Symptoms of anxiety and thyroid axis function during pregnancy

Nerimo simptomai ir skydliaukės ašies funkcija nėštumo metu

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SUMMARY

Objective of the study was to assess the relationship of symptoms of anxiety and thyroid function during pregnancy.

Material and methods: 199 consecutive women, attending antenatal clinic at the University Hospital as well as at the Primary Health Care Center were invited to the study. All women in the first, in the second, and in the third trimester of pregnancy fulfilled anxiety sub-scale of the revised symptom checklist of Derogates for the assessment of anxiety symptoms. At the same assessment points blood samples were collected for the measurement of thyroid axis function: thyroid stimulating hormone (TSH) and free thyroxine (FT4) concentrations.

Results: Significant negative correlation was established between scores on anxiety subscale and TSH concentrations (Spearman's r= –0.164, p=0.021) in the second trimester of pregnancy. Multivariate logistic regression analysis revealed two independent risk factors for presence of anxiety symptoms in the second trimester of pregnancy: lower TSH concentrations (OR=0.44, 95% CI (0.22; 0.89) and employment status (OR=2.42, 95% CI (1.01; 5.79). No significant relationship was found between the scores on anxiety subscale and FT4 concentrations.

Conclusions: This study showed that symptoms of anxiety were related to TSH concentrations in the mid-pregnancy. Moreover, presence of anxiety symptoms was independently associated with low TSH concentrations.

Keywords: symptoms of anxiety, thyroid, pregnancy, thyroid stimulation hormone.

SANTRAUKA

Tyrimo tikslas. Įvertinti nerimo simptomų ir skydliaukės ašies funkcijos ryšį nėštumo metu.

Metodai. Į tyrimą įtrauktos 199 moterys, kurios nėštumo metu lankėsi Kauno medicinos universiteto ir Šilainių pirminės sveikatos priežiūros centro Moterų konsultacijose. Visos moterys pirmojo, antrojo ir trečiojo nėštumo trimestro metu pildė Savęs vertinimo simptomų klausimyno Nerimo subskalę nerimo simptomų pasireiškimui vertinti. Tuo pačiu metu buvo imami kraujo mėginiai skydliaukės stimuliuojančio hormono (TSH) ir laisvojo tiroksino (FT4) koncentracijai nustatyti.

Rezultatai. Antrąjį nėštumo trimestrą nustatytas reikšmingas neigiamas koreliacinis ryšys tarp nerimo simptomų (išreikštų nerimo subskalės balais (ir TSH koncentracijos kraujyje (Spirmeno r=–0,164, p=0,021). Daugiamatės logistinės regresijos analizė parodė dviejų nepriklausomų rizikos veiksnių įtaka nerimo simptomų pasireiškimui antrająjį nėštumo trimestrą: mažesnė TSH koncentracija kraujyje (ŠS=0,44, 95 proc. PI (0,22; 0,89) ir darbas ne namuose (ŠS=2,42, 95 proc. PI (1,01; 5,79). Ryšys tarp nerimo subskalės balų ir FT4 koncentracijos kraujyje buvo nereikšmingas.

Išvados. Šis tyrimas parodė, kad nerimo simptomai buvo susiję su TSH koncentracija nėštumo viduryje. Be to, nerimo simptomų pasireiškimas buvo nepriklausomai susijęs su maža TSH koncentracija.

Raktažodžiai: nerimas, skydliaukė, nėštumas, skydliaukės stimuliacija hormonais.

INTRODUCTION

During pregnancy many changes occur in a woman's life, from changes in hormones metabolism, to changes in stress reactivity and mood.

Pregnancy is accompanied by alterations in thyroid function because of the rise in human chorionic gonadotropin (hCG) concentrations and in thyroglobulin concentrations [1–4].

