

# Reduction of Miscarriages through Universal Screening and Treatment of Thyroid Autoimmune Diseases

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## Key Words

Miscarriage · Pregnancy · Thyroxine treatment · Thyroid peroxidase antibodies · Universal screening

## Abstract

**Background/Aims:** Universal screening for thyroid diseases during pregnancy is controversial. Targeted screening does not identify all women with thyroid dysfunction. Furthermore, antithyroid peroxidase antibodies (TPOAb) are suspected to be associated with an increased risk of fetal loss, premature delivery and hypothyroidism. The aim of our study was to assess the rationale behind universal screening and propose thyroxine treatment in particular cases. **Methods:** Between January 2008 and May 2009, 537 consecutive iodine-supplemented women with a singleton pregnancy [441 TPOAb– controls and 96 TPOAb+ women (47 nontreated and 49 treated)] were evaluated using thyroid and obstetric parameters. According to our algorithm for thyroid screening in pregnancy, if thyroid-stimulating hormone (TSH) exceeded 1 mU/l in TPOAb+ women, 50 µg of levothyroxine (L-T4) was prescribed. **Results:** The miscarriage rate was significantly higher in the nontreated TPOAb+ group compared with the treated group (16 vs. 0%;  $p = 0.02$ ). Compared to the control group, TSH in TPOAb+ patients was higher at the first prenatal visit prior to L-T4 treatment ( $p < 0.01$ ), while free thyroxine was higher than in the control

group after the 20th week ( $p < 0.05$ ). **Conclusions:** Our study supports the potential benefit of universal screening and L-T4 treatment for autoimmune thyroid disease during pregnancy. Efforts are still needed to further decrease miscarriage rates.

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## Introduction

Pregnancy represents a major challenge for the thyroid gland, contributing to thyroid dysfunction in cases where the thyroid fails or is less able to adapt adequately to pregnancy-related changes [1]. In the absence of iodine deficiency, hypothyroidism is often secondary to thyroid autoimmunity, being associated with infertility [2], obstetrical and fetal complications [3–6] and impaired neuropsychological development in children [7]. In a recent randomized trial conducted by Lazarus et al. [8], there was no preventive effect of antenatal screening and hypothyroidism treatment (at a gestational age of 12 weeks) on the intelligence quotient of 3-year-old children.

Thyroid peroxidase antibodies (TPOAb) are detected in 10% of pregnant women. Several studies have showed

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a positive association between TPOAb and miscarriage [9, 10], maternal hypothyroidism [11], preterm delivery [12, 13], postpartum thyroiditis [14], maternal morbidity in later life [15] and impaired neuropsychological development in children [16–18]. In 2006, Negro et al. [19] demonstrated a significant decrease in miscarriage (–75%) and premature delivery (–69%) rates in TPOAb+ women treated with levothyroxine (L-T4) compared with the nontreated group. Due to the lack of intervention studies, the Endocrine Society's Clinical Practice Guidelines of 2007 [20] and, more recently, the American Thyroid Association [21] recommended targeted high-risk case finding to identify women with thyroid dysfunction. However, Vaidya et al. [22] revealed the limitations of targeted screening, which overlooked one third of pregnant women with hypothyroidism. Likewise, Horacek et al. [23] recently reported the benefit of universal screening, which detected twice as many thyroid disorders as targeted high-risk case finding. In 2010, in a study comparing the ability of universal and targeted screening to detect thyroid hormonal dysfunction, Negro et al. [24] showed no significant differences between these two screening strategies. Nonetheless, the question arises as to whether it is acceptable to leave maternal thyroid disease undiagnosed. In 2009, a study conducted by Debiève et al. [25] proposed treating TPOAb+ women with L-T4 substitution if the thyroid-stimulating hormone (TSH) levels were higher than 1 mU/l.

In this study, we assess whether universal thyroid screening should be undertaken in all pregnant women, with L-T4 treatment being implemented in particular cases, and if early L-T4 treatment could decrease the miscarriage rate in TPOAb+ women.

