Clinical Thyroidology / Original Paper

European
Thyroid Journal

Eur Thyroid J 2017;6:82–88
DOI: 10.1159/000453061

Received: February 16, 2016
Accepted after revision: August 11, 2016
Published online: February 3, 2017

Reference Values for TSH and Free Thyroid Hormones in Healthy Pregnant Women in Poland: A Prospective, Multicenter Study

Marta Kostecka-Matyja[a] Anna Fedorowicz[a] Ewa Bar-Andziak[b] Tomasz Bednarczuk[b] Monika Buziak-Bereza[a] Paulina Dumnicka[c] Maria Górska[d] Małgorzata Krasnodębska[b] Beata Niedźwiedzka[b] Dorota Pach[a] Marek Ruchała[e] Katarzyna Siewko[d] Bogdan Solnica[f] Jerzy Sowiński[e] Małgorzata Szelachowska[d] Małgorzata Trofimiuk-Müldner[a] Katarzyna Wachowiak-Ochmańska[e] Alicja Hubalewska-Dydejczyk[a]

[a]Chair and Department of Endocrinology, Jagiellonian University, Collegium Medicum, Krakow, [b]Department of Internal Medicine and Endocrinology, Medical University, Warsaw, [c]Department of Medical Diagnostics, Jagiellonian University, Collegium Medicum, Krakow, [d]Department of Endocrinology, Diabetology and Internal Medicine, Medical University, Bialystok, [e]Department of Endocrinology, Metabolism and Internal Medicine, University of Medical Sciences, Poznan, [f]Department of Diagnostics, Chair of Clinical Biochemistry, Jagiellonian University, Collegium Medicum, Krakow, Poland

Keywords
Pregnancy · Thyroid function · Thyroid tests · Reference values

Abstract
Objectives: The diagnosis and treatment of thyroid diseases in pregnant women remains a challenge. Various medical associations recommend establishing the reference intervals for thyroid hormones by a local laboratory. Considering differences within geophysical, socioeconomic conditions, and iodine prophylaxis in various populations, it is advisable to assess reference intervals for thyroid hormones specific to a region of residence. The objective was to assess trimester-specific reference intervals for TSH, fT_3, and fT_4 for pregnant women in the Polish population. ***Methods and Results:*** We conducted a prospective study in 4 centers representing different regions of Poland (Krakow, Warsaw, Poznan, and Bialystok). Our study included consecutive, healthy pregnant women (172 patients), with an age range of 27–47 years. All women had a negative history for thyroid diseases, normal thyroid peroxidase antibody levels, and proper iodine prophylaxis. All newborns had TSH levels in the appropriate reference range. Serum TSH, fT_3, fT_4, and thyroid-peroxidase antibodies were measured in each trimester. The reference intervals were calculated using the percentile method, as recommended by the International Federation of Clinical Chemistry. The reference values calculated were 0.009–3.177, 0.05–3.442, and 0.11–3.53 mIU/L for TSH; 3.63–6.55, 3.29–5.45, and 3.1–5.37 pmol/L for fT_3; and 11.99–21.89, 10.46–16.67, and 8.96–17.23 pmol/L for fT_4 in consecutive trimesters of pregnancy. Reference intervals for

KARGER

E-Mail karger@karger.com
www.karger.com/etj

Alicja Hubalewska-Dydejczyk
Chair and Department of Endocrinology
Jagiellonian University, Collegium Medicum
Kopernika 17 str, PL–31-501 Kraków (Poland)
E-Mail alahub@cm-uj.krakow.pl

pregnant women when compared to the general population showed a lower concentration of TSH in every trimester of pregnancy and lower fT_4 in the 2nd and 3rd trimesters. ***Conclusions:*** Using appropriate trimester-specific reference intervals may improve care of pregnant women by preventing misdiagnosis and inadequate treatment.

Introduction

The diagnosis and treatment of thyroid diseases in pregnant women is a difficult and real challenge for the treating physician. Thyroid disorders in women of childbearing age are frequent – they affect around 1.2% of pregnancies [1]. If left untreated, they cause obstetric complications and disorders in fetal development, including placental abruption, preeclampsia, intrauterine growth restriction, preterm birth, and fetal death. This applies to both overt and subclinical hypothyroidism and overt hyperthyroidism [2–7]. In addition, the fetuses of mothers with autoimmune thyroid disease are exposed to maternal antibodies, which may be a cause of neonatal thyroid disease [8, 9].

