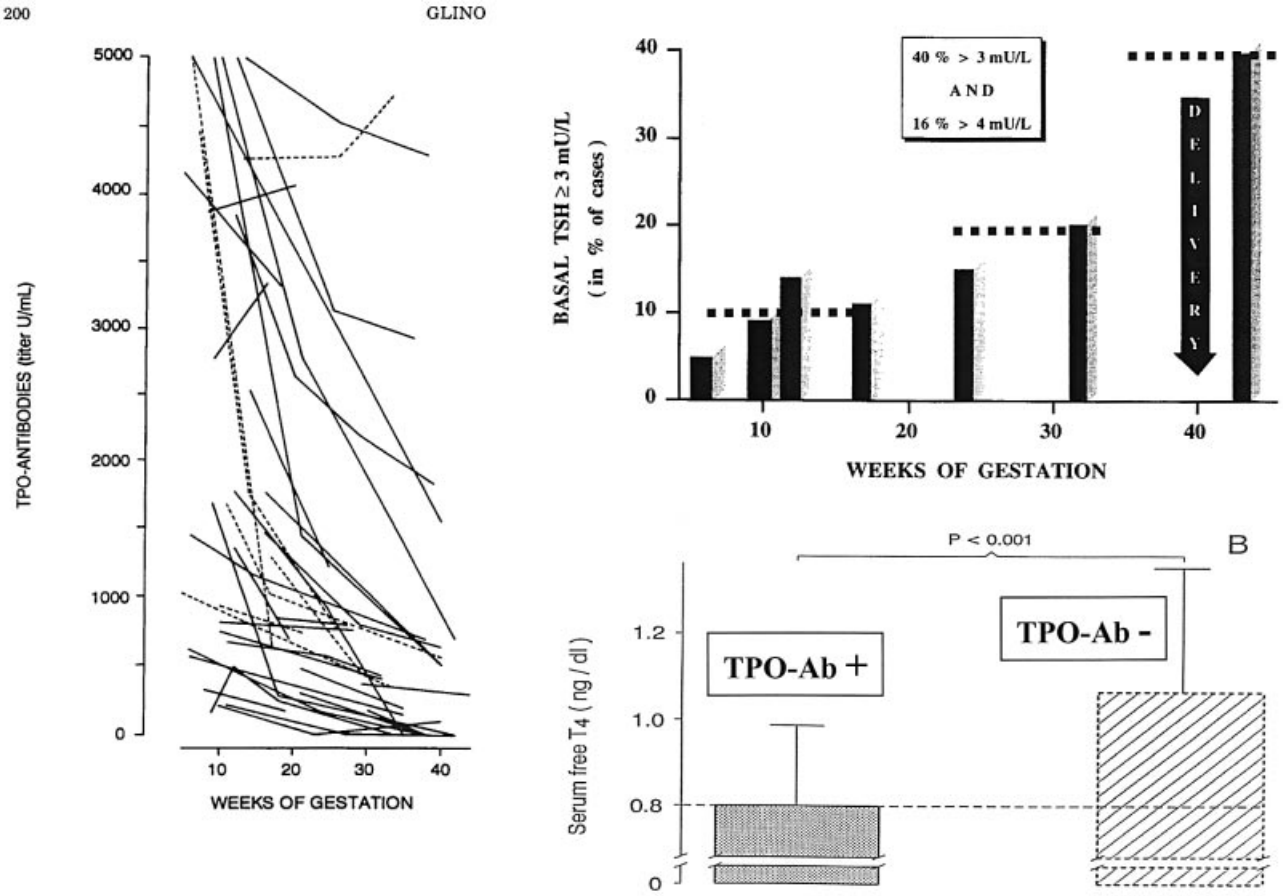

Figure 2. Left: Individual patterns of changes in thyroid antibodies (TPO-Ab) in women with thyroid autoimmunity (TAI) during gestation (dotted lines: hypothyroid women; solid lines: euthyroid women at conception). The graph shows the immunosuppressive effect of pregnancy, with a 50% average TPO-Ab titres reduction, between 10–40 weeks gestation. Right upper: Bars show the proportion of women with TAI in whom serum thyroid-stimulating hormone (TSH) was >3 mU/l, as a function of gestational age; this reached 10% during the first trimester, 20% during the second trimester, and up to 40% immediately after parturition. Right lower: Mean serum free thyroxine (T4) concentrations in women with or without TAI at the end of gestation. In women with TAI, serum free T4 was significantly reduced, with a mean at the lower limit of normality. (Reproduced from Glinoer *et al.*, (1994) *J. Clin. Endocrinol. Metab.*, **79**, 197–204 with permission of The Endocrine Society and Glinoer and Delange, 2000; with permission of the authors and editor).

