Variables Contributing to Thyroid (Dys)Function in Pregnant Women: More than Thyroid Antibodies?

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Keywords

Thyroid function · Variables · Reference values

Abstract

Variability in thyroid function in pregnant women is the result of 2 main determinants, each accounting for approximately half of it. The first is the genetically determined part of which the knowledge increases fast, but most remains to be discovered. The second determinant is caused by an ensemble of variables of which thyroid autoimmunity is the best known, but also by others such as parity, smoking, age, and BMI. More recently, new candidate variables have been proposed, such as iron, endocrine disruptors, and the ethnicity of the pregnant women. In the future, the diagnosis and treatment of thyroid (dys)function may be optimized by the use of each individual's pituitary-thyroid set point, corrected with a factor taking into account the impact of nongenetically determined variables.

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Introduction

Pregnancy is a condition leading to an increased demand in thyroid hormones (TH), resulting from the fetal need (especially before 18–20 weeks), increased renal iodide loss, increased levels of serum thyroxine-binding globulin, and increased degradation of TH by placental deiodinase type 3. Finally, around the 10–12th week of pregnancy, high hCG levels add strain to the maternal thyroid, and increase TH production [1].

In many studies, subclinical hypothyroidism (SCH) and thyroid autoimmunity (TAI) have been associated with adverse pregnancy outcomes, such as miscarriage and premature delivery [2, 3]. In addition, low T4 levels have been correlated with long-term neurocognitive problems in children [1–3]. For the diagnosis of SCH, the American Thyroid Association (ATA) guidelines recommend determining trimester- and population-specific ranges for serum TSH. These ranges should be determined in pregnant women without thyroid peroxidase antibodies (TPO-Abs) and severe iodine deficiency (ID) [4]. Furthermore, it is proposed to use serum TSH and not that of FT4 for the diagnosis of SCH [4]. An adequate diagnosis of SCH is a prerequisite to avoid unnecessary

treatment with LT4 that can lead to adverse outcomes. Indeed, in a recent study, it has been shown that women receiving LT4 for SCH (at that period defined as a serum TSH between 2.5–4.0 mIU/L) had an increased prevalence of preterm delivery and preeclampsia [5].

The prevalence of SCH during pregnancy varies between 3.5 and 18% (depending on the reference range for serum TSH and the iodine intake of the population), and the main cause is the presence of TAI, most often diagnosed by increased levels of TPO-Abs [1, 3].

In a pilot study by Andersen et al. [6], it was shown that the intra-individual variability in TSH and FT4 levels is within a narrow range, whereas the interindividual variability is large. This suggests that every individual has its own unique hypothalamic pituitary thyroid axis set point [7, 8]. It is estimated that 45–65% of the total variation in thyroid function is determined by genetic factors, while the rest is determined by variables such as environmental factors (e.g., iodine status) and individual characteristics (e.g., BMI and parity) [8].

The knowledge of as much as possible variables with an influence on thyroid function could improve target screening of women at risk to develop SCH during pregnancy. However, the systematic screening for SCH in pregnant women leads to a higher detection rate than targeted screening [9, 10].

The aim of this review paper is to describe the impact of established variables on thyroid function such as smoking, parity, and BMI, and that of new candidate variables such as iron, ethnicity, endocrine disruptors, and placental vascular factors.

Established Variables Contributing to Variation in Thyroid Function

Thyroid Peroxidase Antibodies

The presence of increased TPO-Abs is the main variable leading to the development of SCH in iodine-sufficient areas. A positive correlation between TPO-Ab titers and thyroid function has been reported in the NHANES III study, what might be explained by the higher degree of lymphocytic infiltration of the thyroid [11, 12]. In a study in pregnant women by Vaidya et al. [10], the presence of a personal history of raised TPO-Abs increased the risk of high serum TSH (RR: 8.4; $p < 0.001$). In the study by Korevaar et al. [9], a prediction model for elevated TSH became more discriminative when positivity for TPO-Abs was added to the already included variables such as BMI, parity, and smoking.