Thyroid function in pregnant women is modified by additional factors related to pregnancy: plasma volume increased up to 50%, increased levels of proteins binding thyroid hormones, including thyroid-binding globulin, human chorionic gonadotropin (hCG), an increase in the concentration of estrogens, and a relative iodine deficiency [10]. Accordingly, it can be expected that thyrotropin (TSH) and free thyroid hormones concentrations in normal pregnancy differ from those in the general population. Moreover, dynamic changes occur throughout pregnancy.

hCG is produced from the 8th day of pregnancy, initially by the embryo, then consequently by the syncytiotrophoblast. Due to the structural similarity to TSH, it acts as a stimulating agent for the thyroid. The hCG hormone has weak thyrotropic activity (approx. one 10th the potency of TSH) through the activation of the TSH receptor. Chorionic gonadotropin action reaches its peak at the end of the first trimester (max. at 9th to 11th week of gestation), and then gradually decreases. hCG secretion peak corresponds to the decrease in TSH secretion [11].

TSH levels during late pregnancy stay within the reference intervals determined for the general population, but in the first trimester it tends to be lower. The lowest TSH concentrations are found in the 10th to 12th week and then usually normalize in approximately the 18th week of pregnancy. Multiple pregnancy enhances hCG increase and TSH decrease; hCG secretion peak is larger and longer [12].

On the other hand, concentrations of free thyroxine (fT_4) decrease in subsequent trimesters of pregnancy. This is a result of the thyroid response to the increasing level of thyroid-binding globulin, increased demands of the fetus for thyroid hormones in the first trimester of pregnancy, and the altered metabolism of thyroid hormones in the developing placenta in late pregnancy [10].

The Endocrine Society guidelines, published in 2012, regarding the treatment of thyroid disease during pregnancy and postpartum, recommend to determine reference intervals for thyroid hormones by local laboratories [13]. The reference ranges established for the general population are not relevant for pregnant women. Also, since the rapid hormonal changes during pregnancy must be addressed, there is a need for establishing trimester-specific reference intervals.

In Poland there are no published data on thyroid hormone concentrations in healthy pregnant women. The aim of our study was to establish trimester-specific reference intervals for TSH, fT_3, and fT_4 in Polish pregnant women.

Material and Methods

The study included 172 pregnant women examined at 4 locations: Krakow, Bialystok, Poznan, and Warsaw. The median age was 35 years (range: 27–47, interquartile range: 33–39). All women were healthy, had no history of thyroid disease, were using the recommended iodine prophylaxis, and had normal thyroid-peroxidase antibodies (anti-TPO <50 IU/mL). Anti-TPO was only measured as it is considered as a more sensitive marker of thyroid autoimmunity, and so far there are not enough studies confirming the usefulness of measuring both anti-TPO and anti-TG (anti-thyroglobulin antibodies) [14].

We excluded patients with previously diagnosed thyroid disease, taking medication with proven impact on the function of the thyroid gland, with elevated TSH values in relation to the reference values for the general population and those that developed other illnesses during pregnancy. In addition, we retrospectively excluded from the group patients whose newborns had TSH >15 mIU/L in their screening test.

In all of the centers, there was approval from the ethics committee and the patients signed a consent for the study.

TSH, fT_3, fT_4, and anti-TPO serum concentrations were measured 3 times, i.e., in the first, second, and third trimesters of pregnancy. Some women did not come in the recommended time, so for some of them there is no data for all trimesters of pregnancy. Neonatal TSH concentrations were collected from a Polish national screening program of newborns that includes all newborns in Poland.

Table 1. Results of TSH, fT_3, and fT_4 in the study group in consecutive trimesters of pregnancy

