Autoimmune thyroid diseases and pregnancy

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Abstract: Thyroid autoimmunity affects 5–20% of the female population of childbearing age. Even in the absence of overt maternal thyroid dysfunction, thyroid autoimmunity has been reported to be associated with an increased risk of adverse pregnancy outcomes and impaired fetal neurodevelopment. Present evidence indicates that thyroid autoimmunity poses a risk for miscarriage and preterm delivery. By contrast, with regard to infertility most studies failed to find significantly different likelihood of pregnancy in euthyroid women with and without thyroid antibodies undergoing assisted reproduction procedures. Finally, uncertainty surrounds the role of thyroid autoantibodies on fetal and neonatal outcomes, since an increased risk for perinatal death, intrauterine growth restriction (IUGR), and respiratory distress syndrome has been inconsistently reported, and only few studies addressed the impact of maternal thyroperoxidase antibodies (TPOAbs) during pregnancy on cognitive functioning of the child, once again providing mixed results. Whether thyroid antibodies have a direct effect on neonatal outcomes, including neurodevelopment in the progeny, or whether the observed associations are related to maternal autoimmune-related thyroid insufficiency needs to be still clarified.

Keywords: Pregnancy; thyroperoxidase antibody (TPOAb); thyroid insufficiency

Introduction

Thyroid autoimmunity is more common in women than in men and affects 5–20% of the female population of childbearing age (1,2). The spectrum of thyroid autoimmune disorders includes clinically heterogeneous conditions, such as Hashimoto thyroiditis (HT)—characterized by a primarily T cell-mediated autoimmunity, and Graves' disease (GD)—sustained by a predominately humoral autoimmunity (3). During gestation, the clinical course of both HT and GD is significantly influenced either by changes occurring in maternal thyroid economy or by the condition of lowered immune responsiveness taking place throughout pregnancy (4). Even in the absence of overt maternal thyroid dysfunction, thyroid autoimmune diseases have been reported to be associated with an increased risk of adverse pregnancy outcomes,

ranging from pregnancy loss and premature delivery to intrauterine growth restriction (IUGR) and impaired fetal neurodevelopment, among others (5). In addition, a large body of evidence has been provided, showing significant impacts of thyroid autoimmunity on female fecundity and infertility treatment success (6,7). Although knowledge of mechanisms underlying the observed associations is largely incomplete, several factors are more likely involved. These may include, either alone or in combination, general immune diathesis in the woman, possibly affecting the female reproductive system, subtle thyroid dysfunctions, predisposing genetic backgrounds, along with as yet unidentified factors.

This article will focus on the impact of HT on maternal thyroid function, and will examine the association between HT, fertility and obstetric/fetal complications.

Thyroid autoimmunity in pregnancy: epidemiology and impact on maternal thyroid function

HT is the most common autoimmune disorder in women of reproductive age (1,2,8). The reported frequency of thyroperoxidase antibody (TPOAb) and/or thyroglobulin antibody (TgAb) positivity in unselected populations of pregnant women ranges from 2% to 17%, depending on several factors (9).

Results of studies exploring thyroid autoimmunity among pregnant women from different ethnic groups overall provided mixed results, with some showing ethnicity to be a contributing factor to thyroid autoimmunity (10-12) and other not confirming this finding (13-15).

Because of the physiological decline in thyroid autoantibodies with pregnancy progression, different antibody testing times across gestation may also account for the broad variability in the prevalence of thyroid autoimmunity in the pregnant population. Indeed, pivotal studies carried out by Glinoer et al. in the 1990s (16,17) showed that thyroid antibody titers decreased (on the average, by 60%) over the course of gestation, and tended to become undetectable in the third trimester. These findings have been repeatedly confirmed thereafter (18-21), thus indicating the diagnostic accuracy of thyroid autoantibody measurements to be closely related to the gestational age they are obtained. Such notion is of utmost relevance for the diagnosis and management of thyroid disease during pregnancy, since the risk of impaired thyroid function is still increased in women in whom TPOAbs become negative, and increased surveillance may be recommended.