Thyroglobulin Antibodies

Based on large epidemiological studies in the general population, it is generally accepted that TPO-Abs are more frequently increased than thyroglobulin antibodies (Tg-Abs) [11, 13]. In those studies, the prevalence of TPO-Abs was 13 and 24% versus 11.5 and 7% for Tg-Abs, respectively. The difference in the prevalence may be explained by less sensitive assays used at that period. It should, however, be noted that in 2 studies, the prevalence of positive antibodies in women aged 25–40 years was slightly higher for Tg-Abs than TPO-Abs [11, 14]. In a recent study by Unuane et al. [15] in an unselected group of women consulting for infertility, 5% had isolated positive Tg-Abs, compared with 4% with TPO-Abs only. In the NHANES III study, increased levels of Tg-Abs were not associated with thyroid function compared with increased TPO-Abs [11]. However, and in line with the improved detection of Tg-Abs, some studies have shown that they were also associated with higher serum TSH levels compared with those in TAI-negative women [14, 15]. Finally, the importance of Tg-Abs is now also noticed in the ATA guidelines on thyroid and pregnancy, but, at the same time, it is mentioned that in the vast majority of studies, TAI was defined by the presence of TPO-Abs, and, therefore, the committee recommends only measuring TPO-Abs [4].

FT4 and TSH Assay

FT4 testing in pregnancy is challenging, due to the decrease in albumin levels and increase in thyroxine-binding globulin. FT4 immunoassays (IAs) may be sensitive to these changes in a method-specific manner. In a study by Anckaert et al. [16], 3 automated FT4 IAs were compared with a reference procedure (equilibrium dialysis spectrometry), and it was confirmed that the IAs were sensitive to pregnancy-specific protein alterations but to a different extent. In another study by Berta et al. [17], FT4 levels were compared using 5 different assays in 40 pregnant women (at 8–22 weeks of gestation) without thyroidal disease, and the correlation coefficient between the different assays was 0.67–0.89. The ATA guidelines mention, therefore, that if FT4 is measured in pregnant women, assay method-specific and trimester-specific reference ranges should be used [4].

The Committee for Standardization of Thyroid Function Tests of the International Federation of Clinical Chemistry and Laboratory Medicine comparison studies report significant biases between different TSH methods, what prevents establishing universal population or trimester-specific TSH reference ranges that would apply

across methods. Since TSH is a complex glycoprotein, no reference measurement procedure is available. However, a harmonization approach, where methods are recalibrated to the “all method mean,” has been shown to have the potential to eliminate between-method TSH differences [18]. In a recent study (but not in pregnant women), it was shown that differences between TSH assays could be as high as 37% [19]. However, that difference seems to be less prominent in pregnant women, as shown in the study by Berta et al. [17] with a correlation factor of 0.91–0.98 between 5 different TSH IAs.

Iodine

Severe and longstanding maternal ID can lead to overt hypothyroidism and cretinism in children. In case of mild-to-moderate ID, the thyroid is still able to keep TH levels within the normal range, but in the long run, SCH may occur and in the older population toxic nodular goiter with suppressed TSH levels [20]. In a study from China, thyroid function and urinary iodine was determined in >7,000 pregnant women during the first trimester, and women with low urinary iodine (100–149 µg/L) had median serum TSH and FT4 levels comparable with those in the reference group (urinary iodine between 150 and 249 µg/L) [21]. Also, in a study performed in Belgium (an area with a moderate ID), serum TSH concentrations did not significantly vary according to the iodine status [22]. In areas with a longstanding ID, where an iodine fortification program was implemented, transient iodine-induced hyperthyroidism was observed, and, in the long run, an increased prevalence of hypothyroidism was reported, probably as a result of iodine-induced TAI and maybe a decreased deiodinase type 2 activity in the hypothalamus and pituitary [23].

Finally, it should be mentioned that high iodine intake (urinary iodine >500 µg/L) was associated with an up to 2.2-fold higher risk of SCH and a 2.9-fold higher risk of hypothyroxinemia compared with the reference group (urinary iodine 150–249 µg/L) [21].