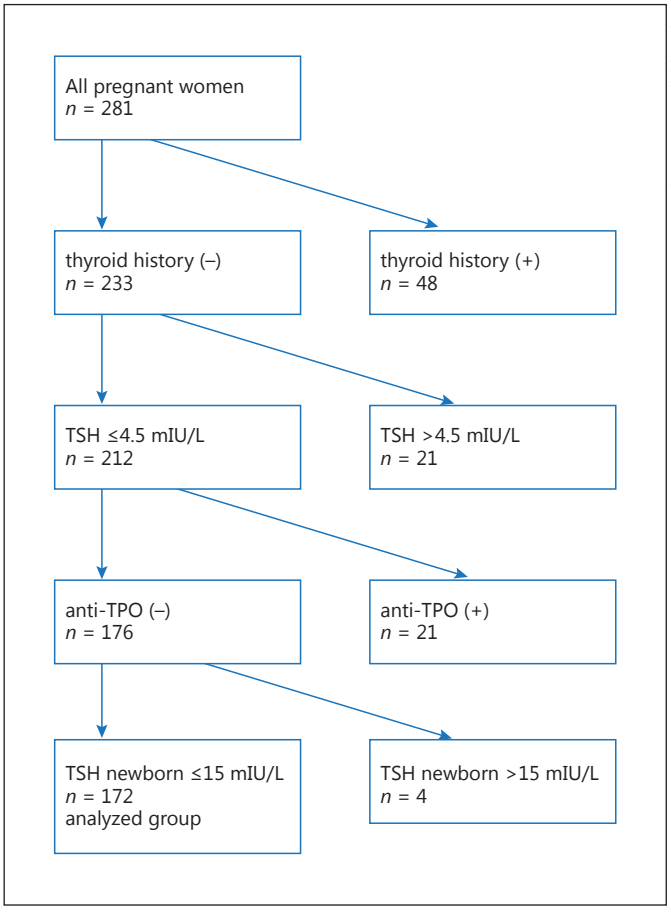
	1st trimester (n = 172)	2nd trimester (n = 172)	3rd trimester (n = 152)
TSH, mIU/L	1.16 (0.400–1.805)	1.26 (0.81–2.01)	1.27 (0.77–1.93)
fT_3, pmol/L	4.88 (4.47–5.29)	4.14 (3.73–4.66)	4.04 (3.78–4.42)
fT_4, pmol/L	15.48 (14.24–17.43)	13.23 (12.09–14.40)	12.36 (11.24–13.81)

Values are presented as medians (lower–upper quartile).

Blood samples from pregnant women were collected in the morning, fasting, or after a light meal. The blood was centrifuged after complete clotting, after 30–40 min from collection. TSH, fT_3, fT_4, and anti-TPO antibodies in serum were measured with an electrochemiluminescence Elecsys analyzer, using reagent kits from Roche. Limits of quantification were 0.005–100 mIU/L for TSH, 0–50 pmol/L for fT_3, 0–100 pmol/L for fT_4, and 5–600 IU/mL for anti-TPO. Reference ranges for adults used in the laboratory in which the assay were performed were 0.3–4.5 mIU/L for TSH, 11–22 pmol/L for fT_4, 3.1–6.8 pmol/L for fT_3, and 0–50 IU/mL for anti-TPO.

Statistical Analysis

As the analyzed variables had nonnormal distributions ($p < 0.05$ in the Shapiro-Wilk and Anderson-Darling tests), data are presented as medians (lower–upper quartile). Also, because of the nonnormal distributions of the variables, nonparametric statistical tests were used, i.e., a Mann-Whitney test to assess the differences between the groups, and Friedman ANOVA to assess differences between the paired variables (repeated measures). The Spearman rank correlation coefficient was calculated to study associations between variables. Results were considered significant at $p < 0.05$. Reference intervals were assessed with the percentile method, using bootstrap, as recommended by the International Federation of Clinical Chemistry (IFCC) [15]. Outliers were detected by the Horn algorithm (with a ratio of 2) [15]. Before calculating the reference intervals, outliers were rejected (Fig. 1 shows the number of patients in each group after outlier rejection). The 2.5 and 97.5 percentiles were accepted as the limits of reference intervals. The software used for calculations was Statistica 10 (StatSoft, Tulsa, OK, USA) and RefVal 4.11 (HE Solberg, Oslo, Norway [16]).



Color version available online

Fig. 1. Flowchart of included/excluded pregnant women.

Results

The concentrations of TSH, fT_3, fT_4, and anti-TPO in all studied patients in consecutive trimesters of pregnancy are shown in Table 1.

Changes in hormone levels in this group of patients are shown in Figure 2. The concentration of TSH was significantly lower in the first trimester compared to the 2nd and 3rd trimesters of pregnancy (median: 0.934, 1.505, and 1.360 mIU/L; $p < 0.0001$ Friedman test); TSH concentrations in the 2nd and 3rd trimesters did not differ significantly. fT_3 concentration was significantly higher in the 1st trimester compared to the 2nd and 3rd trimesters (4.88, 4.04, and 3.94 pmol/L; $p < 0.0001$). fT_4 concentration was highest in the 1st trimester of pregnancy and decreased in subsequent measurements (15.47, 13.20, and 12.61 pmol/L; $p < 0.0001$).