An additional factor seemingly accounting for the high variation in the prevalence of thyroid antibody positivity among pregnant women is dietary iodine intake. Epidemiological studies in non-pregnant populations suggest that thyroid autoimmunity is more prevalent in areas where iodine intake is adequate or more than adequate than in iodine-deficient areas (22). Also, there is evidence of enhanced thyroid autoimmunity following the implementation of iodine prophylaxis programs (23). Mechanisms postulated to explain the iodine-induced thyroid autoimmunity include an increased immunogenicity of a highly iodinated thyroglobulin, a toxic effect of iodine on thyroid cells, and a direct stimulation of immune cells by iodine. Concerning gestation, a recent cross-sectional study on a large cohort of pregnant women from an iodine sufficient region found the prevalence of TPOAb positivity

to be significantly higher in women with both the highest and the lowest iodine intake compared to iodine sufficient pregnant women (24). While the increased prevalence of thyroid autoimmunity among women with the highest iodine intake is an expected finding, the observed equally high prevalence in the opposite condition of iodine intake is an intriguing, though unexplained, result that needs further consideration.

Finally, estimates of thyroid autoimmunity prevalence during pregnancy are generically biased by methodological differences between assays and the different cut-off points employed in various studies.

Whatever the prevalence and factors influencing thyroid autoimmunity in pregnancy, this condition is associated with an increased risk for the mother of both gestational thyroid failure and post-partum thyroid dysfunction.

In the above mentioned prospective study, Glinoer et al. (16) showed a trend towards higher first trimester thyroid stimulating hormone (TSH) levels in TPOAb positive euthyroid pregnant women than in women without evidence of thyroid autoimmunity. Furthermore, serum free T4 levels were found to be significantly lower in the former, with more than 40% of women with thyroid autoimmunity presenting with free T4 levels in the range of hypothyroid values during late gestation (16). Similar results have been subsequently reported in both intervention and observational studies, overall indicating TPOAb positivity at early gestation to be a good predictor of gestational hypothyroidism (25-27).

Mechanisms underlying gestational thyroid insufficiency in women with thyroid autoimmunity are related to a maternal thyroid function capacity that is inadequate to meet the growing demand for hormone production imposed by pregnancy (28). In particular, during the first trimester, thyroid gland is directly stimulated by chorionic gonadotropin (CG), which act as a thyrotropic agonist. In addition, the increase in serum thyroxine binding globulin (TBG) levels, which occurs from the first trimester onwards, is responsible for an increase in total T4 and T3 serum concentrations and a contextual decrease in free thyroid hormone levels. In response to the latter event, following the 1st trimester a slight but definite trend towards an increase in TSH levels occurs, which further promotes thyroid hormone output (about 50% over gestation). The increased hormone production by the maternal thyroid gland is designed to reach the new equilibrium state, and can be achieved provided that the thyroid gland is functionally intact and the iodine intake adequate to the

increased demands of pregnancy (29). Thus, due to the underlying cell damage, the gland involved by thyroiditis displays a reduced ability to respond to both hCG and TSH stimulation, and adequate hormone synthesis and secretion may be not ensured for the whole gestational period. Moreover, in HT thyroid efficiency might be undermined by the concomitant reduction of thyroidal iodine stores, because of an increased turnover of thyroidal iodine under sustained TSH stimulation (30).

Despite this functional impairment, a gradual decrease in the titres of thyroid antibodies during the course of pregnancy is usually observed in HT women, as a result of a pregnancy-induced state of immunological tolerance (4). Similar changes in autoantibody pattern also occur in pregnant women with GD, in whom the level of autoantibodies against the TSH receptor (TRAbs) typically falls during the second half of pregnancy. Accordingly, a spontaneous reduction in serum free T4 and T3 fractions is usually observed at this stage of gestation, which is also sustained by the concomitant rise in maternal serum TBG levels (4,28).

The documented amelioration of thyroid autoimmunity during pregnancy is part of a much wider pattern of immunological changes of the mother during gestation, ultimately aimed at avoiding the fetus to be rejected as foreign tissue, while maintaining the mother and fetus protected against infections. Mechanisms underlying gestational immune tolerance involve a complex interplay between hormonal factors, immunological molecules of trophoblast origin and specific T-cell subsets [regulatory T (Treg) cells] generated within the maternal decidua. As well as maintaining fetal alloantigen tolerance, Treg cells migrating to the maternal circulation indirectly induce a state of generalized and transient immune-suppression, which might explain the observed amelioration of (most) coincidental autoimmune diseases during gestation (4,31,32). In line with this, the abrupt fall of T_{REG} cells following delivery provides an explanation for the rebound of post-partum thyroid autoimmunity, with either worsening/re-exacerbation of GD or occurrence of post-partum thyroiditis in predisposed women (33-35).