## Subjects and Methods

### *Patients and Design*

Thyroid screening of pregnant women based on TSH and TPOAb values was introduced at our institution in 2004. A dose of 50 µg of L-T4 is prescribed if TSH levels are higher than 1 mU/l and the TPOAb titer is positive [25] (>9 U/ml) at the first prenatal visit. This TSH value of 1 mU/l was arbitrarily chosen based initially on results of Glinoe et al. [26] and then on our own. This study showed that mean TSH levels during the first and, to a lesser extent, second trimester never exceeded 1 mU/l. These data were confirmed by our own clinical experience [25]. TSH values were monitored and L-T4 replacement therapy adjusted in order to achieve TSH levels between 1 and 2 mU/l.

Our descriptive study retrospectively reviewed the files of 823 consecutive iodine-supplemented women with a singleton pregnancy who attended the prenatal clinic at the Cliniques Universitaires Saint-Luc, Brussels, Belgium, between January 2008 and

May 2009. The study was approved by the ethical committee. Thyroid function parameters, namely TSH, free thyroxine (fT4) and TPOAb, were assessed at the first prenatal visit during the first trimester. The exclusion criteria were TSH values above the reference range (>3.5 mU/l) at the first prenatal visit, L-T4 treatment starting before the onset of pregnancy, Basedow disease, thyroidectomy, other serious diseases that could influence thyroid hormone levels (i.e. diabetes mellitus, HIV immunization and cirrhosis) and therapeutic abortion. Figure 1 shows the distribution of screened patients. Overall, 96 TPOAb+ women were included in the analysis; 49 were treated at the first prenatal visit (group 1) and 47 were not treated (group 2). Furthermore, 441 TPOAb– women (group 3) served as a control group. All patients included were followed until delivery and received vitamin supplements containing 150 µg of potassium iodide/day.

### *Laboratory Methods*

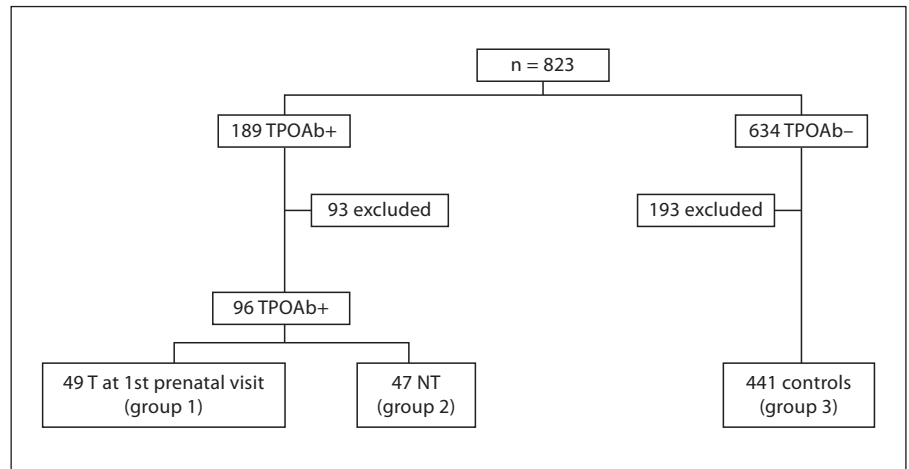
TSH, fT4 and TPOAb titers were measured using automated immunoassays with chemiluminescence detection (DxI 800 Access, Beckman Coulter, USA). The hospital laboratory reference values were 0.2–3.5 mU/l for TSH, 0.6–1.4 ng/dl for fT4 and <9 U/ml for TPOAb. Coefficients of variation were 10.62, 4.96, 4.55 and 3.72% for the TSH assay at concentrations of 0.027, 1, 8.18 and 28.59 mU/l, respectively, and 7.42, 3.28 and 4.56% for the fT4 assay at concentrations of 0.47, 1.21 and 4.3 ng/dl, respectively. For the TPOAb assay, the coefficient of variation was <12% at a concentration of ≥0.6 IU/ml.