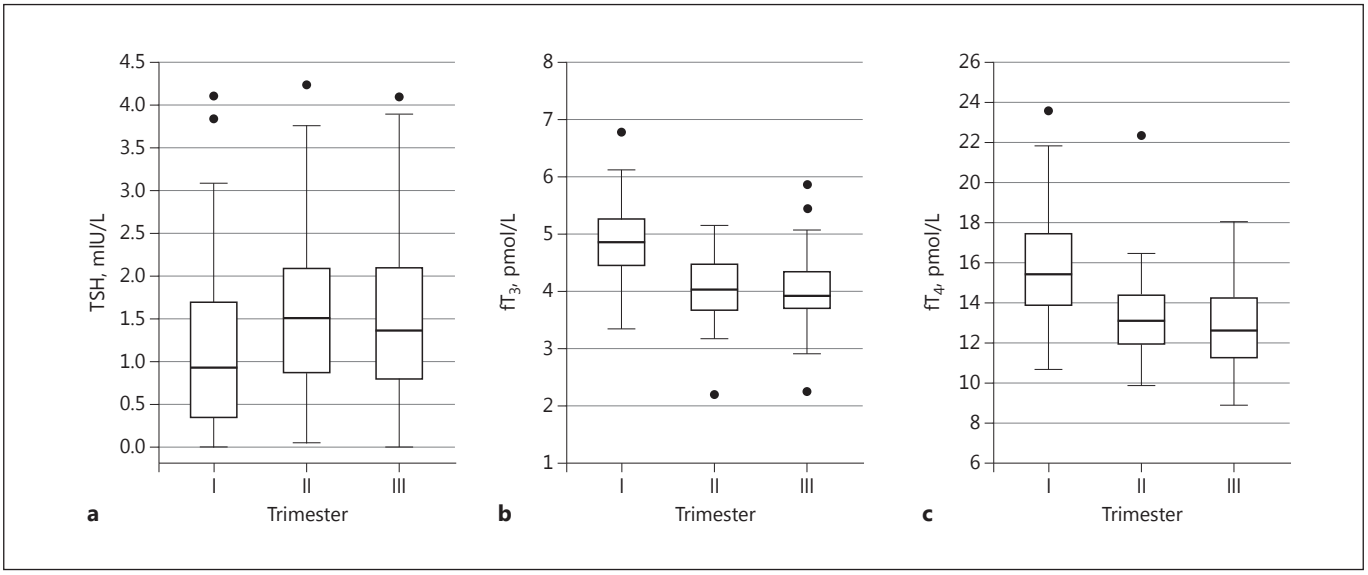


Fig. 2. The concentrations of TSH (**a**), fT_3 (**b**), and fT_4 (**c**). Data is presented as medians, interquartile range (box), nonoutlier range (whiskers), and outliers (dots). Significant differences between repeated measurements are described in the text.

The concentrations of TSH measured in each trimester of pregnancy were strongly correlated (correlation coefficients: $R = 0.69$ between measurements carried out in the 1st and 2nd trimesters; $R = 0.85$ between the 2nd and 3rd trimesters; $R = 0.70$ between the 1st and 3rd trimesters, respectively; $p < 0.0001$ for all correlations). Similar but weaker correlations were observed for fT_3 (R = 0.24, $p = 0.008$; $R = 0.44$, $p < 0.0001$; $R = 0.32$, $p = 0.004$, respectively) and fT_4 concentrations ($R = 0.44$, $p < 0.0001$; $R = 0.56$, $p < 0.0001$; $R = 0.32$, $p = 0.003$, respectively).

Neonatal TSH concentrations did not correlate with the concentrations of TSH and thyroid hormones in the mothers; the exception was a weak negative correlation with 1st trimester fT_4 ($R = –0.18$, $p = 0.036$).