The hCG is a weak thyroid stimulator. HCG concentrations rise sharply shortly after implantation of the ovum and peak concentration are reached near the end of the first trimester. Thereafter they decline, but till the end of pregnancy there are substantial concentrations of hCG [5]. In the first trimester of pregnancy high hCG concentration correlate with a decrease in serum Thyroid Stimulating Hormone (TSH) concentrations [6–9]. The other important change in thyroid economy is the estrogen-driven increase in the Thyroxine-Binding Globulin (TBG) concentrations, the key thyroid hormone-binding protein [6]. It has been determined that two thirds of circulating thyroxine (T4) is carried by TBG and that the proportion increases up to 85% during pregnancy [10], therefore low maternal free thyroxine (FT4) concentration are thought to be physiologically normal during the second and the third trimesters of pregnancy [1]. Delivery leads to a rapid reversal of this process and serum TBG concentrations return to normal within 4–6 weeks. With that, serum T4 and T3 also return to pregestational serum levels [11].

Up to 10% of pregnant women have elevated concentration of thyroid antibodies [12]. Thyroid autoimmunity and thyroid dysfunction are association with symptoms of depression [13, 14] as well as with symptoms of anxiety [15, 16]. Data from epidemiological studies provide conflicting evidence as to associations between thyroid disorders and mental symptoms [17, 18].

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Depressive and anxiety disorders are the most common psychiatric illnesses during pregnancy and the postpartum period. Maternal depression or anxiety during pregnancy has been recognised to affect foetus and to interfere with obstetrical outcomes [19–22], such as gestational hypertension, bleeding during pregnancy [23], spontaneous early labour [24–27], neonatal growth [24, 28], birth weight [28, 29 30, 31, 32] and decreased Apgar scores [28, 33, 34]. Moreover, women, who suffer from depression or anxiety during pregnancy, are at high risk to suffer from depression or anxiety in the postpartum period [35, 36] with all its negative consequences for the mother-infant relationship.

The aim of the study was to assess the relationship between symptoms of anxiety and thyroid axis function during pregnancy.

Study subjects and design

Women, who during a year of 2005 signed for the antenatal follow-up at two antenatal clinics in Kaunas, Lithuania, were invited to participate in the study. Three hundred and seven women signed an informed consent for participation. Women who missed at least one of three assessment points during pregnancy (n=77; 25%) were excluded from the study. Of 230 (75%) women, who attended all three assessment points, 28 women missed one or two blood draws. Moreover, one woman on thyroid medication, as well as one woman with diabetes mellitus, and another woman with sclerosis disseminate were excluded from the study. Therefore 199 (65%) women were eligible for the analyses. Sample characteristics of the subjects are shown in Table 1.

For thyroid function analyses, serum concentrations of TSH and FT4 were measured in the first trimester (at 12–16 weeks of pregnancy), in the second trimester (22–26 weeks of pregnancy) and in the third trimester (32–36 weeks of pregnancy). At the same three assessment points, women fulfilled self-rating scales for the assessment of symptoms of anxiety: the anxiety sub-scale of the revised symptom checklist of Derogates (SCL-90-R) [21].

The study was approved of by the Regional Biomedical Research Ethics Committee in Kaunas, Lithaunia.

METHODS

Thyroid parameters. TSH concentrations were measured using a solid-phase, two site chemiluminescent enzyme immunometric assay (IMMULITE Third generation TSH, Diagnostic Products Corporation, Los Angeles USA). The FT4 concentrations were measured with a solid-phase immunometric assay (IMMULITE Free T4). For both parameters, the above-mentioned non-pregnant reference ranges were used: 0.27–4.2 mIU/l and 10.3–25.7 pmol/l, respectively.

Psychological parameters. Symptoms of anxiety were assessed using the anxiety sub-scale of the revised symptoms checklist of Derogates (SCL-90-R) [37]. This psychometric instrument measure the intensity of anxiety symptoms, but doesn't provide a syndromal diagnosis. SCL-90-R is a self-rating scale, consisting of nine subscales measuring all kinds of psychopathology (somatization, obsessive-compulsive symptoms, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, psychoticism). Although only anxiety subscale of the SCL-90-R was used in this study. Anxiety subscale consists of 10 items and the item's score ranges from one to five. Normally, no cut-off levels are used, but in the present study scores above the third quartile (>75th percentile) of the anxiety subscale in the first trimester defined intense anxiety symptoms during all three trimesters of pregnancy.

