

# Thyroid in Pregnancy

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## 1. Introduction

Many changes in the functioning of the thyroid gland occur during pregnancy and some diseases of the thyroid gland can affect both the pregnant woman and the fetus. (Casey et al., 2006; Lazarus & Premawardhana, 2005; Poppe et al., 2007). Hypothyroidism is the most serious disorder of those occurring during pregnancy, and it might go unnoticed as some 'nonspecific' problem. Pregnant women with subclinical hypothyroidism seem to escape early clinical detection (Lazarus, 2002). While the hyperfunction during pregnancy usually manifests itself by clinical symptoms or a relapse of a previously cured disease (mostly Graves - Basedow) (Abalovich et al., 2007), lowered functioning is much more dangerous because of its non-specific symptoms. During the 1<sup>st</sup> trimester, the fetus is completely dependent upon thyroxin produced by the mother (Smallridge & Landerson, 2001). Even a small unnoticed malfunction of the thyroid gland, which doesn't have to endanger the course of the pregnancy, can affect the psychomotor development of the child (Morreale de Escobar et al., 2004; Mitchell & Klein, 2004)). Some women with subclinical hypothyroidism are absolutely asymptomatic and there is no reliance on the clinical image, while diagnostic of thyroid dysfunction (Klein et al., 2001).

Malfunction of the thyroid gland during pregnancy is long-term, and still not a sufficiently solved problem (Lazarus, 2002). On many pages of scientific literature and specialist literature there are still new arguments to systematically screen pregnant women for thyroid dysfunction and asymptomatic chronic thyroiditis in order to give such women the appropriate treatment (Surks et al., 2004). Results of surface population screenings are slightly varied, depending upon on level of medical care and approach to prevention, geographical conditions, supplementing with iodine, and other circumstances (including used diagnostic criteria) (Vaidya et al., 2007). Evaluating thyroidal function during pregnancy is difficult, considering the other differing influences of pregnancy.

Guidelines for management of thyroid dysfunction during pregnancy and postpartum (Abalovich et al. 2007) recommend not universal but only case finding screening. The first aim of the study was to assess the value of this recommendation. The other aim was to introduce an estimation of thyroid dysfunction during pregnancy, selection of suitable biochemical markers and determination of reference intervals for these markers in pregnancy.

## 2. Investigation of thyroidal dysfunction in pregnancy

In cooperation with General insurance company in Czech Republic was in 2009 started a pilot project for universal screening of thyroid dysfunction among women in the first

trimester of pregnancy. A pilot project was performed during 2009-2010 in 13 regions, (only 4 regions in 2010) of the Czech Republic. The data from 3577 pregnant women with sufficient iodine intake were available. The blood for TSH (thyroid stimulating hormone), TPO Ab (antibodies to thyroid peroxidase) and FT4 (free thyroxine) estimation was collected in 9-11 week of pregnancy. All participating pregnant women gave informed written consent with this subsequent investigation.

## **2.1 Conditions for screening**

First question is what we want to find? Which disorders are mostly indicated in pregnancy and what is really danger for pregnant women. Former studies resolve problems, which laboratory parameters are the best for investigation, the sampling of blood from pregnant women timing and also applicability of commonly used reference intervals for each parameter (Lazarus & Premawardhana, 2005; Poppe et al., 2007). Iodine supplementation is also usually asked (Glinoe et al., 1995).

### **2.1.1 Thyroid disorders in pregnant women**

Evaluating thyroidal function during pregnancy is difficult, considering the other differing influences of pregnancy (Dayan et al., 2002; Lazarus, 2002). New thyroid nodules should be aggressively investigated during pregnancy because of a high incidence of malignancy. Radioactive Iodine is contraindicated in pregnancy. Nursing mothers who have radioactive iodine uptake scans should pump and discard their milk for 48-72 hours after the test.