TSH concentrations higher than 2.5 mIU/L in the 1st trimester were observed in 12 (5%) patients. These patients, as compared with the rest of the group, also had higher concentrations of TSH in the 2nd (2.87 [2.19–3.22] vs. 1.25 [0.76–1.99]; $p < 0.0001$) and 3rd trimesters (2.90 [2.10–3.70] vs. 1.30 [0.75–1.94]; $p = 0.001$). However, the concentrations of fT_3 or fT_4 in these patients were not different from the rest of the group throughout the pregnancies. There were no differences between the described groups in the levels of thyroid hormones in the whole course of pregnancy ($p > 0.3$ for all comparisons). Also, the children born to women who had TSH above 2.5 mIU/L in the 1st trimester did not differ from other newborns with regard to neonatal TSH concentrations (2.15 [1.39–2.67] vs. 2.23 [0.96–3.09] mIU/L; $p = 0.6$).

Reference intervals for TSH, fT_3, and fT_4 calculated for consecutive trimesters of pregnancy are shown in Table 2.

Discussion

We present trimester-specific reference intervals for TSH, fT_3, and fT_4 calculated for pregnant women in Poland.

In Poland, widespread iodine prophylaxis began in 1996, based on mandatory iodination of salt and baby formula. This program was later improved by recommending iodine supplementation in pregnant and breastfeeding women (100–200 mg of potassium iodide). This has provided a reduction in the incidence of goiters in children and has lowered the concentration of TSH in newborns [17, 18]. This is the first study on thyroid hormone concentrations during pregnancy after the beginning of iodine prophylaxis in the Polish population.

TSH

TSH concentrations are low in the first trimester of pregnancy and increase subsequently. In our study, TSH

Table 2. The reference ranges for TSH, fT_3, and fT_4 in consecutive trimesters of pregnancy

	1st trimester (n = 172)	2nd trimester (n = 172)	3rd trimester (n = 152)
TSH, mIU/L	0.009 (0.008–0.010) 3.18 (2.96–3.83)	0.05 (0.01–0.11) 3.44 (3.05–3.77)	0.11 (0.03–0.19) 3.53 (2.94–3.94)
fT_3, pmol/L	3.63 (3.43–3.71) 6.55 (6.23–6.84)	3.29 (3.16–3.41) 5.45 (5.20–5.64)	3.10 (2.92–3.26) 5.37 (5.04–5.55)
fT_4, pmol/L	11.99 (11.52–12.15) 21.89 (20.84–23.92)	10.46 (10.34–10.67) 16.67 (16.03–17.20)	8.96 (8.63–9.62) 17.23 (16.20–18.32)

Lower and upper limits of the reference intervals (2.5 and 97.5 percentiles) are provided with 90% confidence intervals.

was significantly lower in the 1st trimester compared to the 2nd and 3rd trimesters of pregnancy, the concentration in the 2nd and 3rd trimesters did not differ significantly. TSH levels measured in consecutive trimesters of pregnancy were strongly correlated with each other. This is consistent with the results of other researchers who developed the reference intervals for pregnancy [19–22]. Our study shows that the upper limits of the reference for TSH are slightly higher than recommended by the Endocrine Society guidelines [11] in the 1st, 2nd, and 3rd trimesters of pregnancy (i.e., 3.177, 3.442, and 3.530 mIU/L, compared to the recommended 2.5 mIU/L in the 1st trimester of pregnancy and 3 mIU/L in the 2nd and 3rd trimesters, respectively). This is probably related to geographical location, current iodine prophylaxis in Poland, and other specific characteristics of the population.

Springer et al. [19] compared the reference intervals of TSH and fT_4 in early pregnancy in 216 Czech women using the 7 most popular methods of analysis. The upper reference limit for TSH was 3.81 (3.48–4.16) mIU/L, and in our study it was 3.177 (2.963–3.830) mIU/L. Both studies were done on the basis of the results obtained using reagent kits from Roche.

The study by Khalid et al. [20] investigating the reference intervals for thyroid function tests during pregnancy in women in Ireland (n = 351, mean age: 30 years) set the upper reference limit for TSH in the first trimester (12 weeks' gestation) at 3.0 mIU/L. They also used reagent kits from Roche.