degree and precocity of iodine deficiency during pregnancy that drive the potential repercussions for fetal neurological development (Glinoer and Delange, 2000). In 1999, Haddow and colleagues reported the results of a prospective investigation of neuropsychological development in children aged 7–9 years, born to mothers with variable degrees of thyroid deficiency during pregnancy (Haddow *et al.*, 1999). For this aim, the investigators recruited 62 children born to women who had a serum TSH, at 17 weeks gestation, above the 98th percentile of healthy pregnant controls. Neuropsychological testing of these children (and appropriate controls) included performances relating to intelligence, attention, language, reading abilities, school performance and visual-motor performance. The study children performed less well on all tests, and their mean IQ score was 4 points below that of the controls. When the performances were analysed in the children born to hypothyroid mothers left untreated, nine out of 15 tests scored significantly lower, and the average IQ difference reached 7 points, compared with the control children. In contrast, the children born to hypothyroid (but L-T4-treated) mothers had IQs similar to those of the control children. Finally, it is noteworthy that 77% of the mothers in this study had TAI, confirming that chronic asymptomatic autoimmune thyroid disease was the most frequent underlying cause of maternal hypothyroxinaemia.

What can be learned from these studies?

Haddow's recent study underlines the notion that maternal thyroid underfunction (even when it is mild or 'subclinical') during pregnancy, may be associated with an impairment of normal brain development in the offspring. Such impairment may ultimately result from a combination of factors related to perinatal hypothyroidism. When already present in the first half of gestation, maternal hypothyroxinaemia represents a risk for an impaired fetal brain development, because of insufficient transfer of thyroid hormones to the feto-placental unit. Furthermore, in most circumstances where a woman's thyroid function is defective, hypothyroxinaemia is not restricted to the first trimester and hypothyroidism tends to worsen as gestation progresses, especially if left undiagnosed and untreated. Therefore, the fetus may also be deprived of adequate amounts of thyroid hormones during later neurological maturation and development.

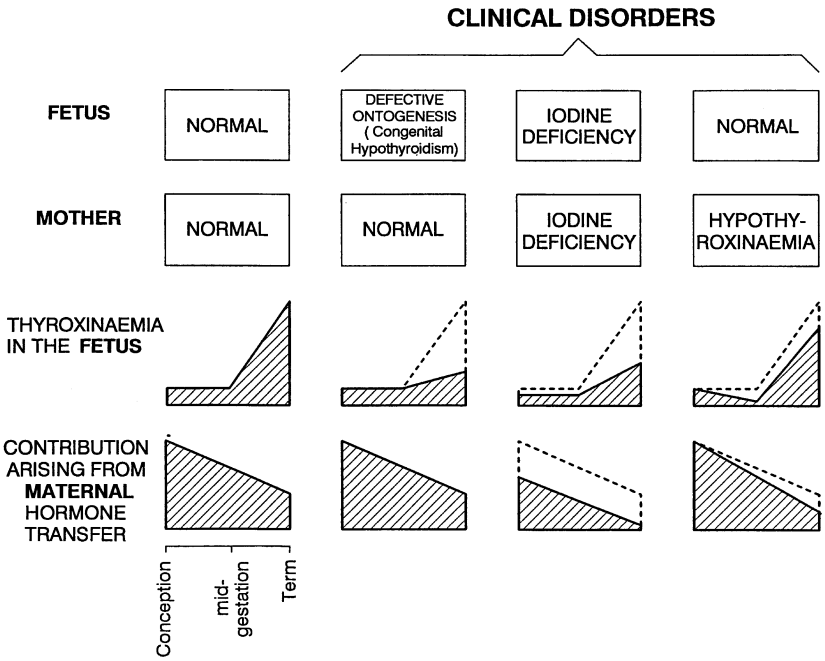

Figure 3. Schematic representation of the three sets of clinical conditions that may affect thyroid function in the mother alone, the fetus alone, or the feto-maternal unit, showing the relative contributions of an impaired maternal and/or fetal thyroid function, that may eventually lead to alterations in fetal thyroxinaemia. (Reproduced from Glinoer and Delange, 2000; with permission of the authors and editor.)

