

## Review

# Recommendations on prenatal screening and the connections to other diseases such as thyroid dysfunction

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## Abstract

The aim of general maternal-foetal care is to ensure an uncomplicated birth of a healthy baby to a healthy mother. There is a large range of screening tests used during pregnancy: for gestational diabetes, infection, rhesus-D status, thyroid dysfunction, as well as other tests. An important part of prenatal care is the screening of major aneuploidies, primarily for Down's syndrome. This screening is possible in either the first or second trimester, or in both. Management of this type of screening is very similar around the world. Hypothyroidism can affect the psychomotor development of the child. Thyroid-stimulating hormone (TSH), autoantibodies against thyroperoxidase (TPOAb), and free thyroxin (FT4) were determined within our group of 7530 pregnant women. Elevated concentrations of TSH were found in 5.1%, suppression was found in 2.9% and 11.5% were TPOAb positive. Either a familial or personal history of thyroid or autoimmune diseases was present in 58.3% of those women who tested positive on any thyroid test. At minimum, 40% of women TPOAb positive during pregnancy have some kind of thyroid disorders after delivery. These results support the efficacy of general thyroid function screening in early pregnancy, as well as the follow-up after delivery of those women who are positive.

**Keywords:** Down's syndrome; prenatal screening; thyroid disease.

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## Introduction

Today's medical advances have given us the capacity to identify many diseases before they occur and at times to apply preventative measures, so that morbidity and mortality may be avoided. As maternal and perinatal mortality has decreased in many countries, the focus of perinatal medicine has expanded to improving the critical quality indicators for both maternal and foetal health (1, 2). The role of the laboratory in risk management strategies varies both with the strategy, as well as the timing of pregnancy in which it is significant.

Screening is a systemic examination in order to identify subjects with a sufficient risk of a specific disorder, who could therefore benefit from further investigation or direct preventive action (3). It is evident that an integrated first physician's visit, plus combining the data from maternal characteristics and history with the biophysical and biochemical test findings, can define the woman-specific risk for a wide spectrum of complications of pregnancy including: miscarriage and foetal death, preterm delivery, preeclampsia, gestational diabetes, foetal growth restriction, and macrosomia (4).

Women should be offered testing for anaemia, blood group, and rhesus-D status early in their pregnancy. Screening for sickle cell diseases and thalassaemias should also be offered to all women as early as possible in their pregnancy; and screening for thyroid dysfunction is recommended (5). Women should be offered routine screening for asymptomatic bacteriuria, bacterial vaginosis, serological screening for hepatitis B virus, HIV infection, as well as for syphilis, toxoplasmosis, and other infectious diseases in different localities. Screening for gestational diabetes mellitus (GDM), which is associated with increased risk of both maternal and perinatal short- and long-term complications, is recommended in a healthy population (4).

The normal function of the thyroid gland ensures that pregnancy takes its proper course, and a sufficient level of thyroxin is necessary for healthy foetus development. Undetected thyroid disease may lead to serious consequences such as psychomotor disorders and/or a decreased intelligence quotient (IQ). Thyroid disorders are quite frequent among young women (6, 7). Recommended laboratory tests are in the Table 1.

## Screening for chromosomal aberrations

Down's syndrome (DS) is the most common abnormal chromosomal syndrome in humans. No exogenous impact

**Table 1** Laboratory tests recommended during pregnancy (according by 8).

Week of pregnancy	Recommended test
8–10	Blood group, anaemia testing, rhesus-D status, hepatitis B, HIV, syphilis, rubeolla, toxoplasmosis, optional FT4, TSH, antiTPO
11–13	Screening of DS (first trimester)
12	Screening for GDM, vaginal infections
16–18	Screening of DS (second trimester)
20	Anaemia testing, rhesus D-status
24	Bacteriuria, vaginal infections
32	Anaemia testing, rhesus-D status, coagulation, selective population – hepatitis B and HIV

occurring before or during pregnancy can cause DS. It occurs in all races, social classes, and in all countries throughout the world (8, 9).

There are currently two elements of antenatal screening testing: one screening test which is offered to all pregnant women; and one which identifies those pregnancies that should be offered a diagnostic test (amniocentesis or chorionic villus sample), thus directly testing the foetus to indicate its genetic karyotype.