### *Obstetric Complications*

Obstetric complications were classified into three groups. The first group involved miscarriages during the first trimester (≤13 weeks). The second group of complications included delivery complications, notably preterm delivery (<37 weeks of gestation), neonatal hypotrophy, cesarean section, placental abruption and delivery hemorrhage. The third group comprised various medical conditions, namely pregnancy-induced hypertension, preeclampsia and gestational diabetes. Gestational hypertension was defined as blood pressure >140/90 mm Hg. Preeclampsia was diagnosed according to the criteria of the American College of Obstetricians and Gynecologists and the National High Blood Pressure Education Program. Gestational diabetes was defined as two or more abnormal values on the oral glucose tolerance test. The distribution of TSH, fT4 and TPOAb levels was studied at different time points during pregnancy, namely at ≤10, 12, 15, 20, 30 and 35 weeks.

### *Statistics*

Statistical analysis was performed using the MedCalc 7.2.1.0 package (Medcalc Software, Mariakerke, Belgium). For obstetric complications, categorical variables were compared using Fisher's exact test owing to the low number of observations.  $\chi^2$  or Fisher's exact test were used to compare patient characteristics. For continuous variables, an analysis of variance test was used. When the distribution was found to be abnormal, data were logarithmically transformed. Logistic regression analysis was used to assess the relationship between certain patient characteristics (i.e. age, TSH, TPOAb titer, maternal weight and weight gain) and the occurrence of miscarriage. A p value of <0.05 was considered significant.



**Fig. 1.** Flow chart of patients screened for thyroid tests. Patients were excluded from the control group for the following reasons: 55 for thyroid dysfunction history or previous L-T4 treatment; 62 missing during pregnancy and 16 with incomplete data; 10 for medical abortions; 5 for hypothyroidism (>3.5 mU/l) at the first prenatal visit; 5 for serious diseases (diabetes mellitus, HIV immunization or cirrhosis); 12 for multiple pregnancies, and 28 were working members. Patients were excluded from the TPOAb+

group for the following reasons: 33 for L-T4 treatment started before the onset of pregnancy; 7 for Basedow disease; 20 for hypothyroidism at the first prenatal visit; 19 missing during pregnancy and 1 with incomplete data; 1 for HIV immunization; 4 for multiple pregnancies, and 8 were working members. First trimester screening (and treatment) rate: 34/49 (69%) for group 1, 31/47 (66%) for group 2 and 311/441 (71%) for group 3. T = Treated; NT = nontreated.

## Results

The clinical characteristics of the patients at the first prenatal visit are shown in table 1. No significant differences were observed between the groups ( $p > 0.05$ ). Screening and treatment rates during the first trimester were 69% in group 1 [34/49; 82% (28/34) at  $\leq 10$  weeks], 66% (31/47) in group 2 ( $p = 0.83$  compared with group 1, Fisher's exact test) and 71% (311/441) in the control group. Patients who were not screened during first trimester, and thus did not receive treatment for group 1, were not considered in the analysis of the miscarriage rate. The numbers of studied patients were 34, 31 and 311 for groups 1, 2 and 3, respectively (fig. 1). The initial L-T4 dose in group 1, started as soon as TPOAb was detected and TSH was  $>1$  mU/l, remained unchanged throughout the pregnancy in 88% of patients (43/49). In order to reach and maintain a TSH level between 1 and 2 mU/l, the L-T4 dose was increased in 4 patients, while the dose was decreased in 2 due to TSH  $<1$  mU/l.

### Obstetric Complications

Among group 1 patients with TPOAb+ who were treated at the first prenatal visit there were no cases of miscarriage (table 2a). A significant difference of 16% was observed in the miscarriage rates between this

**Table 1.** Clinical characteristics of pregnant women in the different groups

Clinical characteristics	Group 1 (n = 49)	Group 2 (n = 47)	Group 3 (n = 441)	p value
Maternal age, years	31.5 $\pm$ 5.5	32.5 $\pm$ 5.3	31.9 $\pm$ 5.1	0.6
Maternal weight, kg	63 $\pm$ 10.4	61.3 $\pm$ 12.5	62.9 $\pm$ 11.7	0.5
Weight gain, kg	13.3 $\pm$ 6	12.8 $\pm$ 4.7	14 $\pm$ 5.6	0.7
Primigravidity, %	32.7	25.5	28.8	0.7
Obstetrical history, %	28.6	42.6	34	0.3
Infertility, %	16.3	8.5	8.6	$>0.1$