Statistical methods

The distribution of thyroid, as well as psychological parameters was evaluated using a Kolmogorov-Smirnov test. To investigate the relationship between thyroid parameters and symptoms of anxiety, Spearmans' correlations were computed. Means of FT4 during different trimesters of pregnancy were compared using general linear model for repeated measures and pairwise comparisons. TSH concentrations, anxiety symptoms during different trimesters of pregnancy were compared using Friedman test and pairwise comparisons (Newman-Keuls test) [38]. In order to investigate independent relationship of the anxiety subscale and TSH concentrations, multivariate logistic regression analysis was performed, using the presence of anxiety symptoms in the second trimester as a dependent variable. All hypothesis were testing two tail and at 95% confidence level. Statistical analysis was performed using the Statistical Package of Social Science (SPSS).

RESULTS

Demographic and psychosocial characteristics of the participants are summarized in Table 1.

Thyroid parameters

The biochemical parameters of thyroid function are given in Table 2. Reference values are expressed as the mean values with the normal range of nonpregnant subjects. TSH concentrations showed the lowest values in the first trimester and the highest values in the second trimester of pregnancy. According to pairwise comparisons [38], TSH concentrations in the first trimester of pregnancy (median 0.73) was significantly different from TSH concentrations in the second trimester (median 0.95) and from TSH concentrations in the third trimester (median 0.91) ($p<0.05$). Median of TSH concentrations in the second and in the third trimesters were not significantly different ($p>0.05$). FT4 gradually decreased during pregnancy: mean FT4 was 17.2 (SD 2.3), 14.6 (SD 1.9) and 14.0 (SD 1.8) respectively in the first, in the second and in the third trimester of pregnancy. All three pairwise FT4 concentrations comparisons show significantly different values ($p<0.001$) (Table 2).

According to reference ranges for non-pregnant subjects, we didn't defined any pregnant woman with overt thyroid dysfunction, nevertheless, some subjects showed low values of TSH: 13.6%, 2.5%, 1.5% in the first, in the second, and in the third trimester respectively; only one woman showed slightly elevated TSH concentration (4.82 mIU/l) with normal FT4 concentration in the first trimester. One women showed slightly elevated FT4 concentration (26.8 pmol/l) with normal TSH concentration in the second trimester of pregnancy and two women showed slightly reduced FT4 (8.64 pmol/l and 9.28 pmol/l, respectively) with normal TSH concentrations in the third trimester of pregnancy.

Table 1. **Demographic and psychosocial characteristics of the 199 study participants**

Characteristic	N (%)
Age (years)	29 (±5)[a]
Parity	
0	125 (62.8%)
1	62 (31.2%)
2-5	12 (6%)
Previous miscarriages in life	
No	152 (76.4%)
Yes	47 (23.6%)
Education	
Low	46 (23.1%)
Middle	57 (28.7%)
High	96 (48.2%)
Working outside home	
No	31 (15.5%)
Part time	33 (16.6%)
Full time	135 (67.8%)
History of anxiety and/or depression:	
No	169 (84.9%)
Yes	30 (15.1%)
History of depression:	
No	179 (89.9%)
Yes	20 (10.1%)
History of depression in the family	
No	160 (80.4%)
Yes	39 (19.6%)
Mother's depression:	
No	176 (88.4%)
Yes	23 (11.6%)
Pregnancy	
Wanted	178 (89.4%)
Unwanted und unplanned	21 (10.6%)
Smoking during pregnancy	
No	195 (98%)
Yes	4 (2%)
Alcohol consumption during pregnancy	
No	148 (74.8%)
Yes	51 (25.6%)

Table 2. **Biochemical parameters of thyroid function during pregnancy**

Thyroid parameters	1st trimester	2nd trimester	3rd trimester
Thyroid Stimulating Hormone (normal range 0.27–4.2 mU/l)			
Median	0.73 [a]	0.95 [b]	0.91 [c]
Interquartile range	0.74	0.73	0.61
<Low value (%)	27 (13.6)	5 (2.5)	3 (1.5)
>High value (%)	1 (0.5)	0	0
Free Thyroxin (normal range10.3–25.7 pmol/l)			
Median	17 [a]	14.5 [b]	13.9 [c]
Interquartile range	3.0	2.2	2.2
<Low value (%)	0	0	2 (1)
>High value (%)	0	1 (0.5)	0
Antibodies		--	--