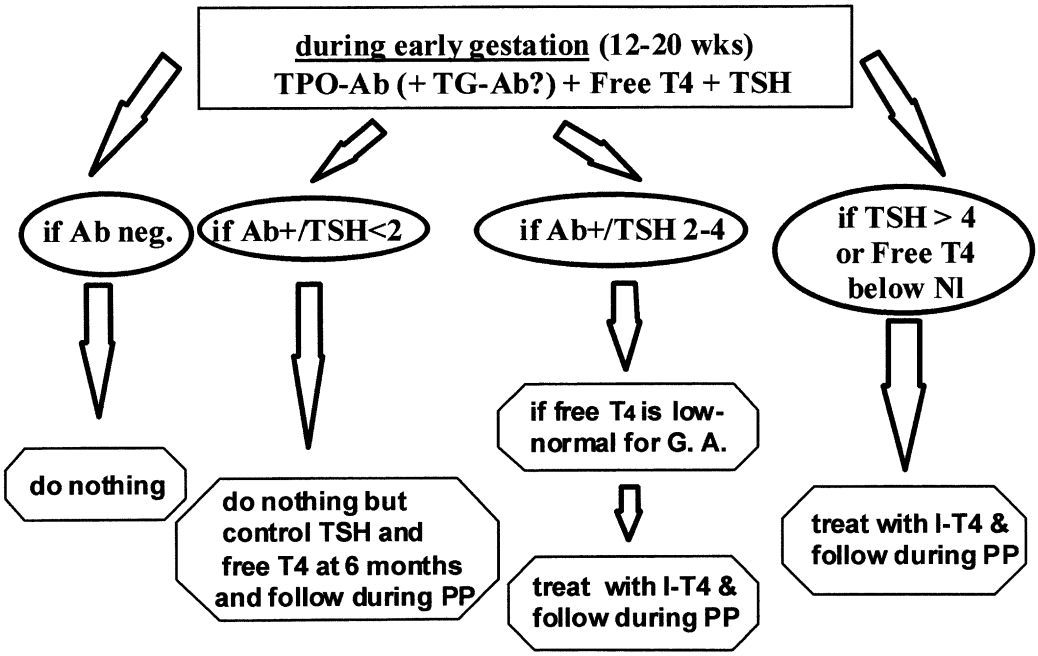

Figure 4. A proposed algorithm for the systematic screening of thyroid autoimmunity (TAI) and hypothyroidism during pregnancy, based on the determination of thyroid antibodies (Ab), serum thyroid-stimulating hormone (TSH) and free T4 (fT4) concentrations during the first half of pregnancy. GA = gestational age; NL = normal limits; PP = post-partum. (Reproduced from Glinoer, 1998; with permission of the author and editor).

Systematic screening for TAI and hypothyroidism

Because thyroid disorders related to TAI are common in young female subjects, SCH may often remain undiagnosed (Weetman, 1992; Weetman and McGregor, 1994; Baker, 1997). Thus, there is a justification to propose the systematic screening for TAI and hypothyroidism in pregnancy (Glinoer, 1998). Among possible algorithms, the following scheme has been proposed and is