Values are given as means  $\pm$  SD or percentages. Primigravidity was defined as first-time pregnancy. Obstetrical history was considered positive if the difference between the gravidity and parity was higher than 1.  $\chi^2$  test was used for comparison of primigravidity and obstetrical history and Fisher's exact test between groups for comparison of infertility. An analysis of variance test was used for continuous variables (maternal age, weight and weight gain).

group and the nontreated group (group 2; 5/31;  $p = 0.02$ ). Four of these 5 nontreated TPOAb+ women with early miscarriage had TSH values above 1 mU/l. The control group (group 3) had a miscarriage rate of 8% (25/311), which was similar to that of the nontreated TPOAb+ patients (group 2). No other significant differences re-

**Table 2.** Obstetric complications in the treated TPOAb+ group (group 1) versus the nontreated TPOAb+ group (group 2) and in the nontreated TPOAb+ group (group 2) versus controls (group 3)

**a** Miscarriage

	TPOAb+		TPOAb-	p value	
	group 1 (n = 34)	group 2 (n = 31)	group 3 (n = 311)	group 1 vs. 2	group 3 vs. 2
Miscarriage, n	0 (0)	5 (16.1)	25 (8)	0.02	0.17

**b** Delivery complications and gestational hypertension/diabetes

	TPOAb+		TPOAb-	p value	
	group 1 (n = 49)	group 2 (n = 47)	group 3 (n = 441)	group 1 vs. 2	group 3 vs. 2
Delivery complications, n					
Preterm delivery	3 (6.1)	4 (10)	29 (7.2)	0.69	0.52
Neonatal hypotrophy	2 (4.1)	0 (0)	5 (1.2)	0.5	1
Cesarean section	8 (16.3)	8 (20)	94 (23.3)	0.78	0.84
Placental abruption	1 (2)	0 (0)	2 (0.5)	1	1
Delivery hemorrhage	0 (0)	2 (5)	7 (1.7)	0.2	0.19
	14 (26.5)	14 (22.5)	137 (28.8)	0.81	0.47
Gestational hypertension/diabetes, n					
Hypertension	1 (2)	2 (5)	13 (3.2)	0.59	0.64
Preeclampsia	1 (2)	2 (5)	8 (2)	0.59	0.23
Gestational diabetes	2 (4.1)	1 (2.5)	7 (1.7)	1	0.53
	4 (8.2)	5 (12.5)	28 (6.2)	0.73	0.17

Numbers in parentheses represent percentages, and totals are a percentage of the different patients with (at least) one obstetric complication.

lating to delivery and medical conditions, such as gestational hypertension or diabetes, were observed (table 2b).