Serum hCG Levels and Gestational Week

Serum hCG has a weak thyroid-stimulating activity, especially when levels peak at 10–12 weeks of gestation. During that period, in 10–20% of pregnant women, serum FT4 and FT3 levels can be elevated, and TSH decreased. In one study, all women with serum hCG >400,000 IU/L had temporarily suppressed TSH levels [24]. In another study, it was shown that mean free β-hCG levels of women with suppressed TSH were twice those of women without suppressed serum TSH ($p < 0.05$) [25].

Besides the amount of hCG levels, TSH action can also be impaired due to the presence of increased TPO-Abs, higher BMI, and parity (≥ 2) [26]. In 2 case reports, gestational thyrotoxicosis has been described in the presence of normal levels of serum hCG due to a mutation endowing the TSH receptor with increased sensitivity to serum hCG compared with that of the wild-type receptor [27, 28].

In a Danish study, it was nicely documented that during the first trimester of pregnancy, thyroid function varied according to the gestational week [29]. Therefore, the use of one reference limit for the entire first trimester is probably a simplification. Based on their study results, the authors proposed using TSH reference values of nonpregnant women up to the 7th week of pregnancy, and to decrease the upper TSH limit of nonpregnant women value with 0.4 mU/L during weeks 9–12. For the period between 7 and 9 weeks, a lower TSH reference limit of 0.1 mU/L was proposed. Serum FT4 variation seems to be limited to higher values during weeks 9–12, and it was, therefore, suggested to increase the nonpregnant reference limit by 4% [29].

Body Mass Index

In several studies, TSH values were different in pregnant women as BMI increased, with a TSH distribution shifted to higher values and FT4 to lower ones. In a study performed in Chile, BMI had a small but significant effect on TSH and FT4, which persisted after correction for maternal age, increased TPO-Abs, parity, gestational age, and smoking [30]. In a study in Finland, the upper limits for TSH in women with a BMI between 20 and 25 and with a BMI >30 were 2.86 and 3.50 mU/L, respectively [31]. In some studies, higher serum TSH levels were not observed in women with higher BMIs, what may be explained by differences in iodine intake, the ethnic background, and the number of pregnant women included in the studies [32, 33].

The association between lower FT4 levels and higher BMI in the first trimester appears to be a uniform finding. In the study by Mannisto et al. [31], FT4 levels decreased from 12.3 to 11.6 pmol/L when women with BMI <20 were compared with those with BMI >30. Bestwick et al. [34] expressed FT4 values in multiples of the median and found a decrease in FT₄ of 0.009 multiples of the median per 10-kg increase in BMI.

There are several mechanisms that may lead to increased TSH levels in obesity. Adipose tissue produced cytokines and other inflammatory factors, and leptin increased thyrotropin-releasing hormone (TRH) levels

through a direct action on TRH neurons. Furthermore, an increased deiodinase activity has been described, which leads to a higher conversion of T4 to T3 [35]. Finally, obesity has been associated with a higher prevalence of TPO-Abs [36]. The guidelines of the ATA recommend TSH screening in morbidly obese pregnant women (BMI ≥ 40) [4].

Age

In a Danish study, a multivariate logistic regression analysis of demographic and environmental factors, maternal age >30 years was a risk factor for the development of all types of thyroid disease before, during, and/or up to 5 years after pregnancy [37].

Also, in the general population, the prevalence of TAI and serum TSH increases with age [11]. In most studies in pregnant women, age >30 years was not associated with increased serum TSH levels [9, 10, 38, 39] or TAI [39, 40]. In contrast, in the study by Veltri et al. [40] serum TSH was significantly lower in women >30 years, and, in a study by Korevaar et al. [9], serum FT4 levels were significantly lower. Differences in serum TSH levels observed between studies may be explained by a different iodine and BMI status of the women. The guidelines of the ATA recommend TSH screening in pregnant women >30 years [4].