#### **2.1.1.1 Hypothyroidism**

Hypothyroidism is the most serious disorder of those occurring during pregnancy, and it might go unnoticed as some 'nonspecific' problem. Pregnant women with subclinical hypothyroidism seem to escape early clinical detection. The implications are staggering when one considers that there is a significant increase in intrauterine deaths, spontaneous abortions, premature births, and pre-eclampsia; also the development of the fetus, such as major malformations and loss of IQ (Haddow et al., Pop et al., 2003). It has been clearly proven that even slight (subclinical) hypothyroidism affects not only the course of pregnancy, but (especially later-on) the neuropsychological development of the child. Symptoms of hypothyroidism (fatigue, lowered performance, sleepiness, psychological lability) can also accompany the physiological pregnancy; some women with subclinical hypothyroidism are absolutely asymptomatic and there is no reliance on the clinical image, while diagnostic of functional failure. Untreated patients with hypothyroidism rarely conceive and carry a pregnancy. Treated hypothyroidism usually has no associated pregnancy complications. Patients will require increased levothyroxine doses during their pregnancies. Monitoring of thyroid function tests each trimester and at other clinically indicated times is recommended (Dashe 2005).

Prenatal vitamins can decrease the absorption of levothyroxine.

#### **2.1.1.2 Hyperthyroidism**

The hyperfunction during pregnancy usually manifests itself by clinical symptoms or a relapse of a previously cured disease. 95% of hyperthyroidism in pregnancy is secondary to Graves - Basedow disease. A good pregnancy outcome can be expected in patients with good control. Untreated hyperthyroidism is associated with decreased fertility, an increased rate of miscarriage, intrauterine growth retardation (IUGR), premature labor, and perinatal

mortality (Poppe et al., 2007). Poorly controlled thyrotoxicosis is associated with thyroid storm especially at labor and delivery. Beta blockers and propylthiouracil (PTU) can be safely used in pregnancy and in nursing mothers. PTU crosses the placenta but does not usually cause fetal hypothyroidism and goiter unless used in high doses. Treatment goals favor mild hyperthyroidism over hypothyroidism. Like other immune mediated diseases in pregnancy, Grave's disease tends to improve in the third trimester. Exacerbations may occur in the first trimester and postpartum. Neonatal and fetal thyrotoxicosis may occur because of transplacental passage of thyroid stimulating antibodies.

### **2.1.1.3 Postpartum thyroiditis**

Postpartum thyroiditis is a destructive autoimmune thyroiditis that begins with a period of hyperthyroidism followed by a period of hypothyroidism (Negro et al., 2007). The gland is often enlarged. There is usually complete recovery but a chance of recurrence in subsequent pregnancies exists. 80-85% of patients will have positive antithyroid antibodies. A radioactive iodine uptake scan can differentiate postpartum thyroiditis from an exacerbation of Graves- Basedow disease.

TPO Ab antibodies are markers of autoimmune process in the thyroid gland, their determination is diagnostically and prognostically important. Presence of TPO Ab during pregnancy also alerts to the danger of development of postpartum thyroiditis (Nicholson et al., 2006; Dosiou et al., 2008); about 50% of TPO Ab positive women have some thyroid dysfunction after delivery (Premawardhana et al., 2004; Nicholson et al., 2006), so it is necessary to follow-up these women. Postpartum thyroiditis is in an important consideration in women with postpartum depression.

### **2.1.1.4 Hyperemesis gravidarum**

Hyperemesis is associated with abnormal thyroid function tests in a significant number of cases. Hyperthyroidism may be the cause of hyperemesis or hyperemesis may be the cause of the hyperthyroidism (Goodwin et al., 1992).

## **2.1.2 Iodine supplementation in pregnancy**

The iodine requirement during pregnancy is sharply elevated because of an increase in maternal thyroxine production to maintain maternal euthyroidism and to transfer thyroid hormone to the fetus, iodine needs to be transferred to the fetus for fetal thyroid hormone production in later gestation and a probable increase in renal iodine clearance. The recommended dietary allowance for nonpregnant, nonlactating women aged  $\geq 14$  year is 150  $\mu\text{g}/\text{d}$ , for pregnant women is it 220  $\mu\text{g}/\text{d}$  (Zimmermann & Delange, 2004). In Czech Republic has been iodized salt in regular use since the 1950s, a good level of iodine supplementation can be expected also on Zamrazil study (Zamrazil, 2004). Women in this study were in addition supplemented by 100-150  $\mu\text{g}$  of iodide daily.

## **2.1.3 Timing of the blood taking**

The study group consists of 3 577 asymptomatic pregnant women (in their 9<sup>th</sup> - 11<sup>th</sup> week of pregnancy, 99% Caucasian) who were undergoing their first trimester prenatal screening. In the pilot project were used laboratories, which were able to investigate serum for the first trimester screening (investigation of PAPP-A and free  $\beta$  hCG) and simultaneously in the same sample determine TSH (thyroid stimulating hormone), TPO Ab (antibodies to thyroid peroxidase) and FT4 (free thyroxine).