Prenatal screening for chromosome abnormalities started in the 1930s with the discussion of the maternal age-related risk of having a baby with trisomy 21, or other chromosomal abnormalities (10). The simplest of the screens simply involves asking a woman her age (11). The first karyotype on a culture of amniotic cells was performed in 1966 (12). In the 1970s, it was proposed that all women who were 35 years (and over) should be offered amniocentesis, which could prevent most of the Down's syndrome births (13).

Biochemical markers from the screenings have been used from the 1980s; the first used was  $\alpha_1$ -fetoprotein (AFP) (14–17), followed later by human chorionic gonadotrophin (hCG) (18) and unconjugated oestriol (uE3) (19), which were combined into the antenatal Down's screening 'triple test' (19, 20). By the 1990s, other markers had been identified: free  $\beta$  hCG, pregnancy associated plasma protein A (PAPP-A) (21), inhibin (22), and the ultrasound measurements of nuchal translucency (NT) (23).

Analyses of biochemical markers are performed on immunoanalytical systems with different types of detection. In some countries, where the screening of aneuploidies is directed by the government, only one instrument manufacturer may be preferred. In other countries, both the acceptance criteria reproducibility and coefficient of variation have been established by legislation. Most laboratories are using medians that are specific to their own distinctive laboratory.

For the risk evaluation, different software is used. These software use a woman's age, the levels of screening markers, and other information about the pregnant woman (e.g., such as mother's weight, race, etc.) in order to estimate the woman's risk of having a pregnancy with Down's syndrome, Edward's syndrome or neural tube defect (NTD). Screening markers are recalculated to multiples of the median (MoMs), which allows the values of these markers to be separated from the length of gestation from which they were determined.

## Screening strategies

Since the introduction of antenatal serum screening for DS almost three decades ago (24), several screening approaches have been utilised in routine clinical practice. The risk at the time of screening is higher, since many foetuses with Down's syndrome spontaneously abort around the time of the screening or afterwards (25). The current DS screening strategies involve the more traditional second trimester serum biochemistry tests, the first trimester tests that combine both ultrasound markers and serum biochemistry, and/or the integration of the first- and second trimester markers (26–28).

### First trimester screening tests

First trimester screening for DS is a relatively novel practice. The major breakthrough of early screening was the identification (29, 30) and implementation (31) of nuchal translucency measurements between the 11th and the 14th weeks' of gestation. During the early 1990s, several studies reported the association between DS and low levels of the pregnancy-associated plasma protein A (PAPP-A) (7) with high levels of hCG (32); plus the use of these for screening in the first trimester (33). The combination of the NT measurement with these two serum biochemical markers in the first trimester make up the combined test, with a significant and important decrease in the false positivity rate (34, 35).

Improvements in the performance of first trimester screening can be achieved by first carrying out the biochemical test at the 9th to the 10th week with a following scan at the 12th week. Additionally, with its inclusion into the ultrasound examination, the assessment of the nasal bone and flow in the ductus venosus, hepatic artery, and across the tricuspid valve bring improvements in the screening (36). A similar increase in screening performance can be achieved by examining the additional ultrasound markers in all cases, as well as by a contingency procedure in which the first-stage combined screening categorises the patients into high-, intermediate-, and low-risk categories. In such a case, the new markers are only assessed in the intermediate-risk group in order to stratify the women into either low- or high-risk (1, 2, 37).

### Second trimester screening tests

Screening for DS by maternal age started three decades ago when amniocentesis was only offered to older women.

The finding of an association between low serum AFP and elevated serum hCG with foetal chromosomal abnormalities, including DS (15), has led to the double test (AFP and hCG) (38). The third marker for DS was unconjugated oestriol, which was found to be lower in the affected pregnancies (19). This led to the establishment of the triple test, which is still very commonly used (20). The most recent addition to the second trimester serum markers has been inhibin-A, which is found at higher levels in affected pregnancies (39, 40). The quadruple test (the combination of AFP, hCG, uE3, and inhibin) is currently the most popular second trimester screening test in the USA. The used screening strategies are on the Figure 1.

### Integrated/sequential tests

Integrated/sequential tests use strategies incorporating measurements obtained from both the first and the second trimester. Their efficacy is the best of all of the screening types (more than 90%); additionally, these tests are superior to the others due to their safety and cost efficiency. Compared with other tests, the lower false positive rate with the integrated test means that the unaffected foetal losses are lower as compared to the use of any other test. Screening using the integrated test is less costly than might be expected, because the extra screening costs are outweighed by the savings in the cost of diagnoses arising from the low false-positive rate (41–43).