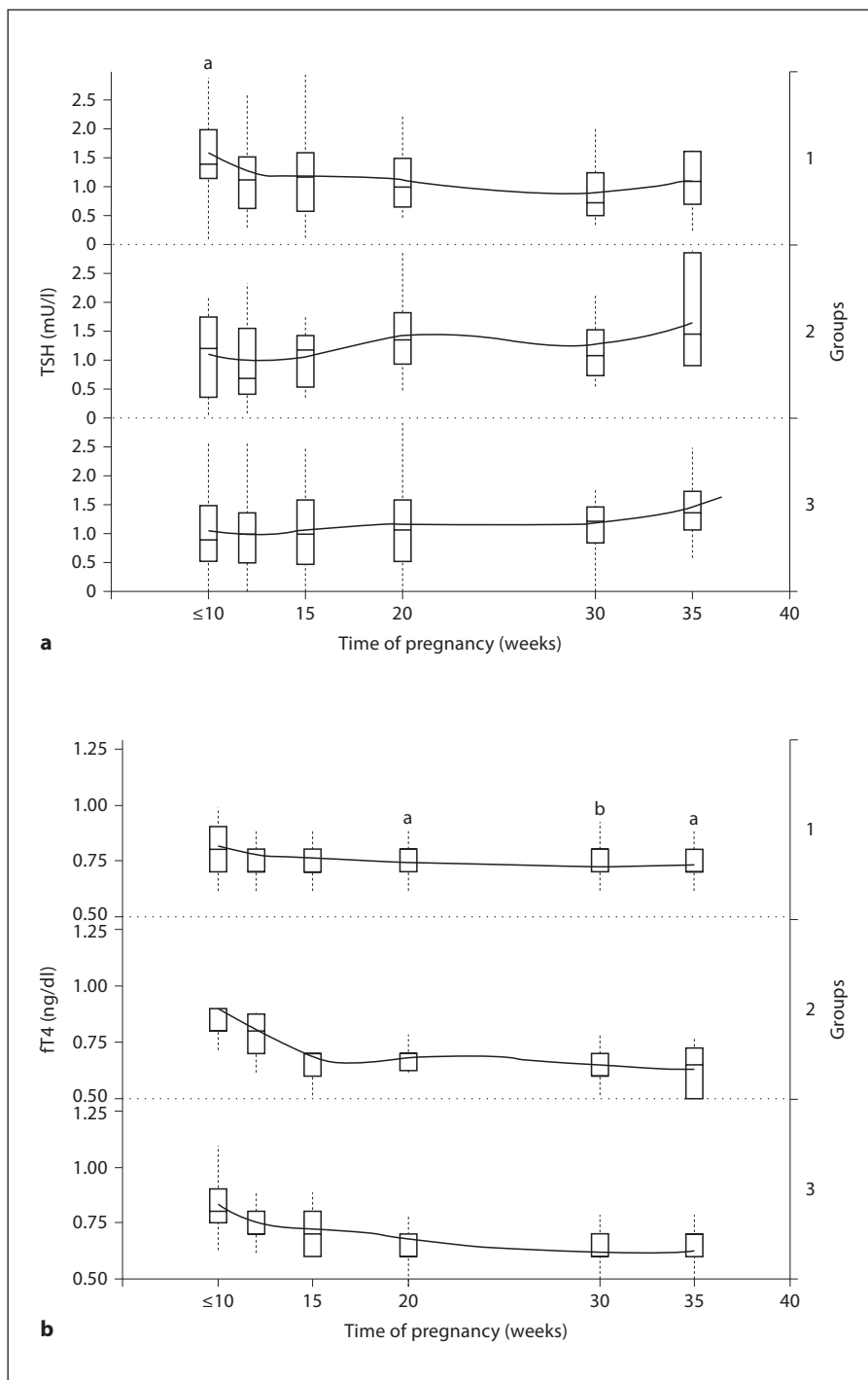
*Evolution of Thyroid Function Tests*

Figure 2 illustrates the TSH and fT4 levels at different time points throughout pregnancy for groups 1 (treated at the first prenatal visit), 2 (nontreated) and 3 (control). At baseline prior to L-T4 treatment, mean TSH values were significantly higher in the treated group compared with the control group ( $1.61 \pm 0.77$  vs.  $1.05 \pm 0.7$  mU/l;  $p = 0.005$ ). After initiating L-T4 therapy, TSH values decreased and then remained stable. No other difference was subsequently found. Despite higher values in the nontreated group, fT4 distribution did not reveal any significant differences at baseline. Appropriate L-T4 substitution resulted in stable fT4 values in the treated group during pregnancy. In contrast, in the two other groups (nontreated and control), fT4 decreased in relation to

baseline values. From week 20 onwards, fT4 values in the control group differed significantly from those in the treated group ( $0.75 \pm 0.09$  vs.  $0.68 \pm 0.12$  ng/dl,  $0.72 \pm 0.1$  vs.  $0.62 \pm 0.08$  ng/dl, and  $0.74 \pm 0.1$  vs.  $0.63 \pm 0.09$  ng/dl at 20, 30 and 35 weeks, respectively;  $p < 0.05$ ). TPOAb titers were 2–3 times higher in the treated group compared with the nontreated group throughout pregnancy. Lastly, antibody levels decreased by 65–70% between the first trimester and 9th month of pregnancy.