Thyroid autoimmunity and infertility

Epidemiological studies clearly show the prevalence of thyroid autoimmunity to be higher among infertile women than among fertile women (6). Despite the large number of studies specifically aimed at investigating the association

between thyroid autoimmunity and infertility, this issue still remains a matter of debate. Indeed, the strength of pertinent evidence is relatively burdened by a number of biases, such as differences in size, ethnicity and iodine intake of the studied populations, variable sensitivity and cut-offs employed for thyroid antibody detection, along with the retrospective and uncontrolled design of the vast majority of the studies. Despite these limitations, an overall higher relative risk of 2.1 of thyroid antibody positivity has been estimated in infertile women (6,36,37). Infertility is defined as the failure to achieve a successful pregnancy following 12 months of unprotected intercourse or therapeutic donor insemination. Both male and female factors may be responsible for infertility, although in approximately 15% to 30% of infertile couples the underlying cause remains unexplained using standard fertility investigations (38). Interestingly, a recent meta-analysis summarizing data from 334 patients with anti-thyroid antibodies and 1,679 controls, found the risk of unexplained subfertility to be significantly associated with the presence of thyroid antibodies [odds ratio (OR) 1.5, 95% confidence interval (CI): 1.1–2.0] (39).

Early (and mild) maternal thyroid failure has been brought into play to explain the observed reduction in implantation rate in women with thyroid autoimmunity seeking a pregnancy. Indeed, T3 controls follicle stimulating hormone and luteinizing hormone action on steroid biosynthesis, and TSH and thyroid hormone receptors have been located in human granulosa cells and in human oocytes at different stages of follicular development (7,40). Therefore, even mild hypothyroidism might theoretically affect oocyte quality and function, eventually leading to subfertility. Several studies have examined the question of whether subclinical hypothyroidism could affect fertility, and results have been collectively inconsistent. Indeed, the prevalence of mildly supra-normal TSH levels in infertile women has been reported to be either similar (41,42) or increased (43) as compared to fertile controls, whereas two uncontrolled studies showed levothyroxine (LT4) treatment to increase the likelihood of spontaneous conception in subclinically hypothyroid women (44,45). In the setting of assisted reproduction, the vast majority of the studies failed to find significant differences in fertility outcomes between women with very mild TSH elevations and those with normal TSH values (<2.5 mU/L). Nonetheless, in a meta-analysis of randomized clinical trials assessing the effect of LT4 supplementation on pregnancy outcome in subfertile women with subclinical hypothyroidism and/or thyroid autoimmunity undergoing assisted reproduction

technologies (ARTs), LT4 treatment resulted in a significantly increased delivery rate [pooled relative risk (RR) 2.76, 95% CI: 1.20–6.44; P=0.018] and a lowered miscarriage rate (MR) (pooled RR 0.45, 95% CI: 0.24–0.82; P=0.010) compared to placebo/no treatment (46).

In a context of generalized immune imbalance, a direct role for either thyroid antibodies or other autoantibodies has also been suggested to play a critical role in female infertility. Indeed, thyroid autoimmunity often coexists with other autoimmune abnormalities, which may be either associated with or directly responsible for subfertility. By way of example, some studies reported of a strong association between thyroid autoimmunity and endometriosis (42,43,47,48). The latter is found in 20–50% of infertile women and has been frequently associated with a variety of both organ-specific and non-specific serum autoantibodies, in some cases specifically targeting endometrial antigens (49). Furthermore, up to 30% of women with premature ovarian failure (POF) have a concurrent autoimmune disease, amongst which thyroid autoimmunity is the most prevalent condition (25–60%) (50). In this context, a role for autoimmunity in pathophysiology of POF has been proposed, mainly because of the presence of a number of serum anti-ovarian autoantibodies and the evidence of histopathological features of autoimmune oophoritis (51).