### 2.1.4 Selection of laboratory parameters

The thyroid gland increases slightly in size during pregnancy.

Determining TSH in the serum is a basic searching procedure in the diagnosis of function of the thyroid gland in the general population. Its regulation is based on feedback, however during pregnancy there are also other mechanisms taking place. Suppressed serum TSH concentration during gestation follow hyperthyroidism as well as hyperemesis gravidarum or high hCG levels. Lower serum TSH in pregnancy is influenced by the thyrotropic activity of elevated circulating human chorionic gonadotropin concentrations, mainly in the first trimester (Abalovich 2007; Dashe 2005).

The comparison two groups of women, on pregnant and the other nonpregnant shows shift levels of TSH in pregnancy. On Fig.1 is possible to see only low levels of TSH.

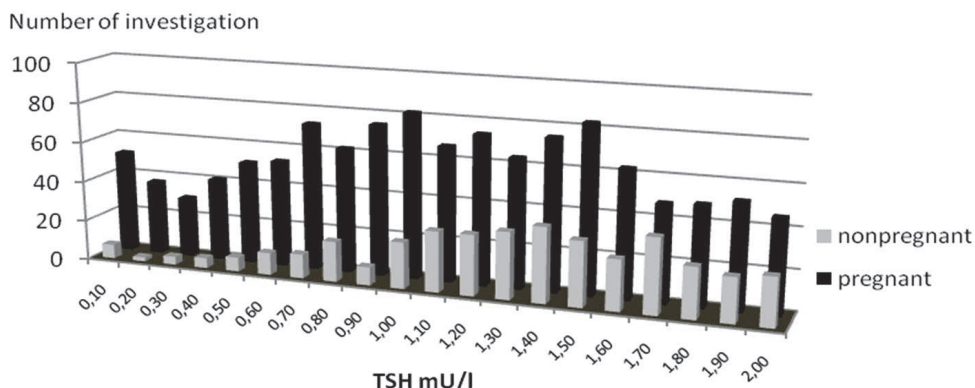


Fig. 1. Comparison TSH in group of pregnant (first trimester of pregnancy) and nonpregnant women in part with low TSH levels

In the group of pregnant women, with suppressed TSH, the average level of hCG was almost double ( $M=95.6$  mg/ml), in comparison with the group with TSH in the reference interval ( $M=68.9$  mg/ml) or with  $TSH >3.67$  mU/l ( $M=62.1$  mg/ml). Differences between the normal and raised TSH groups in hCG levels were not significant at  $p < 0.050$ . The other authors confirm that sub-normal serum TSH levels in the first trimester are coincident with rising hCG levels (Surks et al., 2004).

On Fig.2 is possible to see, how high is hCG in women with low TSH. (Springer et al., 2009) By using the classical reference interval for serum TSH one might misdiagnose as healthy those women who already have a slight TSH elevation and, conversely, one might suspect hyperthyroidism in normal women who have a lowered serum TSH value.

Determining FT4 is by watching the amount of biologically active hormone which is available to the organism of a pregnant woman (as well as the fetus), and is not affected by the concentration of binding proteins. Its concentration during pregnancy is partly effected by inflow of iodine and the duration of the pregnancy. Free thyroxine levels remain within the normal range during pregnancy (though total thyroxine levels are increased secondary to increased TBG). Some consider it even more informative than TSH during pregnancy (Lazarus, 2002). During the 1<sup>st</sup> trimester, the fetus is completely dependent upon thyroxin produced by the mother. Even a small unnoticed malfunction of the thyroid gland, which doesn't have to endanger the course of the pregnancy, can affect the psychomotor

development of the child. Early maternal hypothyroxinemia alters histogenesis and cerebral cortex cytoarchitecture of the progeny.