In those cases where ultrasonography is not available, the serum-integrated test is recommended. The risk is only calculated from the biochemical markers (free  $\beta$  hCG, PAPP-A, AFP, uE3, and inhibin), and the efficacy of this approach is similar to the first trimester combined screening (41, 42).

### Confirmation genetic tests

Even the best combinations of ultrasound findings (plus other variables) are only predictive, without a diagnostic value. For confirmation of the diagnosis, the chromosomes of the foetus must be examined.

### Amniocentesis

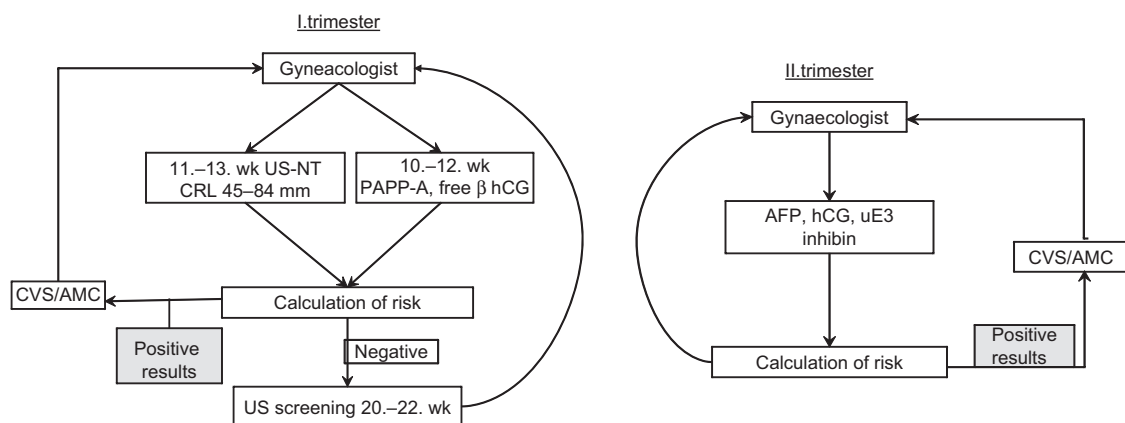
Amniocentesis is usually carried out between the 14th and the 18th weeks of pregnancy. There is a slight increase in the risk of miscarriage; the normal rate of miscarriage at this time in pregnancy is from 2% to 3% and amniocentesis increases the risk by an additional 0.5%–1% (44, 45). The current recommendations by professional obstetric groups are that women with a positive screening test, assessment based on age, the serum analyte levels, and nuchal translucency measurement if available, should be offered amniocentesis (46). It takes about 2–3 weeks to determine if the foetus has any chromosomal aberrations. The other way is to use the multiplex fluorescence polymerase chain reaction (PCR) technique for the identification of chromosome 21 trisomy; or to identify other anomalies such as the trisomy of chromosomes 13 or 18, sex chromosome aneuploidy, and other similar phenomena. These investigations take a few days to finish (47, 48).

### Chorionic villus sampling (CVS)

CVS is usually carried out between the 10th and the 12th weeks of pregnancy. In this procedure a small amount of tissue is taken from the young placenta (chorionic layer) instead of amniotic fluid (47). The risk of miscarriage after CVS is slightly higher than with amniocentesis. The same recommendations for amniocentesis apply for CVS (49, 50). The decision on whether to use amniocentesis or CVS is an individual one and should be thoroughly discussed between the pregnant woman and her physician.

### Screening of Down's syndrome

A wide range of policies have been developed in different countries (including Europe), as well as in different areas within the countries. The availability of different resources, laws about the termination of pregnancy, as well as social and cultural factors constitutes the crucial issues. Countries with a national policy had the highest proportion of prenatally diagnosed DS cases (51, 52). These policies, as well as health care system and



**Figure 1** Strategies of screening in the first and second trimester.

cultural factors, are associated with the wide-ranging country variations in prenatal detection rates for DS (53, 54).

Second trimester screening is the one most widely used in countries with the applied screening of DS just before 30 years; plus, it has also been widely accepted by the population. Countries that have only introduced the screening within the last few years mainly use the first trimester screening due to the widely available ultrasonography in the gynaecologists' practices.