It is also difficult to determine the lower limit of the reference for TSH, especially in the 1st trimester of pregnancy. As mentioned, the strong interference with hCG significantly reduces the concentrations of TSH in this period, which is not synonymous with the diagnosis of hyperthyroidism. Many researchers who want to determine the lower limit adopt different exclusion criteria in their studies. In the Irish study [20], women with TSH <0.1 mIU/L were excluded only if the clinical diagnosis of hyperthyroidism was made, and the Czech study [19] excluded women with TSH <0.01 mIU/L and fT_4 >23 pmol/L, and/or elevated anti-thyroid peroxidase antibodies. In our study, for the determination of reference intervals we included pregnant women with normal anti-thyroid peroxidase antibodies and excluded hyperthyroidism. Respectively, the lower reference limit for TSH in the 1st trimester was 0.1 mIU/L in the Irish study [20], 0.25 mIU/L in the Czech study [19], and 0.009 mIU/L in our study. Decreased TSH levels during pregnancy must be interpreted by an experienced clinician, including other laboratory and clinical parameters.

TSH reference intervals in the 2nd and 3rd trimesters were higher, respectively 0.050–3.442 and 0.110–3.530 mIU/L, which is also described by other authors. However, the lower reference limit in the second and third trimester of pregnancy in our observations is still lower than in the general population.

fT_4 and fT_3

fT_3 concentrations were significantly higher in the 1st trimester compared to the 2nd and 3rd trimesters (median: 4.88, 4.04, and 3.94; $p < 0.0001$). fT_4 concentrations were highest in the 1st trimester of pregnancy and decreased in subsequent measurements (median: 15.47, 13.20, and 12.61; $p < 0.0001$). Our data are consistent with the observations in the Czech [19] and Irish [20] studies, in which the reference intervals for fT_4 in the first

trimester of pregnancy equaled 11.5–18.6 and 11–19 pmol/L, respectively. In our study, reference intervals calculated for Polish women in the 1st trimester were 11.99–21.89 pmol/L, and in subsequent trimesters 10.46–16.67 pmol/L and 8.96–17.23 pmol/L. The concentrations of free thyroxine decrease in consecutive trimesters of pregnancy. This is a result of the thyroid response to the growing level of thyroid-binding globulin, increased fetal demand for thyroid hormones in the 1st trimester of pregnancy, and the altered metabolism of thyroid hormones in the developing placenta in late pregnancy. A significant decrease in the level of fT_4 in late pregnancy for healthy pregnant women is a common phenomenon and some authors report that isolated hypothyroxinemia does not affect pregnancy and child development [23, 24]. However, there are studies that show hypothyroxinemia, especially in the early stages of pregnancy, is a predictor of lower motor and intellectual development and pregnancy outcomes [25–27].

Comparing the reference intervals for TSH and thyroid hormones is very difficult. In the studies we chose for the comparison, the researchers used the same laboratory methods and reagent kits as we did, and the populations analyzed in those studies were as close as possible to the Polish population. However, it is important to underline, as shown in the study of Bliddal et al. [21], that even in the same region, the use of gestational-age-specific reference ranges from different laboratories led to misclassification due to differences in the immunoassays used. Up to 100% of maternal fT_4 levels fell outside the other cohort's reference range despite similar TSH levels.

As recommended by the Endocrine Society, it is advisable to determine the reference intervals for pregnant women in a given geographical area. Our results confirm the validity of recommendations for developing own reference intervals for thyroid hormones in different countries. Ethnicity, a degree of nutritional deficiency, and/or iodine supplementation have a significant effect on thyroid function during pregnancy [14]. The results of our study will help in the proper care and treatment of Polish women with impaired thyroid function in pregnancy.

Disclosure Statement

The authors have nothing to disclose.