**Discussion**

Our study evaluated the rationale behind universal thyroid function screening in women and the potential benefits of thyroxine treatment in particular cases during early pregnancy. The analysis of obstetric complications revealed a significant difference in miscarriage rates in TPOAb+ women treated at the first prenatal visit (group



**Fig. 2.** Distribution of TSH (a) and ft4 levels (b) at different time points during pregnancy. Continuous lines represent the mean, and the box plots represent the first quartile, median and third quartile. <sup>a</sup>  $p < 0.05$ : group 1 vs. group 3; <sup>b</sup>  $p < 0.05$ : group 1 vs. groups 2 and 3.

1) as compared with the nontreated group (group 2), with no miscarriages being observed in the treated TPOAb+ women. In contrast, 4 TPOAb+ women with a TSH value  $>1$  mU/l had an early miscarriage before initiating L-T4 therapy.

The impact of TPOAb levels on miscarriage rates is controversial. The studies of Iijima et al. [27] and Stagnaro-Green et al. [9] did not find any correlation between these two parameters. In contrast, another study reported higher TPOAb titers in women with miscarriage com-



**Table 3.** Differences in age and TSH levels in TPOAb+ women compared to TPOAb- women, in studies on the association between thyroid autoimmunity and miscarriage

	TPOAb+ women	TPOAb- women	Difference	p
<b>Age, years</b>				
Bussen and Steck [41]	31 ± 5.2	30.3 ± 4.5	+0.7	NS
Bagis et al. [42]	27.7 ± 6.2	25.9 ± 5.2	+1.8	<0.0009
Glinoeer et al. [43]	29.3 ± 1	27.3 ± 2	+2	<0.001
Lejeune et al. [44]	28.2 ± 9.5	27.2 ± 6.8	+1	0.06
Pratt et al. [45]	33 ± 2.9	34 ± 3.4	-1	NS
Iijima et al. [27]	30.2 ± 4.8	30 ± 4.3	+0.2	NS
Muller et al. [46]	32.4 ± 3.3	32.4 ± 4.4	0	NS
Rushworth et al. [47]	34 (20-41)	34 (22-46)	0	NS
Poppe et al. [48]	33.2 ± 4.6	31.6 ± 5.4	+1.6	NS
Poppe et al. [49]	33 ± 2.9	34 ± 3.4	-1	NS
Kim et al. [50]	34.3 ± 6.4	31.2 ± 6.7	+3.1	NS
Present study	31.5 ± 5.5	31.9 ± 5.1	-0.4	NS
<b>TSH, mU/l</b>				
Stagnaro-Green et al. [9]	2.35	1.6	0.75	0.12
Glinoeer et al. [43]	1.4	0.9	0.5	<0.01
Muller et al. [46]	3.5 ± 3.6	1.7 ± 0.9	1.8	<0.005
Bagis et al. [42]	1.86 ± 1.8	1.17 ± 0.9	0.69	<0.001
Poppe et al. [48]	1.6 (0.02-4.1)	1.3 (0.05-3.6)	0.3	NS
Mecacci et al. [51]	3.62	1.29	2.33	0.009
Present study	1.61 ± 0.77	1.05 ± 0.7	0.56	0.005

Values are shown as means ± SD or medians (range). NS = Not significant.

pared to those without [28]. Recent meta-analyses have emphasized the association between the presence of autoimmune thyroid antibodies and pregnancy outcomes [10, 29]. Mild thyroid failure or decreased capacity to modify thyroid hormones appeared to play a predominant role. As summarized in table 3, in our population the mean TSH levels were significantly higher in women with TPOAb+ before LT-4 treatment (group 1; 1.61 ± 0.77 vs. 1.05 ± 0.7 mU/l in the TPOAb- group; p = 0.005). Another important finding to consider is age, as we know that greater maternal age is a risk factor for miscarriage. Most of the studies reported a slightly greater age in TPOAb+ women (table 3). However, despite a trend toward higher age and TSH levels in patients with miscarriage, parameters such as age, TSH, TPOAb titer and maternal weight were not significantly associated with this observation, probably because of the low number of patients who miscarriage in the TPOAb+ group.