In the Czech Republic, both forms of screening are recommended and investigations of chromosomal aberrations in the second trimester have been performed for more than 20 years. Prenatal diagnoses of DS have increased in last 15 years up to 88% of all DS cases in 2010. Termination of pregnancy is accepted in an overwhelming majority of DS diagnoses. Two-thirds of all DS diagnoses are from the second trimester screening in the Czech Republic.

### Foetal DNA in the mother's blood – future trends

New developments in the area of screening include the possibility of testing for DS by extraction of foetal cell-free nucleic acids from a maternal serum sample (55).

In January of 2011, a Chinese research group published a study demonstrating a high rate of correct diagnosis for Down's syndrome prenatally, only using foetal DNA from the mother's blood. While the results were remarkable, further testing will need to be performed before this test becomes commercially available. If this test becomes accepted as a screening test, it could eliminate more than 90% of all invasive diagnostic testing. Massive parallel DNA sequencing of cell-free foetal DNA from maternal blood as well as an optimised algorithm could detect trisomy 21, as well as other foetal chromosomal abnormalities (56–58).

### Thyroid diseases in pregnancy – possibilities for screening

Undetected thyroid disease can have serious consequences during the course of a person's life (59). It is the aim of medical care to diagnose thyroid function failure as early as possible, when the disease is at its most easily curable stage. The normal level of thyroid hormones and/or normal thyroid gland function is necessary for physiological reproduction, as well as being extremely important for pregnancy (60–62). Pregnant women with subclinical hypothyroidism seem to escape early clinical detection. While the hyperfunction during pregnancy usually manifests itself by clinical symptoms or a relapse of a previously cured disease (mostly Graves-Basedow), lowered function is much more dangerous due to its non-specific symptoms. Symptoms of hypothyroidism (fatigue, lowered performance, sleepiness, and psychological instability) can also accompany the physiological pregnancy; however, some women with subclinical hypothyroidism are completely asymptomatic, where there is no reliance on the clinical image, while being diagnostic of functional failure. The implications are staggering when

one considers that there is a significant increase in intrauterine deaths, spontaneous abortions, premature births, and preeclampsia; additionally, poor development of the foetus, such as major malformations and loss of IQ. It has been clearly proven that even slight (subclinical) hypothyroidism not only affects the course of pregnancy, but (especially later on) the neuropsychological development of the child (60, 63, 64).

The elevated levels of autoantibodies against thyroperoxidase (TPOAb) and a personal history of thyroid disease increased the risk of thyroid dysfunction (65). Based on experimental animal studies, Morreale de Escobar has shown the negative impact of insufficient levels of thyroid hormones during pregnancy on the growth of brain tissues (66, 67). Up until the 12th to the 14th week, the embryo depends completely on the mother's thyroxine; and is even still partially dependent on it, afterwards. Many papers have been published on the potential impact of subclinical hypothyroidism on both maternal and foetal health (63, 68, 69). There is evidence that maternal thyroid hormones can cross the placenta, and act to modulate the foetal central nervous system's development prior to the foetuses' own endogenous thyroid hormone secretion begin. Even minor perturbations in foetal thyroid hormone status may have effects in terms of the neurodevelopmental outcome (70, 71). Evaluating thyroid function during pregnancy is difficult, considering the many other different influences on a pregnancy (60). In pregnancy, the increase in oestradiol leads to an increase in the thyroid binding globulin (TBG) levels, which increases and reaches the new plateau at the end of the first trimester. The preparation for an in vitro fertilisation leads to very high oestradiol levels before and during the very early stages of pregnancy (comparable with those in the late pregnancy stages). Thus, the impacts with autoimmunity should be considered.

During pregnancy, suppression of thyroid-stimulating hormone (TSH) is well known; presumably, this is due to the thyroid-stimulating activity of hCG, mainly during early pregnancy (72). HCG has thyrotrophic activity; high levels of hCG suppress TSH by approx. 18%. Recent investigations have clarified the structural homology, not only with the hCG and TSH molecules, but also with their receptors; this homology suggests the basis for the reactivity of hCG with the TSH receptor (73).