References

1 Cotzias C, Wong SJ, Taylor E, et al: A study to establish gestation-specific reference intervals for thyroid function tests in normal singleton pregnancy. Eur J Obstet Gynecol Reprod Biol 2008;137:61–66.
2 Abalovich M, Gutierrez S, Alcaraz G, et al: Overt and subclinical hypothyroidism complicating pregnancy. Thyroid 2002;12:63–66.
3 Benhadi N, Wiersinga WM, Reitsma JB, et al: Higher maternal TSH levels in pregnancy are associated with increased risk for miscarriage, fetal or neonatal death. Eur J Endocrinol 2009; 160:985–991.
4 Idris I, Srinivasan R, Simm A, et al: Maternal hypothyroidism in early and late gestation: effects on neonatal and obstetric outcome. Clin Endocrinol (Oxf) 2005;63:560–565.
5 Lazarus J, Brown RS, Daumerie C, et al: 2014 European Thyroid Association Guidelines for the Management of Subclinical Hypothyroidism in Pregnancy and in Children. Eur Thyroid J 2014;3:76–94.
6 Nazarpour S, Ramezani Tehrani F, Simbar M, et al: Thyroid dysfunction and pregnancy outcomes. Iran J Reprod Med 2015;13:387–396.
7 Saki F, Dabbaghmanesh MH, Ghaemi SZ, et al: Thyroid function in pregnancy and its influences on maternal and fetal outcomes. Int J Endocrinol Metab 2014;12:e19378.
8 Nazarpour S, Ramezani Tehrani F, Simbar M, et al: Thyroid autoantibodies and the effect on pregnancy outcomes. J Obstet Gynaecol 2016; 36:3–9.
9 Bliddal S, Feldt-Rasmussen U: TPOAbs as a risk factor in pregnancy. Thyroid Int 2014; 3:1–20.
10 Glinoer D: The regulation of thyroid function in pregnancy: pathways of endocrine adaptation from physiology to pathology. Endocr Rev 1997;18:404–433.
11 Hershman JM: The role of human chorionic gonadotropin as a thyroid stimulator in normal pregnancy. J Clin Endocrinol Metab 2008;93:3305–3306.
12 Ashoor G, Muto O, Poon LC, et al: Maternal thyroid function at gestational weeks 11–13 in twin pregnancies. Thyroid 2013;23:1165–1171.
13 DeGroot l, Abalovich M, Alexander EK, et al: Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2012;97:2543–2565.
14 Unuane D, Velkeniers B, Anckaert E: Thyroglobulin autoantibodies: is there any added value in the detection of thyroid autoimmunity in women consulting for fertility treatment? Thyroid 2013;23:1022–1028.
15 Solberg HE: The IFCC recommendation on estimation of reference intervals. The RefVal program. Clin Chem Lab Med 2004;42:710–714.
16 Solberg HE, Lahti A: Detection of outliers in reference distributions: performance of Horn's algorithm. Clin Chem 2005;51:2326–2332.
17 Zygmunt A, Lewinski A: Iodine prophylaxis in pregnant women in Poland – where we are? (update 2015). Thyroid Res 2015;8:17.
18 Szybinski Z: Iodine prophylaxis in Poland in light of the WHO recommendation on reduction of the daily salt intake. Pediatr Endocrinol Diabetes Metab 2009;15:103–107.
19 Springer D, Bartos V, Zima T: Reference intervals for thyroid markers in early pregnancy determined by 7 different analytical system. Scand J Clin Lab Invest 2014;74:95–101.

20 Khalid AS, Marchocki Z, Hayes K, et al: Establishing trimester-specific maternal thyroid function reference intervals. Ann Clin Biochem 2014;51:277–283.
21 Bliddal S, Feldt-Rasmussen U, Boas M, et al: Gestational age-specific reference ranges from different laboratories misclassify pregnant women's thyroid status: comparison of two longitudinal prospective cohort studies. Eur J Endocrinol 2013;170:329–339.
22 Amouzegar A, Ainy E, Khazan M: Local versus international recommended TSH references in the assessment of thyroid function during pregnancy. Horm Metab Res 2014;46:206–210.
23 Pop VJ, Brouwers EP, Vader HL: Maternal hypothyroxinaemia during early pregnancy and subsequent child development: a 3-year follow-up study. Clin Endocrinol (Oxf) 2003;59:282–288.
24 Craig WY, Allan WC, Kloza EM: Mid-gestational maternal free thyroxine concentration and offspring neurocognitive development at age two years. J Clin Endocrinol Metab 2012;97:E22–E28.
25 Korevaar TI, Schalekamp-Timmermans S, de Rijke YB, et al: Hypothyroxinemia and TPO-antibody positivity are risk factors for premature delivery: the Generation R Study. J Clin Endocrinol Metab 2013;98:4382–4390.
26 Finken MJ, van Eijsden M, Loomans EM, et al: Maternal hypothyroxinemia in early pregnancy predicts reduced performance in reaction time tests in 5- to 6-year-old offspring. J Clin Endocrinol Metab 2013;98:1417–1426.
27 Berbel P, Mestre JL, Santamaría A, et al: Delayed neurobehavioral development in children born to pregnant women with mild hypothyroxinemia during the first month of gestation: the importance of early iodine supplementation. Thyroid. 2009;19:511–519.