outlined in Figure 4. As a first step, serum TSH and thyroid antibodies should be measured in early gestation. Based on recent findings that hypothyroxinaemia might perhaps occur in some women without a concomitant serum TSH elevation, it appears reasonable to include systematically a free T4 determination in the algorithm (Pop *et al.*, 1999; Morreale de Escobar *et al.*, 2000). When serum TSH is elevated or free T4 is clearly below normal, irrespective of the presence (or absence) of TAI the woman should be considered as highly suspect of having thyroid underfunction and treated with L-T4 throughout pregnancy. The second step in the algorithm concerns women with TAI and a normal thyroid function. We propose to base the medical response on serum TSH measured during early pregnancy. When serum TSH is <2 mU/l (most frequently associated with low antibody titres and normal free T4 levels), systematic L-T4 treatment is not warranted, but serum TSH and free T4 should be monitored during later gestation, preferably at the end of the second trimester. For women with TAI and a serum TSH that is still within the normal range, but already between 2–4 mU/l in early gestation (most frequently associated with higher antibody titres and low-normal free T4 levels), physicians should consider treatment with L-T4. It is important to keep in mind that serum TSH is down-regulated (under the influence of peak hCG values) during the first half of gestation (TSH nadir around 9–14 weeks), and also that the thyroid deficit tends to deteriorate as gestation progresses in TAI-positive women (Glinoer *et al.*, 1990; 1994). Because the potential deleterious effects (for both mother and progeny) are not due to high serum TSH *per se* but to low free T4 concentrations, clinical judgement should be based on serum free T4: if low or low to normal for gestational age, then treatment with L-T4 is probably justified. In daily practice, when such a scheme is systematically applied, most—if not all—of the pregnancies followed are successful and uneventful (Rotondi *et al.*, 1999). Clearly, more prospective studies are needed to assess the final clinical relevance of such scheme. Even though there is not as yet sufficient direct evidence for the advantage of treating pregnant women with SCH, many indirect arguments suggest that no harm can be done and that L-T4 treatment can only be beneficial for both the patient and her offspring. Finally, the systematic screening for TAI during early pregnancy should also allow the delineation of a subgroup of women who are prone to developing thyroid dysfunction after parturition. Thus, even when no specific treatment is warranted during gestation, systematic screening will be of great help to clinicians for organizing a close monitoring of post-partum thyroid dysfunction (Kamijo *et al.*, 1990; Matsuura and Konishi, 1990; Glinoer, 2000).

Conclusions

Pregnancy affects the natural course of thyroid autoimmunity and, conversely, TAI affects the course of pregnancy. In the present review, an attempt was made to describe the present knowledge and concepts concerning the complex relationships that link TAI and hypothyroidism with female and male infertility, as well as abnormalities occurring during pregnancy, such as pregnancy loss and maternal and fetal repercussions associated with hypothyroidism. With regard to infertility, and even though the clinical relevance of TAI remains somewhat controversial, when all available information is considered together, the results strongly suggest that in infertility due to well-defined female causes, autoimmunity is involved and TAI constitutes, at least, a useful marker of the underlying immune abnormality, independently of thyroid function disorders. With regard to pregnancy loss, most available studies clearly have established that TAI, even without overt thyroid dysfunction, is associated with a significant increase in the risk of miscarriages. To find an association, however, does not imply a causal relationship, as the aetiology of increased pregnancy loss associated with TAI remains presently incompletely understood. With regard to maternal repercussions during gestation, the main risk associated with TAI is the occurrence of hypothyroidism and obstetric complications (e.g. premature birth, pre-eclampsia). Thus, systematic screening of TAI and hypothyroidism during early pregnancy, monitoring of thyroid function, administration of L-thyroxine treatment in selected cases and follow-up during the post-partum period have proved to be helpful and important in order to manage these patients adequately. Finally, with regard to potential repercussions affecting the offspring, recent evidence suggests that maternal thyroid underfunction—even when it is considered mild (or subclinical)—may be associated with an impairment of fetal brain development. When present only during the first half of gestation, maternal hypothyroxinaemia is a risk factor for impaired fetal brain development, due to insufficient transfer of maternal thyroid hormones to the feto-placental unit. When hypothyroidism is not restricted to the first trimester and worsens with the progression of gestation (untreated hypothyroidism), the fetus may also be deprived of adequate amounts of thyroid hormones during later neurological maturation and development, leading to poorer school performances and lower IQs. Although, during the past decade, new and important information has been gathered that has considerably helped to improve our understanding of the intricate interrelationships between thyroid autoimmunity disorders and hypothyroidism with both pre-gestational and gestational abnormalities, much remains to be learned and better understood through future research and prospective intervention trials.

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