Values are given as the median ±interquartile range. Reference ranges for nonpregnant subjects are indicated in parentheses.
TSH: a–b, a–c; p<0.05, b–c; p>0.05
FT4: a–b, b–c, a–c; p<0.001

Psychological parameters

Characteristics of the anxiety subscale of SCL-90-R during pregnancy are summarized in Table 3. Higher scores of the anxiety subscale of SCL-90-R were in the first trimester, lower – in the second and in the third trimesters. Median of the anxiety subscale scores were 0.4, 0.3 and 0.3 in the first, in the second and in the third trimester of pregnancy. (Table 3). According to pairwise comparisons [38], anxiety subscale of the SCL-90-R in the first trimester was significantly different from anxiety subscales in the second and in the third trimesters ($p<0.05$); anxiety subscale in the second and in the third trimesters were not significantly different ($p>0.05$). Incidence of intense anxiety symptoms gradually decreased during pregnancy: 27%, 22%, 17%, respectively in the first, in the second and in the third trimester of pregnancy. (Table 3).

Thyroid parameters and symptoms of anxiety

The relationship of thyroid parameters and symptoms of anxiety are summarised in Table 4. Spearman correlations showed a low but significant negative relationship between the scores on anxiety subscale and TSH concentrations only in the second trimester of pregnancy ($r=–0.16$, $p<0.05$). No significant relationship was found between the scores on anxiety subscale and FT4 concentrations. In order to investigate the independent relationship of the anxiety subscale and TSH concentrations, logistic regression analysis was performed, using presence of anxiety symptoms in the second trimester as a dependent variable. Independent variables included at the univariate level, were: TSH concentrations, age, working outside home, low education, unwanted and/or unplanned pregnancy, nulli-parity, miscarriage earlier in life, smoking or alcohol intake during pregnancy, history of depression, history of anxiety and /or depression, history of psychiatric treatment, depression in the family, mothers' depression, psychosocial stressors during a year. Univariate logistic regression analysis revealed four significant variables, associated with greater risk of intense anxiety symptoms in the second trimester of pregnancy: TSH concentrations, psychosocial stressors during a year, not working outside home and history of anxiety and/or depression during pregnancy. Multivariate logistic regression analysis revealed two independent significant risk

Table 3. **Characteristics the anxiety subscale of SCL-90-R during pregnancy**

Characteristics	1st trimester	2nd trimester	3rd trimester
SCL-90-R anxiety subscale			
Median	0.4	0.3	0.3
Interquartile Range	0.4	0.5	0.4
SCL-90-R anxiety subscale >75%			
N (%)	54 (27.1)	44 (22.1)	33 (16.6)

Table 4. **Correlation of TSH concentrations and the SCL-90-R anxiety subscale scores during different trimesters of pregnancy**

Symptoms of anxiety measured by anxiety subscale of the SCL-90-R	Thyroid Stimulating Hormone		
	1st trimester	2nd trimester	3rd trimester
Anxiety subscale of the SCL-90-R:			
Spearman's r	-0.1	**-0.164**	-0.12
p-value	0.162	**0.021**	0.092

Table 5. **Univariate and multivariate logistic regression analysis in 199 women. Dependent variable: severe anxiety symptoms in the 2nd trimester according to the anxiety subscale of SCL-90-R (odds ratios (OR), 95% confidence interval (CI))**

Independent	Univariate regression analysis			Multivariate regression analysis		
variables	OR	95% CI	p-value	OR	95% CI	p-value
TSH*	**0.44**	0.22-0.87	0.017	**0.44**	0.22-0.89	0.022
Psychosocial stressors during a year**	**2.1**	1.06-4.19	0.034	1.46	0.68-3.15	0.33
Not working outside home**	**2.68**	1.18-6.09	0.018	**2.42**	1.01-5.79	0.047
History of anxiety and /or depression**	**2.85**	1.25-6.52	0.013	2.29	0.93-5.64	0.072

*Continuous variable, odds ratios shows greater risk "per unit".
**Categorical variables, their values are "yes versus no".
Significant odds ratios are shown in bold.

factors for intense anxiety symptoms in the second trimester of pregnancy: TSH concentrations (OR=0.44, 95% CI (0.22; 0.89) and "not working outside home" (OR=2.42, 95% CI (1.01; 5.79) (Table 5).