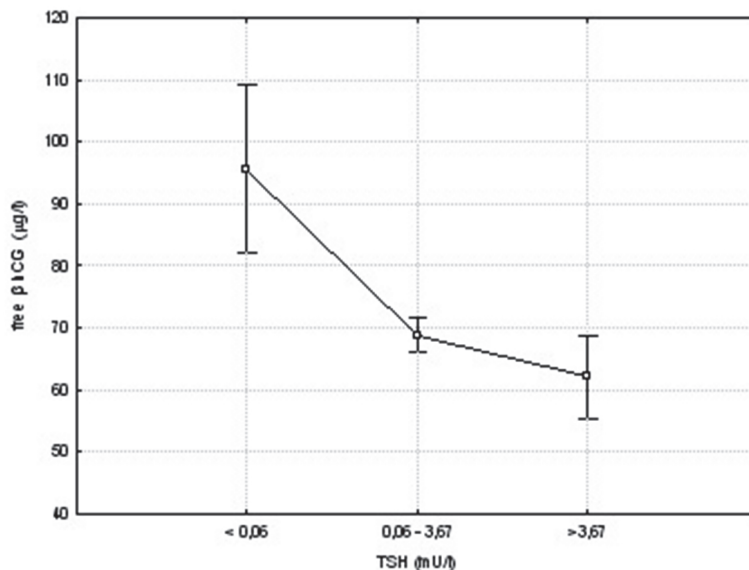


Fig. 2. Free  $\beta$  hCG in groups with increasing TSH levels

Anti-TPO antibodies (TPO Ab) are markers of autoimmune process in the thyroid gland, their determination is diagnostically and prognostically important. Presence of TPO Ab during pregnancy also alerts to the danger of development of postpartum thyroiditis; about 50% of TPO Ab positive women have some thyroid dysfunction after delivery, so it is necessary to follow-up these women. The relationship between TPO Ab and TSH is not definite, despite it being known that women with high level of TSH more frequently have positive TPO Ab.

### 2.1.5 Reference intervals

Reference intervals for different methods and manufacturer's may vary, they have been established using pools of nonpregnant normal sera and with different antibodies. Such reference ranges are not valid during pregnancy. A reference interval is the range of values of a test result for a defined population. In older references the reference interval is often designated as the reference range.

The main problem in setting of reference intervals for used laboratory markers is in case of using different immunoanalytic assays. Several factors can affect the setting of reference intervals, in particular manufacturer's methodology, euthyroid definition and iodine status. Alterations in thyroid hormone concentrations during pregnancy differed at different stage of gestation and to those of a non-pregnant state. If the non-pregnant TSH reference range was applied to pregnant women whose serum TSH concentration was within the first trimester specific reference range would be misclassified as having subclinical hyperthyroidism, or those with a TSH concentration above the first trimester specific upper reference limit would not be identified.

Determining the reference range suitable for the 1<sup>st</sup> trimester of pregnancy is possible by using the suggestion of the National Academy of Clinical Biochemistry (NACB) on selected samples from the population, or as 95<sup>th</sup> percentile from the cohort of women (Demers & Spencer, 2003).

Evaluating thyroidal function during pregnancy is difficult, considering the other differing influences of pregnancy (Dayan et al., 2002). TSH regulation is based on feedback, however during pregnancy there are also other mechanisms taking place - mainly there is suppression of TSH, presumably due to a thyroid-stimulating activity of hCG early in pregnancy when hCG levels are the highest. (Goodwin et al., 1992).

#### 2.1.5.1 Determination of own reference intervals

TSH, TPO Ab, and FT4 were assayed by ADVIA® Centaur™ (Siemens), with chemiluminometric detection. TSH was determined by sandwich immunoanalysis with direct chemiluminometric technology; for TPO Ab and FT4 competitive immunoanalysis with direct chemiluminometric technology was used.

Reproducibility of this method is expressed by the interassay variability. For TSH, it is 5 - 7% for levels of 0.43 - 15.00 mU/l; for TPO Ab it is 10% for the level of 70 kU/l and 7% for the level of 170 kU/l. Interassay variability for FT4 is 7 - 9% for levels 10.1 - 33.0 pmol/l.

For mostly used systems were possible to use comparable TSH reference intervals, that were determined on large group of pregnant women (Springer et al., 2009). For evaluation of the reference interval, a selected group was created in accordance with the recommendations of the NACB. From the group of pregnant women (5,520), all those with a history of thyroid disease were excluded; TPO Ab > 60 kU/l (the manufacturer's cut-off) and free  $\beta$  hCG higher than triple of the median (Mdn=56.6  $\mu$ g/l), in view of the suppression of TSH by a high level of hCG, were also excluded. TSH do not follow a normal distribution, data have to be normalized using log transformation. The reference interval - 95<sup>th</sup> percentile - was than determined using this log transformed data. The TSH reference interval for ADVIA:Centaur Siemens was determined to be 0.06 - 3.67 mU/l.