A direct role of anti-thyroid antibodies in affecting fertility has been postulated in 2011 by Monteleone and co-workers in what the authors called the "ovarian follicle hypothesis" (52). In that study, TgAb and TPOAb were measured in both follicular fluid and serum on the day of oocyte retrieval from euthyroid infertile women with thyroid autoimmunity undergoing *in vitro* fertilization (IVF). Anti-thyroid antibodies were measurable in follicular fluid, and their levels were significantly correlated with serum concentrations. In addition, decreased rates in oocytes fertilization, top quality embryos, and pregnancies, along with an increase in early MR were found among women with anti-thyroid antibody positivity. On the basis of their findings, the Authors concluded that anti-thyroid antibodies might be responsible for both antibody mediated cytotoxicity in the growing ovarian follicle and damage to the maturating oocyte, thus impairing its quality and developmental potential (52). On the other hand, thyroid antibodies were also suggested to alter fertility by targeting zona pellucida, since the zona pellucida and thyroid tissue seem to share similar antigens (51). Such a hypothesis would be supported by the observation that pregnancy rates

following intracytoplasmic sperm injection (ICSI), which requires no interaction between the sperm cell and the zona pellucida, are similar in women with or without thyroid autoimmunity (53).

The impact of thyroid autoimmunity on IVF/ICSI cycles has been recently systematically reviewed and meta-analyzed (7). The primary outcome of the study was the assessment of live birth rate (LBR), and secondary outcomes were number of oocytes retrieved (NOR), fertilization rate (FR), implantation rate (IR), clinical pregnancy rate (CPR) and MR. Overall 12 cohort studies (6 prospective and 6 retrospective) fulfilled the selection criteria, for a total of 4,876 women, of which 700 with and 4,176 without thyroid autoimmunity. Overall, the pooled analysis showed that, while not affecting IVF/ICSI in terms of NOR and likelihood of fertilization, implantation and CPR, thyroid autoimmunity might compromise pregnancy outcome by inducing an increased risk of miscarriage (OR 1.44, 95% CI: 1.06–1.95) and a decreased chance of live birth (OR 0.73, 95% CI: 0.54–0.99) (7). At variance with these findings, two additional studies not included in the above meta-analysis failed to demonstrate a significant role of thyroid autoimmunity on IVF/ICSI outcome data in infertile women. In particular, in a prospective case-control study Sakar *et al.* (54) showed comparable pregnancy and MRs comparing 31 anti-thyroid antibody positive women and 121 anti-thyroid antibody negative after intracytoplasmic sperm injection-embryo-transfer (ICSI-ET). Unuane and co-workers (55) retrospectively investigated the association between thyroid autoimmunity and fertility outcome following one treatment cycle of intrauterine insemination (IUI). Comparison of euthyroid women with (n=187) and without (n=2,956) TPOAb positivity revealed no significant differences in live birth delivery, pregnancy and MR, nor significant differences were observed when women with a TSH value between 2.5 and 5 mIU/L before IUI were compared to women with a TSH value <2.5 mIU/L. Based on their results, the Authors concluded that neither TPOAb positivity nor TSH ≥2.5 mIU have negative effects on IUI outcome (55).

Overall, most studies in euthyroid women undergoing ART procedures have not found significantly different likelihood of pregnancy in women with thyroid antibodies, thus supporting the idea that thyroid auto-antibodies, while playing a more pronounced effect over the course of pregnancy, would not affect fertilization and implantation (5). Whether mild alterations in TSH and/or T3–T4 levels associated with thyroid autoimmunity may negatively influence oocyte quality and function, thereby

lowering the chance of a successful pregnancy, is controversial and needs to be further investigated. At the same time, there is evidence that LT4 therapy improves the success of pregnancy following ART in subclinically hypothyroid women with thyroid antibodies and, though with a lower quality of evidence, in euthyroid TPOAb positive women.

Thyroid autoimmunity: obstetric and fetal outcomes

Miscarriage and preterm delivery are the most common obstetric complications in pregnant women with HT (6). Miscarriage is a spontaneous pregnancy loss occurring before 20 weeks of gestation. Often miscarriages occur earlier, within the first weeks of gestation, and when they occur two or more times are defined recurrent. Overall, the prevalence of miscarriage is between 15% and 25% of the all pregnancies (56). Delivery is defined as "preterm" when birth occurs before 37 weeks of gestation, and as "very premature" when birth occurs before 34 weeks of gestation.