Parity

In most studies, parity has been investigated in relation to the presence of TAI. The hypothesis is that after each pregnancy the risk for TAI increases through fetal microchimerism, implying that fetal cells that were transferred into the maternal circulation persist after birth and trigger autoimmune diseases [41]. However, the conclusions on this association are unequivocal, maybe due to the number of previous pregnancies that were included and differences in the definition of TAI [42, 43]. Furthermore, in a recent study, the significant association between parity and TAI was lost after adjustment for age [43]. Finally, in one study, a lower prevalence of TAI was observed in women with higher parity [9].

Some studies have investigated the impact of parity on TSH and FT4 levels, and the changes coincided often with those in TAI. In some studies, no impact was observed on serum TSH [9, 10], while in other studies, lower serum TSH levels were observed [29, 44]. Regarding FT4 levels, data are limited to one study in which lower values were noted in pregnant women [9] and another in which no impact was observed [29].

Smoking

In a recent study performed in pregnant women in Belgium, it was shown that 10% smoked, but that the prevalence varied between 3% in women with an African background and 23% in women with a Caucasian (Ca) background [45]. Smoking is known to affect thyroid function, but the magnitude and direction of the effect varied greatly between studies. Data can be summarized as no impact on serum TSH and a slight decrease in FT4 levels [9, 10, 29, 31].

Smoking has been associated with a lower risk for TAI, a change in deiodinase type 2 activity through the effects of nicotine [46], and, finally, with lower serum hCG levels [47].

In a recent study in pregnant women without TAI, smoking was associated with higher serum TSH levels [44]. Disparities between study results may reflect variations in populations and the iodine status. Furthermore, the duration of smoking cessation (that is associated with a higher prevalence of new-onset TAI) and the number of pack-years are not always documented [31, 48].

TSH Diurnal Variation

In a small study including 4 pregnant women during late pregnancy (weeks 34–38), and 2 studies performed during early pregnancy, women had a clear diurnal rhythm, with the highest levels in late evening or early night. Sampling frequency was insufficient for pulsatility analysis, but the data were in line with those in nonpregnant women [49]. This variation does not influence the diagnostic interpretation of test results since most TSH measurements are performed in pregnant women between 8 a.m. and 6 p.m. However, whether reference interval determinations are adjusted for the collecting time is never clearly stated in most studies.

New Candidate Variables Contributing to Variation in Thyroid Function

Iron Status

Iron plays an important role in the normal functioning of TPO, a heme-dependent protein, and it also facilitates the actions of iodine in the thyroid [50, 51]. In pregnant women, iron deficiency (Fe-D) arises since physiological requirements cannot be met by iron absorption from the diet. In industrialized countries, the prevalence of Fe-D in pregnant women ranges from 24 to 44%. Fe-D can be diagnosed by low serum ferritin levels (<15 $\mu\text{g/L}$ has a specificity of 98% and a sensitivity of 75% for Fe-D) [52].

The pilot study investigating the impact of Fe-D on thyroid function in pregnant women in the second and third trimester of pregnancy was published in 2007 by Zimmerman et al. [53] and performed in Switzerland (a borderline ID region). In the third trimester, nearly 40% of women had Fe-D, and 6% had TSH >4.0 mIU/L. Serum ferritin was inversely correlated with serum TSH ($p = -0.506$; $p < 0.0001$) and total T4 ($p = 0.679$; $p < 0.0001$). In a study performed in a Chinese area without ID in 7,953 pregnant women during the first trimester, FT₄ levels were lower in pregnant women with Fe-D ($p < 0.05$). Logistic regression indicated that Fe-D was an independent risk factor for hypothyroxinemia (OR: 2.440, 95% CI: 1.324–4.496, $p = 0.004$; and OR: 3.278, 95% CI: 1.443–7.446, $p = 0.005$, respectively) [54]. In both studies, TAI was not taken into account or an exclusion criterion. In a recent study by Veltri et al. [40] in 1,900 pregnant women performed in Belgium (mild ID), TAI was also analyzed in relation to Fe-D. In the Fe-D group (all over 35%), the prevalence of TAI and SCH was higher than in the non-Fe-D group (10 vs. 6 and 20 vs. 16%, respectively; $p = 0.011$ and 0.049 , respectively). Ferritin was inversely correlated with serum TSH ($p = -0.076$; $p = 0.001$) and positive with FT₄ levels ($p = 0.112$; $p < 0.001$). In the logistic regression and after correction for confounding factors, Fe-D remained associated with TAI ($p = 0.017$) but not with SCH. Finally, it is important to highlight that in the multivariable analysis, Fe-D explained <1% of the variability in log TSH [40].