FT4 levels fit a Gaussian distribution, so reference intervals were derived using nonparametric analyses such as the 95<sup>th</sup> percentile. The calculated reference interval (9.55 - 23.0 pmol/l) was almost identical to the manufacturer's (9.8 - 23.1 pmol/l) for all populations.

Differences in TPO Ab manufacturer's reference interval are not comparable from 0.5 to 100 kU/l (Haddow et al., 2004; Hollowell et al., 2002; Negro et al., 2006). Reference intervals for thyroid antibody tests should be by the NACB recommendation; established from young male subjects, free from any history of thyroid disease or predisposition for any autoimmune disease (Demers & Spencer, 2003). Establishment of decision values for thyroid antibodies in the healthy population is difficult and results are method dependent (Jensen et al., 2006). The pregnancy positivity cut-off for TPO Ab was calculated at the 95<sup>th</sup> percentiles. From all of the women, women with a known history of thyroid disease were separated, as well as those with TSH lower than 0.1 and higher than 4.0 mU/l. This interval had been used earlier for the evaluation of positive results in pregnancy; it was deduced from both specialized literature and own experience. The positivity of TPO Ab in nonpregnant individuals is about 11% (Hollowell et al., 2002); in the pregnant population it is very similar. Negro mentioned 11.7% TPO Ab positive pregnant women (Negro et al., 2006); Dossioui selected groups by age and the positivity was 10.4 and 12.6 for ages 25 and 35 years, respectively (Dossioui et al., 2008). When was used the reference interval recommended by the producer of reagents (> 60 kU/l),

in study group was 22.1% positivity. If was used the 90<sup>th</sup> percentile (143 kU/l) as the cut-off for the group of pregnant women, was the positivity 11.2%.

## 2.2 Results

The pilot project for universal screening was performed during 2009-2010 in 13 regions of the Czech Republic with the financial support of the General Insurance Company. Cooperation in 10 regions was good or suitable; 3 regions cooperated poorly and their data was not used in the first year of pilot project. In the second year were used only four laboratories for project. Thyroid examination was offered to women in the 9-11th week of pregnancy. The women with any positivity were offered immediate to endocrinological examination. Blood tests (TSH, FT4 and TPO Ab) were carried out in 3577 asymptomatic pregnant women.

On Fig. 3 is showed the map of Czech Republic with selected regions. The number under town name is number of implement investigations in the pilot project, the red one are excluded regions, green number included investigations also from second part of pilot project in 2010.



Fig. 3. The map of Czech Republic with cooperating regions. Under name of the town are number of investigations, green number indicate laboratories worked on second part of levels. The red marked regions were excluded from statistic.

There were used different analytical systems for analysis: the radio-immunoanalysis in five laboratories, chemilumino-immunoanalysis in six and electrochemilumino-immunoanalysis in two of them. Specific reference intervals for TSH, FT4, and positivity cut-off for TPO Ab during pregnancy were applied in all laboratories.

In all 3577 women investigated in pilot project were found 679 (19.0%) pregnant women with some positivity.

### 2.2.1 TSH

A raised concentration of TSH was found in 7.63% of women; and a suppression of TSH was found in 3.05% of women. The prevalence of hypertyreosis in pregnant women is 1.7%, and 0.4% of these women had an elevated serum FT4 level. This is similar to that reported for non-

pregnant individuals. Low level of TSH with high FT4 level were only in 0.48%, which is in concordance with previous hypotheses, as well as with Haddow study (Haddow at all., 2004). Many authors have determined the prevalence of hypothyreosis (overt and subclinical) in pregnancy and it is estimated to be 0.3 - 0.5% for overt hypothyroidism and 2 - 3% for subclinical hypothyroidism (Haddow at all., 2004). In this study there were 7.63% of pregnant women with TSH over determined own reference interval; it is evident, that no all higher TSH means hypothyreosis. Also selection of pregnant women maybe was influenced by gynaecologists, which prefer high-risk women for investigation in pilot project.. On Fig. 4 is schema with positivity in TSH levels:

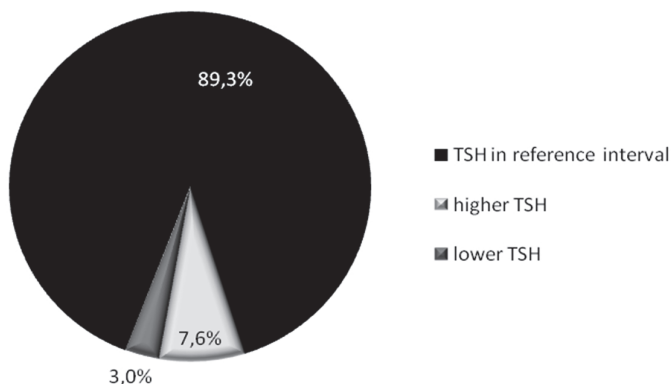


Fig. 4. Distribution of TSH levels in study group.