A doubling of the prevalence of miscarriages in euthyroid TPOAb positive pregnant women compared to TPOAb negative was first reported by Stagnaro-Green and co-workers in 1990 (57). More recently, the above association has been systematically reviewed and meta-analyzed by pooling data of 12,126 women from 19 cohort and 12 case-control studies (58). Meta-analysis of the cohort studies showed more than tripling in the odds of miscarriage with the presence of thyroid autoantibodies (OR 3.90, 95% CI: 2.48–6.12; P<0.001). In addition, meta-analysis of five cohort studies, overall including 12,566 women, and evaluating the association between thyroid autoantibodies and preterm birth, showed a significant increase in the odds of preterm birth in the presence of thyroid autoantibodies (OR 2.07, 95% CI: 1.17–3.68; P=0.01) (58). Similarly, van den Boogaard found the risk of both miscarriage and recurrent miscarriage to be significantly increased in thyroid antibody positive pregnant women as compared to thyroid antibody negative women (OR for miscarriage 3.73, 95% CI: 1.8–7.6; OR for recurrent miscarriage 2.3, 95% CI: 1.5–3.5). The above association was still confirmed when only studies using age-matched control groups were considered (OR 5.4, 95% CI: 1.8–16) (39). This finding is of relevance, since older age is a recognized independent risk factor for miscarriage (59,60), and a meta-analysis showed TPOAb positive pregnant women to have slightly higher age (age difference, 1.29 years, 95% CI: 0.43–2.16, P=0.003) than those without thyroid autoimmunity (61).

Thus, while remaining plausible that older age in thyroid antibody positive women may contribute to explain some of the increased risk of miscarriage, a number of other independent harmful factors - such as karyotype abnormalities, antiphospholipid antibody syndrome, uterine malformations, cervical incompetence - may circumstantially be involved in early fetal loss. Among these, a role for even mild serum TSH elevations has been increasingly suggested by findings from both observational and intervention studies. In the above quoted meta-analysis, Chen and colleagues showed women with thyroid autoimmunity to have slightly higher TSH levels compared with those without thyroid autoimmunity (TSH difference, 0.61 mIU/L, 95% CI: 0.51–0.71, P<0.00001) (61). A large prospective cohort study involving more than 3,000 iodine-sufficient pregnant women, recruited at 4–8 weeks of gestation, showed the combination of thyroid autoimmunity and increased TSH levels to be more heavily associated with miscarriage (62). In particular, compared to euthyroid women, the adjusted ORs for miscarriage progressively decreased from 9.56 (95% CI: 3.76–24.28, P=0.000) and 4.96 (95% CI: 2.76–8.9, P=0.000) among thyroid antibody positive women and TSH levels of 5.22–10 and 2.5–5.22 mIU/L, respectively, to 3.4 (95% CI: 1.62–7.15, P=0.002) in thyroid antibody negative women and TSH levels of 5.22–10 mIU/L, and to 2.71 (95% CI: 1.43–5.12, P=0.002) in thyroid antibody positive women and TSH values <2.5 mIU/L. Conversely, antibody negative women with TSH values within the reference range for the pregnant population (i.e., <5.22 mIU/L) did not have an increased risk of miscarriage (62).

Overall, intervention studies investigating the effectiveness of LT4 treatment in euthyroid or mildly hypothyroid women on fetomaternal outcomes have provided inconsistent results. Some of the observed discrepancies are likely explained by different TSH thresholds used to define maternal euthyroidism (from below 2.5 up to 5.0 mU/L), along with significant differences in the design of the studies, with some enrolling euthyroid women only and other grouping euthyroid and subclinically hypothyroid women.

In 2006, Negro et al. (25) carried out a prospective study aimed at determining whether LT4 treatment given to women with thyroid autoimmunity and TSH levels between 0.27 and 4.2 mIU/L had some beneficial effects on obstetrical complications. In this study, the percentage of miscarriages and premature deliveries in thyroid antibody positive women who were not treated with LT4