The pathophysiological mechanisms explaining this association between Fe-D and SCH/TAI remain largely speculative. One explanation could be impaired TPO activity, with decreased iodine incorporation into Tg and the coupling of iodotyrosines, finally leading to lower FT₄ and higher TSH levels [51, 55]. Fe-D can also be a consequence of TAI due to the concomitant presence of autoimmune gastritis, which was present in 33% of TAI patients in one study [56].

Concerning the higher TSH levels/SCH, besides a lower TPO activity, the binding of T₃ to hepatic nuclear receptors, oxygen transport, and finally the conversion from T₄ to T₃ can be impaired [51, 55]. Another hormone that plays an important role in iron metabolism is hepcidin, a systemic iron-regulatory hormone. Only in one study in nonpregnant women with Graves disease, hepcidin levels were correlated with TH, and they were lower in the euthyroid phase than in the hyperthyroid phase when measured with mass spectrometry [57]. No difference in hepcidin levels was found when measured with an ELISA method, and this methodological problem

is one of the reasons why few studies investigated the relationship between hepcidin and thyroid function.

In daily practice, pregnant women often receive multivitamins, of which some contain iron (18 mg) and iodine (150 µg). In this regard, it also deserves attention that the intake of these preparations should be separated from that of LT₄ by at least 4 h to avoid LT₄ malabsorption. To date, no studies in pregnant women have been published providing evidence that iron supplements ameliorate thyroid function. Fe-D as such is a known risk factor associated with obstetrical complications, and this impact might thus in part have been mediated through the thyroid pathway [58]. In order to know whether Fe-D, TAI, or SCH hampers a normal pregnancy evolution, prospective studies are needed.

Ethnic Background

In many metropolitan areas, the population is multi-ethnic. Ethnicity is a whole of genetic, dietary, environmental, and cultural factors. Several studies have shown a difference in the prevalence of thyroid function and TAI between individuals with different ethnic backgrounds, both in pregnant women and the general population [11]. In one study in the USA, the prevalence of TAI was lower in African-American women than in women with a Ca background [59]. In one study in the Netherlands, no difference was observed in the prevalence of TAI between pregnant women of Turkish, Moroccan, Surinamese, and Dutch origin, but in a more recent Dutch study, women of Turkish origin had a higher prevalence of TAI [60, 61]. In 2 studies in the USA, African-American women had significantly lower TSH levels than Ca women [62, 63]. In one of the Dutch studies, no differences in serum TSH levels were observed [61].

The most recent results on this issue come from a cross-sectional study performed in Belgium in 1,683 pregnant women [45]. The prevalence of TAI was significantly lower in women of sub-Saharan descendent (Sa) compared with that in women with a North African (Na), and Ca background (3.3 vs. 8.6 and 11.1%; $p < 0.001$, respectively). Median TSH was significantly lower in Sa and Na than in Ca women (1.3 and 1.4 vs. 1.5 mIU/L; $p = 0.006$ and 0.014 , respectively). The prevalence of SCH was significantly higher in Ca than Na women (5.4 vs. 2.1%, $p = 0.008$).