### 2.2.2 FT4

A raised concentration of FT4 was found in 0.48% of women; and a suppression of FT4 was found in 3.44% of women. On Fig. 5 is showed distribution of FT4 in the study group of pregnant women.

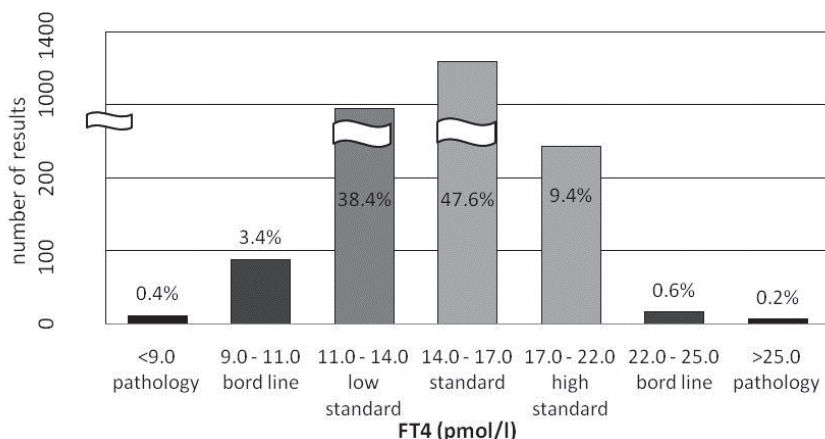


Fig. 5. Distribution of FT4 in the study cohort.



Differences of FT4 in euthyroid women with suppressed, normal and elevated TSH were found and are showed on Fig. 6.

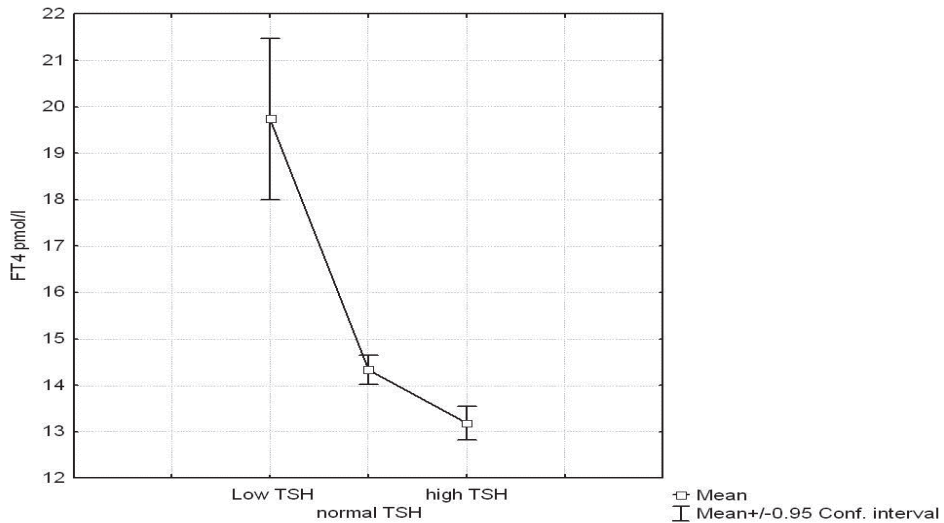


Fig. 6. FT4 in euthyroid women with suppressed, normal and elevated TSH

### 2.2.3 TPO Ab

8.78% of pregnant women were found TPO Ab positive and there were also 5.4% of women, which had only TPO Ab positivity without another differences in TSH or FT4 levels. This distribution of results for whole study group is on Fig. 7 showed.