was significantly higher than the rate of miscarriage and preterm delivery in treated thyroid antibody positive women as well as in thyroid antibody negative controls (2.4% *vs.* 3.5%, *vs.* 13.8%, P<0.05 for miscarriage; and 22.4% *vs.* 7.0% *vs.* 8.2%, P<0.01 for preterm delivery) (25). A second prospective interventional trial from the same research group evaluated the impact of LT4 therapy on thyroid antibody positive pregnant women with a TSH above 2.5 mIU/L (63). TPOAb positive women with a TSH >2.5 mIU/L treated with LT4 had a significant decrease in the composite of adverse pregnancy and fetal outcomes when compared with TPOAb positive women with similar TSH levels not treated during pregnancy with LT4 (63). A further randomised study, this one focusing on the impact of LT4 in euthyroid (i.e., first trimester TSH <2.5 mIU/L) TPOAb positive women, reported that, although LT4 therapy decreased the preterm delivery and MR in TPOAb positive women, the rates were not statistically different when compared with thyroid antibody negative controls (64). Finally, a more recent randomised controlled study by Nazarpour *et al.* (65) found no benefit from LT4 therapy in euthyroid and subclinically hypothyroid (TSH ≤10 mIU/L) TPOAb positive women in terms of MR. However, LT4 therapy significantly reduced the risk of preterm delivery in TPOAb positive women whose baseline TSH values were ≥4 mIU/L compared with untreated TPOAb positive women with similar TSH levels (5.3% *vs.* 29.4%; P=0.01) (65).

Maternal thyroid autoimmunity has been associated with fetal and neonatal complications, including IUGR, perinatal mortality and respiratory distress. In addition, several studies are indicative of an association between maternal thyroid autoimmunity and impaired neurodevelopment in their children.

IUGR refers to a fetus with an estimated fetal weight <10th percentile on ultrasound that, because of a pathologic process, has not attained its biologically determined growth potential. IUGR is considered to be a proxy for the term small for gestational age (SGA), since the latter also refers to fetus with an estimated fetal weight <10th percentile on ultrasound, but this diagnosis does not necessarily imply pathologic growth abnormalities, and may simply describe a fetus at the lower end of the normal range (66).

A systematic review and meta-analysis was carried out in 2016 to evaluate the association between maternal subclinical thyroid dysfunction and autoimmunity and the risk for IUGR (67). Meta-analysis showed that SCH was associated with IUGR only (OR 1.54, 95% CI: 1.06–2.25)

while there was no effect of subclinical hyperthyroidism, TPOAb positivity or isolated hypothyroxinemia (67). An increased risk of perinatal mortality in terms of stillborns and early neonatal deaths (<7 days after birth) was reported by Mannisto and co-workers in 2009 in a study including 9,247 singleton pregnancies (68). Perinatal mortality was 2- to 3-fold higher in the infants of TPOAb- and TgAb-positive mothers compared with those of antibody-negative women (adjusted OR 3.2, 95% CI: 1.4–7.1 in TPOAb, and 2.5, 95% CI: 1.1–5.9 in TgAb positive mothers). The observed association was not affected by maternal thyroid hormone status, whereas an increased risk for large-for-gestational age infants was found in mothers TPOAb positive or in those with low TSH and high FT4. Also, placental weights were higher in mothers with low TSH and high FT4 or high TSH and low FT4 level as well as among TPOAb positive mothers. These findings, along with other similar observations, suggest that thyroid dysfunction at early gestation could affect both fetal intrauterine and placental growth (68-72).

In 2011, Negro *et al.* found the risk of respiratory distress to be significantly more likely among infants of women who were thyroid antibody positive than among those born to women who were thyroid antibody negative (73). By contrast, Abbassi-Ghanavati and co-workers retrospectively examined data from 17,298 women screened in the first 20 weeks of gestation, and did not find any association between TPOAb status and birth weight, fetal growth restriction, respiratory distress syndrome, stillbirth, neonatal death, and a number of other adverse perinatal outcomes (74).

Besides perinatal complications, children born to euthyroid mothers with thyroid autoimmunity seem to be at increased risk for neurodevelopmental delays, including cognitive deficits. In 1995, Pop and colleagues assessed neuro-intellectual performances in 230 children 5 years after delivery and found that euthyroid children of mothers with TPOAb during late gestation scored 10.5 points lower on the McCarthy Scales of Children's Abilities than those born to women who were TPOAb-negative (75). Maternal TPOAbs, along with maternal subclinical hypothyroidism and hypothyroxinaemia at 16–20 weeks of gestation, were all found to be statistically significant predictors of lower motor and intellectual development in the progeny at 25–30 months (76). In two subsequent studies, Wasserman and colleagues reported of a detrimental effect of maternal TPOAb positivity on hearing (77) and cognitive function (78). In particular, a significant association was found between