By using the standard reference interval for serum TSH in the healthy population, one might misdiagnose as healthy those women who already have a slight elevation of TSH; conversely, one might suspect hyperthyroidism in normal women who have a lowered serum TSH value (74). The determination of free thyroxin (FT4), biologically active hormone which is available to the organism of a pregnant woman (as well as to the foetus), is not affected by the concentration of binding proteins (75), which are changed during pregnancy. Its concentration during pregnancy is partly affected both by the inflow of iodine and the duration of the pregnancy. Its concentration during pregnancy is partly affected both by the inflow of iodine and the duration of the pregnancy. Some consider it even more informative than TSH during pregnancy (76); however, the value of this information is currently under discussion.

The recommended dietary allowance of iodine for non-pregnant, non-lactating women aged  $\geq 14$  years is 150  $\mu\text{g}/\text{day}$ . 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 foetus. Iodine needs to be transferred to the foetus for foetal thyroid hormone production in later gestation, as well as the probable increase in renal iodine clearance. The recommended dietary allowance for pregnancy is 220–250  $\mu\text{g}/\text{day}$  (61, 77). In iodine-abundant areas, the most important course of thyroid disease is usually autoimmune thyroiditis.

TPO antibodies are markers of an autoimmune process in the thyroid gland, and their determination is both diagnostic and prognostic important (78, 79). The presence of TPOAb during pregnancy also alerts the medical professional to the risk of development of postpartum thyroiditis (65); therefore, it is necessary to follow-up on those women. TPOAb positivity may endanger not only the current, but also subsequent pregnancies.

Some data support the efficacy of early thyroid function screening, especially in women during their childbearing age – at the very latest when pregnant. Alterations in thyroid hormone concentrations during pregnancy differed at different stages of gestation, as well as in those in the non-pregnant state (59, 80).

For many years, there has been a professional discussion about the benefits of case finding or universal screening of thyroid dysfunction in pregnancy (64, 81, 82). Recently, a number of recommendations and guideline statements relating to aspects of the thyroid and pregnancy have been published. The key guidelines of the Endocrine Society (US) for the management of thyroid dysfunction during pregnancy and postpartum were published in 2007 (60). This guideline recommended case finding among pregnant women identified as being at high risk for thyroid disease. In the following years, some other studies have been published (83–86) which demonstrated that only minimally screening high-risk pregnant women failed to detect 30% of hypothyroid women. The latest recommendations were published by the American Thyroid Association in 2011 (61). They also recommended case-finding investigations, but the list of indications is relatively large. The serum TSH values should be obtained early in pregnancy in the women with history of thyroid dysfunction, prior thyroid surgery, older than 30 years, symptoms of thyroid dysfunction, the presence of goitre, TPOAb positivity, diabetes type 1, other autoimmune disorders, and a history of either miscarriage or preterm delivery. Other reasons for investigation in pregnancy include a family history of thyroid dysfunction, morbid obesity (BMI 40  $\text{kg}/\text{m}^2$ ), infertility, and other risk factors.

TSH is the main analyte for the detection of thyroid failure; determination of the specific reference intervals for TSH for pregnant women is one of the basic requirements when implementing a general examination of the thyroid gland in early pregnancy. If a trimester-specific reference interval for TSH is not available in the laboratory, the latest (and not yet universally accepted) recommended reference interval for TSH should be 0.1–2.5 mIU/L in the first trimester (61).

Reference intervals have been established using pools of healthy non-pregnant women, as well as using different antibodies (some of them not relevant during pregnancy). Moreover, the use of different analytical systems could lead to a misdiagnosis, considering the differences among reference intervals for different analytical systems (80, 84, 87).

Our first study was performed between 2006 and 2008, and examined 7530 consecutive asymptomatic pregnant women (between the 9th and the 11th week of pregnancy; 99% Caucasian) who were undergoing their first trimester prenatal screening for aneuploidy, at the same time they were having TSH, FT4 and TPOAb measured. The aim of this study was to evaluate the prevalence of thyroid disorders in pregnant Czech women, and to identify the optimal reference intervals in evaluations of maternal thyroid function during the first trimester of pregnancy. The analyses were performed on an ADVIA Centaur Siemens automated immunoassay analyser (Siemens, Healthcare Diagnostics Inc., Tarrytown, NY, USA).