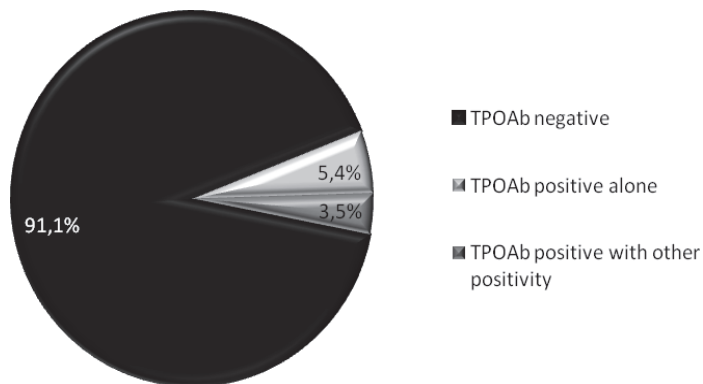


Fig. 7. TPO Ab in whole study group

### 2.3 General or only high-risk pregnant women testing?

Presently available information that supports the hypothesis that an inappropriate first trimester surge in maternal FT4, whatever the circulating TSH, would interfere with the

development of the cerebral cortex, even if maternal euthyroidism is maintained by normal circulating T3. There is at present increasing consensus (Morreale et al., 2004) that maternal hypothyroidism, both clinical and subclinical, requires early detection and prompt treatment, because of its important negative effects for the woman, the pregnancy and the child. There also exists a positive association between the presence of thyroid antibodies and pregnancy loss with postpartum thyroiditis.

The most practical approach is to screen all pregnant women for hypothyroidism as early in pregnancy as possible (or before conception). In the case of the mother, screening would reset in early diagnosis and treatment of subclinical hypothyroidism. Unfortunately, pregnant women with subclinical hypothyroidism seem to escape early clinical detection. In Mitchel study (Mitchel & Klein, 2004), 58% of the hypothyroid women were unaware of their disorder, and it took a median of 5 years from the time of the pregnancy for the clinical diagnosis to be made.

Vaidya study shows that targeted thyroid function testing of only high-risk pregnant women would miss nearly one-third of women with overt/subclinical hypothyroidism during early pregnancy (Vaidya et al., 2007). In Czech Republic, case finding screening is able to disclose less than 20% of asymptomatic mild or deep hypothyroidism or women with positive TPO Ab in pregnancy (Springer et al., 2009).

#### 2.4 Relationship between TPO Ab and TSH, resp. FT4

The relationship between TPO Ab and TSH is not definite, despite it being known that women with high level of TSH more frequently have positive TPO Ab. In study group, divided by serum TSH concentration, were 44.1% TPO Ab positive (in part), with TSH >3.67 mU/l and 10.1% or 9.15% in the group with TSH < 0.06 mU/l or TSH in the reference interval, as is showed on Fig. 8.

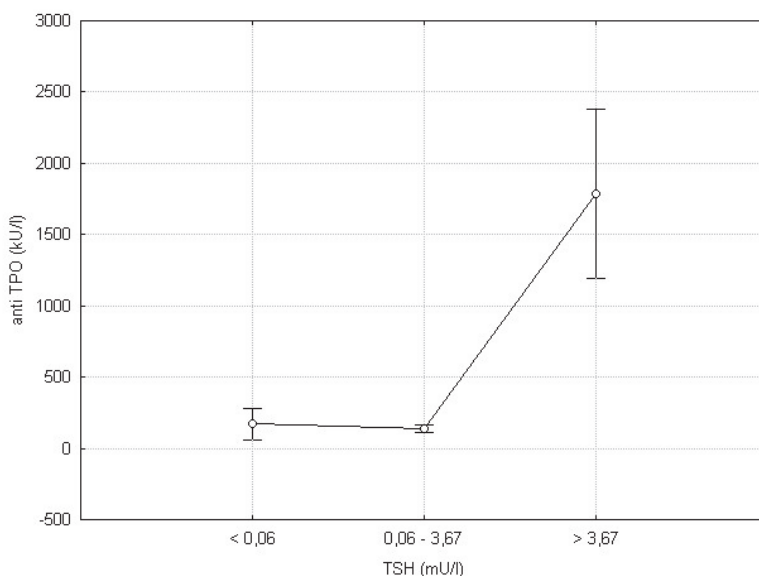


Fig. 8. TPO Ab in groups with different TSH level

Glinoeer (Glinoeer et al., 1995) also documented somewhat higher TSH levels among the sub-population of women with elevated antibody levels and these findings are confirmed in the present study.

Serum concentrations of FT4 were lower in TPO Ab positive as compared to TPO Ab negative women as is showed on Fig. 9.