TPOAb positivity in women during the third trimester of pregnancy with sensorineural hearing loss in their children (prevalence OR 7.5, 95% CI: 2.4–23.3), the strength of the association becoming more robust as the TPOAb concentration increased (77). In the second study, the Authors found an effect of maternal third-trimester TPOAb positivity on IQ scores in early childhood (at the age of 4 years), but the effect was attenuated in both magnitude and significance among older (7 years) children (78). Since even slight fluctuations in auditory perception may affect neurocognitive outcomes (79), the authors concluded that, taken as a whole, the results of their studies might suggest that TPOAb-associated sensorineural hearing loss may be part of the neurodevelopmental pathway of later cognitive delays (78). In 2012 Ghassabian and co-workers demonstrated a higher risk of attention deficit/hyperactivity disorders in children born to mothers with elevated titers of TPOAbs during gestation which was only partially explained by increased maternal TSH levels (80). In contrast to previous research, no association was found between maternal levels of TPOAb and TSH with neurodevelopment in the Generation R study (81). In this study maternal levels of TSH, TPOAbs, TgAbs, T4, and FT4 at 10 and 34 weeks and at delivery, and cord levels of T4, FT4, TPOAbs, and TgAbs were measured. The association of cord thyroid hormone parameters with McCarthy scale scores adjusted for the major confounders of neurodevelopment at 5.5 years, was also carried out. Lower perceptual performance and motor scores were found with TgAb-positive women and lower perceptual performance scores with TgAb-positive cord levels. Maternal levels of TPOAb, TgAb, TSH, and cord levels of FT4, TPOAb and TgAb were not associated with neurodevelopment, whereas low cord T4 levels were unexpectedly associated with significant increments in the McCarthy scales in the domains that tested cognitive and verbal abilities (81). More recently, a multicenter randomized trial designed to evaluate the effects of LT4 treatment given to subclinically hypothyroid mothers on several adverse neonatal outcomes, including intelligence quotient of children at 5 years, showed no benefit of LT4 therapy, and a *post hoc* analysis found no significant interaction according to TPOAb levels (82).

Diagnosis and treatment of pregnant women with autoimmune thyroid diseases according to current guidelines

Given the prevalence and potential harmful effects of thyroid autoimmunity on pregnancy outcomes, several international guidelines addressing the subject of thyroid and pregnancy have been released in the last years (9,83,84). Published guidelines of the American Thyroid Association (ATA) (9) and of the European Thyroid Association (ETA) (84), overall agree that thyroid autoimmunity is the leading cause of gestational thyroid insufficiency, at least in areas with sufficient daily iodine intake (85). However, some differences actually exist between the above guidelines in the definition of TSH reference range upper limits, as well as in the further diagnostic workup in the case of elevated TSH levels at early pregnancy (*Table 1*). According to ETA guidelines (84), trimester-specific reference ranges for TSH and T4 (total or free) should be established in each antenatal hospital setting. Alternatively, if TSH trimester-specific reference ranges are not available, the following reference range upper limits are recommended: 1st trimester, 2.5 mU/L; 2nd trimester, 3.0 mU/L; 3rd trimester, 3.5 mU/L. If TSH is elevated, both FT4 and TPOAb should be determined, in order to distinguish subclinical from overt hypothyroidism and to ascertain autoimmunity as the aetiology of maternal thyroid insufficiency. In the case of elevated TSH and negative TPOAb, the same guidelines recommend TgAb measurement, and thyroid ultrasound to evaluate hypo-echogenicity or an inhomogeneous thyroidal echo pattern. The recommended treatment of maternal hypothyroidism, irrespective of its etiology, is administration of oral LT4, with the aim of normalizing maternal serum TSH values within the trimester-specific reference range (84).