DISCUSSION

Our study showed, that symptoms of anxiety were related to TSH concentrations in the mid-pregnancy. Moreover, intense anxiety symptoms were independently associated with lower TSH concentrations, and with "not working outside home".

It is well known that manifest thyroid dysfunction causes mood disorders. In the literature there are few studies related with subclinical thyroid dysfunction and anxiety. Mood changes especially anxiety due to subclinical thyroid dysfunction may have an important impact on the patient's quality of life [39].

Some recent works referred that there was an inverse association between TSH and anxiety score in both genders [40]. There may be a neurobiological explanation for the relation of intense anxiety symptoms and lower TSH concentrations but although the underlying mechanism is not clear. The association between thyroid parameters and anxiety symptoms may be explained by findings of recent studies on depression in which alterations in both hypothalamic – pituitary – thyroid (HPT) axis activity and serotonin (5 – HT) function were found [41, 42].

A number of changes occur in the thyroid gland and in levels of thyroid axis hormones during pregnancy. Serum TSH values decrease during the first trimester in response to hCG elevation and, in approximately one fifth of healthy pregnant women, serum TSH values may be transiently lowered to subnormal values at this time of gestation [1–4]

Already in the past decade it has been noticed, that reference ranges of thyroid parameters are not always the same for pregnant and nonpregnant women and men [5]. Recently data, highlighted the need of valid gestational reference ranges for serum TSH concentrations and FT4 [1, 43–47]. Nevertheless up-to-date thyroid dysfunctions during pregnancy are diagnosed on the basis of reference ranges for non-pregnant subjects. Even so by using the classical non pregnant reference range for serum TSH (0.4 mU/L for the lower limit and 4.0 mU/L for the upper limit), one might therefore misdiagnose as "normal" women who already have a slight TSH elevation and, conversely, wrongly suspect hyperthyroidism in normal women who simply have a transiently blunted serum TSH. During the remainder of pregnancy, serum TSH returns progressively to the normal range. As it was the case for free thyroid hormone measurements, it has recently been proposed to use "trimester-specific" reference ranges for serum TSH levels during pregnancy [48–50].

There is convincing epidemiologic data to show that suboptimal thyroid function in pregnancy is associated with impaired neurointellectual development [51] as well as increased risk for obstetrical complications such as intrauterine fetal death, gestational hypertension, placental abruption, and poor perinatal outcome [1].

It is important to diagnose both hypo- and hyperthyroidism accurately and carefully because of increased risk to mother and fetus. As it was demonstrated in our study suppressed TSH concentrations during mid pregnancy, representing increased thyroid hormone activity, are associated with presentation of symptoms of anxiety. Thyroid hyperfunction results in activation of noradrenergic system and this hyperactivation may cause symptoms of anxiety [52]. In non-pregnant hyperthyroid women symptoms of anxiety respond to compensation of hyperthyroidism, as well as to treatment with beta adrenoblockers indicating causal role of activation of adrenal axis for presentation of symptoms of anxiety [53]. However, in pregnant women changes in thyroid axis hormone patterns may have physiological role and interventions on thyroid axis managing symptoms of anxiety are contraindicated. Further studies are needed to assess the relationship of antenatal symptoms of anxiety and thyroid parameters as well as the specific aspects of thyroid function associated with pregnancy.

CONCLUSION

The study showed that anxiety was related to thyroid stimulating hormone concentrations in the mid-pregnancy. Moreover, intense anxiety symptoms were independently associated with lower thyroid stimulating hormone concentrations. Further work is indicated to confirm this association, as it may in future add to a better identification of women at risk for mental health problems during pregnancy.

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