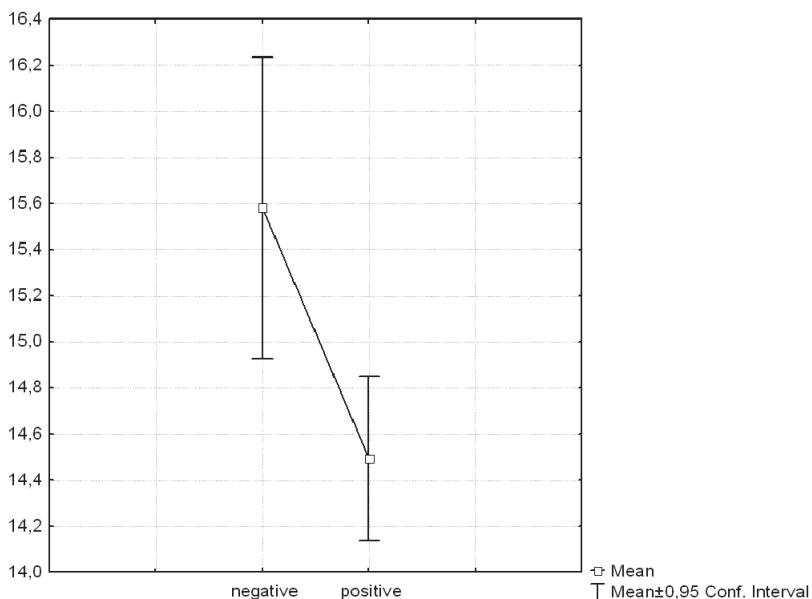


Fig. 9. Serum concentrations of FT4 in TPO Ab positive and TPO Ab negative women

### 2.5 Cost effectiveness of the thyroid failure screening

An answer to the question of screening cost-effectiveness of thyroid function in pregnancy was already presented by Dosiou (Dosiou et al., 2008). In this study is not defined cost-efficiency, but it is unquestioned fact that early diagnosis of thyroid disorder is cost-effective and beneficial for both mother and child.

### 3. Conclusion

The importance of maternal thyroxine for the development of the fetus brain early in pregnancy has received increasing acceptance. It has more recently become evident that maternal hypothyroxinemia results in the birth of children with decreased mental and psychomotor development.

This project proved the usefulness of universal screening of thyroid disease in pregnancy. The occurrence of pathological results in laboratory tests was 679/3577. Determination of the specific reference intervals for TSH, FT4, and TPO Ab in pregnancy is one of the basic requirements when implementing the general examination. Cooperation with gynaecologists differed, the main stumbling block was the willingness of gynaecologists to inform pregnant women about the project.

In Czech Republic, case finding screening is able to disclose less than 20% of asymptomatic mild or deep hypothyroidism or women with positive TPO Ab in pregnancy. Investigation of combination of TSH and TPO Ab is necessary. Maternal hypothyroxinemia appears to be a much more frequent cause of deficits in the progeny than congenital hypothyroidism, for which we have successful neonatal thyroid screening programs. This study maybe will help define the impact of universal screening (TSH, FT4, TPO Ab) on the health care system. The introduction of general screening of thyroid failure in pregnancy needs to be emphasized in public education; moreover, interdisciplinary cooperation of gynaecologist, endocrinologist and general practitioner, not to mention midwives should be improved. The other analysis would be more clearly identify the causal relationships between mild thyroid hormone deficiency and thyroid autoimmunity, on the one hand, and fetal neurological development on the other. In the meantime, physicians and obstetricians must use their own judgment about the optimal management for their individual patients.

#### 4. Acknowledgment

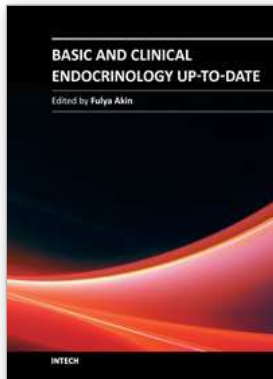
The authors are grateful to the General Insurance Company of the Czech Republic for founding of the pilot project. The special thank belongs to all cooperating laboratories for help with blood sampling and perfekt resolving all administrative problems. Last but not least thank technicians from the Institute of Clinical Biochemistry and Laboratory Diagnostics Charles University, Prague, Czech Republic for their support in setting of reference intervals for pregnancy.

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