Our results, along with those of Negro et al. [19], confirmed the beneficial effects of L-T4 substitution, as reflected by the decreased miscarriage and premature delivery rates in TPOAb+ women treated with low-dose L-T4 [30]. In our study, nontreated TPOAb+ women ex-

hibited TSH values similar to those of the control group. Based on our algorithm, women with TSH values <1 mU/l were not offered any treatment. In our population, fT4 levels were lower than in previous studies [31], which may be accounted for by the slight iodine deficiency in the Belgian population [32].

Another important parameter to consider is the normal TSH cutoff value in pregnant TPOAb- women. Negro et al. [33] found an increased pregnancy loss during the first trimester in women with TSH values between 2.5 and 5 mU/l compared to women with TSH ≤ 2.5 mU/l. These results support revising the established cutoff of 'normal' TSH in pregnant women up to 2.5 mU/l.

Although universal thyroid screening is not totally accepted, several studies in favor of universal screening demonstrated the potential consequences of thyroid dysfunction on maternal and fetal health as well as the beneficial effects of thyroxine treatment [2-19, 22, 23]. Despite finding no significant decrease in obstetric complications with universal screening and case finding, the results of Negro et al. [24] showed fewer obstetric complications in the low-risk group identified by universal screening and benefiting from hypo-/hyperthyroidism

treatment, thus providing strong evidence that universal screening for TPOAb and TSH in pregnant women should be considered [34]. Moreover, the first study evaluating the cost-effectiveness of screening all pregnant women for autoimmune thyroid disease during the first trimester demonstrated a cost-saving result compared with no screening [35].

Despite a lack of consensus among professional organization guidelines regarding thyroid dysfunction screening, a survey conducted in Maine, USA, showed that many practitioners have already implemented routine TSH testing in pregnant women [36]. Recently, a European survey found similar results, with 42% of responders screening all pregnant women for thyroid dysfunction [37]. Klubo-Gwiedzinska et al. [38] clearly demonstrated the necessity of updating and promulgating new guidelines for L-T4 treatment during pregnancy.

The distinctiveness of this present study is its use of an algorithm, which has been employed at our institution since 2004, allowing us to highlight the benefits and difficulties of universal screening and treatment of autoimmune thyroid diseases. In spite of our algorithm, the differences observed in the incidence of miscarriages in the two TPOAb+ groups reflect the difficulties inherent in early pregnancy screening. For this reason, we suggest conducting screening prior to pregnancy rather than at 6–7 weeks in order to reduce the incidence of miscarriage in TPOAb+ women. Improved cooperation and communication between endocrinologists and obstetricians in addition to an increased awareness about the risks of thyroid dysfunction among the general population should be emphasized [39].

One of the strengths of our study is its concern for the real-life treatment of patients, which helped to highlight some of the erroneous parts of our algorithm. In addition, a wide range of parameters for obstetric complications were evaluated. To our knowledge, this is the first study evaluating the different aspects of universal screening and autoimmune thyroid disease treatment in daily clinical practice. One limitation of this retrospective study with a descriptive design was the lack of comparisons with another form of screening (e.g. case finding). Other limitations include the cross-sectional analysis of TSH and fT4 distribution, use of nonspecific reference values for pregnancy in the algorithm and the absence of certain variables, such as socioeconomic status, body mass index and patient ethnicity, as significant differences relating to ethnicity are found for specific reference intervals for thyroid function tests [40].

A longitudinal study involving normal TPOAb and iodine-supplemented women should be performed in order to establish the gestational age-specific reference intervals for TSH and fT4 and better adapt possible L-T4 treatments for TPOAb+ pregnant women.

## Conclusions

Our study supports the potential benefit of early universal thyroid screening, as L-T4 treatment for TPOAb+ pregnant women who were diagnosed via universal screening appeared to reduce miscarriage rates. Furthermore, L-T4 therapy was offered to women with TPOAb+ and TSH values >1 mU/l. To further decrease miscarriage rates, efforts are still required to conduct universal thyroid screening prior to pregnancy or as soon as pregnancy is confirmed. Optimal cooperation and communication between endocrinologists and obstetricians is also necessary. Ideally, randomized placebo-controlled studies are needed in order to confirm the potential benefits of universal screening and treatment of autoimmune thyroid disease during pregnancy.

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