The reason for the lower prevalence of TAI in African-American and Sa women remains speculative. Smoking and smoking cessation have been associated with a lower and a higher prevalence of Hashimoto disease, respectively [46, 48]. In the Belgian study, women

Fig. 1. Illustration of the impact of variables on thyroid function is shown in a semi-quantitative way. =, no impact; ↑ or ↓, mild impact; ↑↑ or ↓↓, moderate or severe impact; N/A, not applicable; ID, iodine deficiency; Fe-D, iron deficiency; Sa, sub-Saharan; AfAm, African-American; SNPs, single nucleotide polymorphisms; PGF, platelet growth factor; Tg-Abs, thyroglobulin antibodies; TPO-Abs, thyroid peroxidase antibodies.

Impact on TSH	Variable	Impact on FT4	Ref.
↑↑/↑/=	TPO-Abs+	=/↓	9, 10
↑↑/↑/=	Tg-Abs+	=/↓	14, 15
N/A	FT4 assay ¹	=/↓	16, 17
↑/=/↓	TSH assay	N/A	17, 19
↑/=	Mild-to-moderate ID	=/↓	20–23
↑	BMI (≥30)	=/↓↓	30–34
=	Smoking	=/↓	9, 10, 29, 31
↑	Circadian rhythm	=	49
↑/=	Fe-D (ferritin <30 µg/L)	=/↓	40, 53, 54
↓/↓↓/=	Serum hCG (↑ weeks 9–12)	=/↑	27, 28, 47
↓/=	Ethnicity North African ²	=	45
↓/=	Ethnicity (Sa/AfAm) ²	=	45, 62, 63
↓/=	Parity	=/↓	9, 10, 29, 44
↓/=	Age (≥30 years)	=/↓	9, 10, 38–40
↑/=/↓	Genetics (SNPs)	↑/=/↓	8
↑↑/↑	Antiangiogenic PGF	↓/↓↓	73, 74
↑	Proangiogenic PGF	↓/↓↓	73, 74
↑/=	Endocrine disruptors	=/↓	69, 70

⊗: Variables not (yet) determined in daily practice

¹ Versus equilibrium dialysis isotope dilution-mass spectrometry.

² Versus women with Caucasian background.

with a Ca background smoked more than the other women, but they had the highest prevalence of TAI [45]. The impact of smoking might have been wrongly interpreted since smoking cessation was not recorded, and the latter has been associated with the appearance of TAI [48]. In the study of La’ulu and Roberts [59], the lower age of women in the African-American study group compared with the Ca group was a possible explanation for the lower prevalence of TAI. However, in the study by Veltri et al. [45], mean ages were comparable between the groups. Obesity has also been associated with an increased prevalence of TAI, but the prevalence of obesity was the highest in women with other backgrounds than Sa or African-American [35, 36, 45]. Low vitamin D levels have been linked with the presence of TAI [for review, cf 64]. However, in the Belgian context, low vitamin D levels were equally distributed among women with different backgrounds [65]. Furthermore, urinary iodine (median: 117 µg/L; interquartile range: 70–189 µg/L) was not associated with a particular ethnicity [22, 66]. According to Walker et al. [63], the lower TSH levels in African-American women were due to higher hCG levels compared with Ca women. Also, in the study by Korevaar et al. [61], Ca women had lower hCG levels than Moroccan women.

Ethnicity is strongly related to genetics, determining up to 50–60% of the variation in thyroid function [8]. In a recent study, it was shown that mean TSH levels differed according to the ethnicity of the babies in blood spots performed for birth screening [67].

Some studies investigated what the impact of ethnic-specific reference ranges was on the prevalence of SCH in pregnant women [45, 61]. In studies by Korevaar et al. [61] and Veltri et al. [45], it was shown that this would change the diagnosis of SCH in 13 and 16%, respectively. Ethnic-specific reference ranges could be useful in certain groups, but their real additional value should be investigated in relation to pregnancy outcomes before they would be implemented in daily practice. In the ATA guidelines, it is not proposed to determine ethnic-specific TSH reference ranges [4].