In the ATA guidelines (9) the use of serum TSH population-based trimester-specific reference ranges to assess maternal thyroid function is recommended as well. In the lack of specific TSH gestational ranges, a TSH upper reference limit of 4.0 mU/L (corresponding to a reduction in the non-pregnant TSH upper reference limit of approximately 0.5 mU/L) is regarded as applicable beginning with the late first trimester (weeks 7–12), with a gradual return towards the non-pregnant range in the 2nd and 3rd trimesters. Reflex anti-TPOAb measurement should be performed to investigate thyroid autoimmunity in pregnant women if TSH concentrations at early pregnancy are 2.5–10 mU/L, whereas TgAb testing is not recommended (9). Regarding treatment of gestational thyroid insufficiency, ATA guidelines base their recommendation on either TSH levels at early pregnancy or TPOAb positivity. In particular, LT4 therapy is recommended for TPOAb positive women with a TSH

Table 1 Early pregnancy testing and treatment of thyroid dysfunction according to ATA (9) and ETA (84) guidelines

Testing/treatment	ETA guidelines	ATA guidelines
Recommended TSH reference range upper limits[1]	1st trimester: 2.5 mU/L; 2nd trimester: 3.0 mU/L; 3rd trimester: 3.5 mU/L;	1st trimester: 4.0 mU/L; 2nd and 3rd trimester: non-pregnant upper limits
Free or total T4 measurement	Recommended if TSH is elevated	Not recommended
TPOAb measurement	Recommended if TSH is elevated	Recommended in high risk women if TSH is 2.5–10 mU/L
TgAb measurement	Recommended if TSH is elevated and TPOAbs are negative	Not recommended
Thyroid ultrasonography	Advised if TSH is elevated and TPOAbs are negative	Not mentioned
LT4 treatment	Recommended if TSH elevated (see above). LT4 to be considered in isolated hypothyroxinaemia detected in the 1st trimester	Recommended in (I) TPOAb +ve women with a TSH > the upper limit for pregnancy, and (II) women with a TSH >10 mU/L; LT4 to be considered in (III) TPOAb +ve women with TSH >2.5 mU/L and < the upper limit for pregnancy, and (IV) TPOAb –ve women with TSH> the upper limit for pregnancy and <10.0 mU/L

[1], if TSH trimester-specific reference ranges are not available; TPOAb +ve, TPOAb positive; TPOAb –ve, TPOAb negative; ETA, European Thyroid Association; ATA, American Thyroid Association; TSH, thyroid stimulating hormone.

greater than the pregnancy specific reference range and in women with a TSH greater than 10.0 mU/L, irrespective of TPOAb positivity. Conversely, LT4 treatment may be considered in TPOAb positive women with TSH concentrations >2.5 mU/L and below the upper limit of the pregnancy specific reference range, and in TPOAb negative women with TSH concentrations greater than the pregnancy specific reference range and below 10.0 mU/L (9).

Finally, if LT4 therapy is given, both ETA and ATA guidelines recommend a close follow up (every 4–6 weeks) of maternal TSH values, in order to adjust LT4 dose to maintain TSH <2.5 mU/L or within the trimester-specific reference range (9,84).

Conclusions

Present evidence indicates that thyroid autoimmunity poses a risk for miscarriage and preterm delivery. However, it is still unclear whether thyroid antibodies actually exert a direct pathogenic effect at the fetal-maternal interface, or they merely represent an epiphenomenon of other autoimmune abnormalities, which are in turn causally linked to the above obstetrical complications. Some evidence supports the potential benefit of LT4 treatment for TPOAb positive pregnant women in terms of decreased rates of obstetrical complications, which argues in favour of a pathophysiological role of a decreased thyroid ability to function adequately during pregnancy in the occurrence of obstetrical complications. Nonetheless, since the effectiveness of LT4 therapy has not yet been conclusively demonstrated, current guidelines do not recommend for or against treating euthyroid, thyroid autoantibody positive pregnant women with levothyroxine to prevent miscarriage or preterm delivery (9).

With regard to infertility, most studies failed to find significantly different likelihood of pregnancy in euthyroid women with and without thyroid antibodies undergoing ART procedures. However, low doses of LT4 (i.e., 25–50 μg/day as starting dose) should be considered in euthyroid TPOAb positive women undergoing ART to prevent any TSH elevations which may impact ART outcomes (9). Finally, uncertainty surrounds the role of thyroid autoantibodies on fetal and neonatal outcomes, since an increased risk for perinatal death, IUGR, and respiratory distress syndrome has been inconsistently reported. Few studies addressed the impact of maternal TPOAbs during pregnancy on cognitive functioning of the child, once again providing mixed results. Whether thyroid antibodies have a direct effect on neonatal outcomes, including neurodevelopment in the progeny, or whether the

observed associations are related to maternal autoimmune-related thyroid insufficiency needs to be still clarified.

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