Pollutants/Endocrine Disruptors

Perchlorate and thiocyanate decrease thyroidal iodine uptake by competitively inhibiting the sodium iodide symporter (NIS), and, therefore, they can influence thyroid function. Pregnant women with increased iodine needs are more vulnerable to the side effects [68]. This statement was confirmed in a study in 200 nonsmoking pregnant women in Thailand (mild ID area), in which it was shown that low-

level exposure to perchlorate was positively correlated with TSH and inversely with FT4. These associations persisted after correction for gestational age and urinary disruptor concentration to creatinine ratio [69]. In a recent study in pregnant women in New York, the co-occurring exposure to perchlorate, nitrate, and thiocyanate was investigated by using the weighted quantile sum regression (examining mixture effects in epidemiological studies) and suggested that increasing exposure to perchlorate was associated with a significant increase in the odds of a serum TSH in the highest 10th percentile. Perchlorate had the largest weight in the index, and no associations between any exposure and FT4 were found [70]. Discrepancies in the study results may be explained by differences in urinary iodine levels, the degree of exposure, the fact that one or more disruptors were investigated, the use of different statistical methods, and other detection techniques. Endocrine disruptors used in plastics and flame retardants are also able to exert thyroid effects. However, long-term studies on thyroid-related outcomes such as growth and development are lacking [71].

Placental Factors besides hCG

The thyroid has a high vascular density that may be influenced by pregnancy-specific angiogenic factors, both proangiogenic (placental growth factor) and antiangiogenic (vascular endothelial growth factors), such as the soluble FMS-like tyrosine kinase-1 [72].

In a cohort of Norwegian pregnant women with preeclampsia, serum TSH levels were increased 2.42 times above baseline compared with 1.48 in controls, and FT3 levels decreased (case ratio to control ratio: 0.96, 95% CI: 0.92–0.99). Both in women who developed preeclampsia and in controls, the increase in serum TSH levels was strongly associated with increasing levels of predelivery soluble FMS-like tyrosine kinase 1 ($p < 0.001$). Furthermore, women with a history of preeclampsia in their first pregnancy were more likely to have TSH levels >3.5 mIU/L (adjusted OR: 1.7, 95% CI: 1.1–2.5), and the association persisted after the exclusion of TAI [73]. These results were confirmed in a Dutch study, in which the impact of high placental growth factor levels led to a decrease in TSH levels ($p < 0.001$) and an increased risk of hypothyroxinemia (OR: 1.77; 95% CI: 1.02–3.06) [74]. In analogy with the Norwegian study, the antiangiogenic factors were also associated with a decrease in (F)T4 ($p < 0.001$), an increased risk of SCH (OR: 2.37; 95% CI: 1.16–4.83) and isolated hypothyroxinemia (OR: 3.05; 95% CI: 1.42–6.55). The presence of TPO-Abs amplified both the effect of the antiangiogenic profile and proangiogenic placental growth factors.

In Figure 1, the impact of variables on thyroid function is shown in a semiquantitative way.

Conclusions and Perspectives

Although clinical characteristics affect reference ranges within populations, they are poor predictors of (sub-clinical) hypothyroidism in individuals. Therefore, it remains to be elucidated whether the implementation of trimester-, BMI- or ethnicity-based reference ranges can improve the management and outcome of pregnancy. Future studies should aim to identify the impact of novel variables such as endocrine disruptors, iron, and placental factors on the development of thyroid disease to relevant patient subgroups. In the future, all of these markers could be added as a correction factor to an individual's pituitary-thyroid set point and then be used as optimal individual treatment target.

For the time being, TAI remains the variable that is the strongest associated with SCH and altered pregnancy outcomes, and, therefore, its diagnosis should be improved for example with the measurement of Tg-Abs and/or a thyroid echography.

Disclosure Statement

Flora Veltri received no support from any organization.

Kris Poppe was supported by speaker fees for a satellite meeting of the European Thyroid Association (ETA) (IBSA Institut Biochimique SA) in 2016 and the ETA Educational Thyroid Meeting (Berlin-Chemie AG Company) in 2017.

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