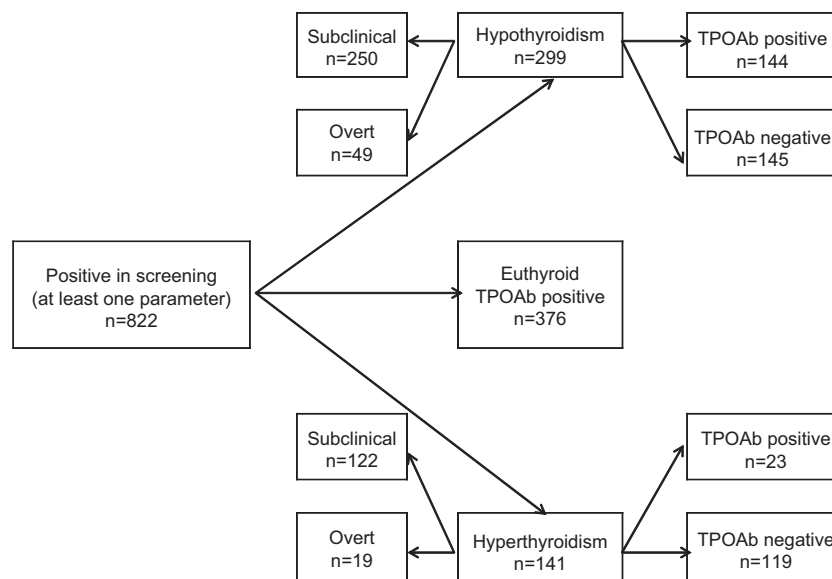
The average age in the group of pregnant women was 31.2 ( $\pm 4.3$ ) years.

Sufficient levels of iodine supplementation could be expected, as iodised salt has been in regular use in the Czech Republic since the 1950s; with the Zamrazil study confirming this hypothesis (88).

For the evaluation of our results, we determined the acceptable reference intervals for TSH, TPOAb, and FT4 in the first trimester of pregnancy. TSH and TPOAb do not follow a normal distribution; they have to be normalised using a log transformation. We established the reference interval for TSH in pregnant women in the first trimester of pregnancy, such as the 2.5th percentile and 97.5th percentile of this group: 0.06–3.67 mU/L. The limit for TPOAb positivity was determined to be 143 kU/L. The FT4 reference interval was determined to be the same as that of the manufacturer for adult population (9.8–23.0 pmol/L) (84).

## Incidence of thyroid disease in pregnancy

Our study group consisted of 7350 women, of which 1205 had some of thyroid markers out of reference interval. Women with a positive screening result were advised to visit an endocrinologist within a few days. Raised concentrations of TSH were found in 5.1% of the women, suppression of TSH was found in 2.9% of the women, and 11.5% of the pregnant women were found to be TPOAb positive. Serum concentrations of FT4 were lower in TPOAb positive women, compared to those TPOAb negative; additionally, in euthyroid women with suppressed, normal, and elevated TSH differences of FT4 levels (medians: 17.89 vs. 13.98 vs. 12.91 pmol/L,  $p < 0.05$ ) were found. Guidelines for the investigation of thyroid gland function during pregnancy have recommended case sensitive screening for women with a family history of thyroid disease, a personal history of diabetes, or previous treatment for thyroid disease (61). This condition was only present in 58% of the positively screened pregnant women in our study group. The distribution of thyroid dysfunctions in the group of screening positive women shows the Figure 2.



**Figure 2** Positivity in thyroid disease screening.

In the group of positive women ( $n=822$ ), 49 women were diagnosed with overt and 250 with subclinical hypothyroidism, and 23 women with overt and 122 women with subclinical hyperthyroidism. There were 376 euthyroid women with TPO Ab positivity, whilst altogether there were 543 TPO Ab positive women in the whole group.

In this study, there was a higher prevalence of pregnant women with an elevation of TSH (5.1%), compared to other iodine-sufficient countries, where the prevalence of pregnant women with TSH elevation reaches 2%–3% (63, 83). Obviously, these numbers depend on the TSH upper limit of the reference range used. In the Czech studies, a cut-off at 3.67 mU/L was used. At present, world authorities recommend to use of an upper cut-off at 2.5 mU/L (61). Therefore, for the Czech population either: this cut-off either lies too low, there is a higher prevalence of hypothyroidism among pregnant Czech women, or our analytical method used for TSH measurements gives higher numbers than the methods used by others. However, our analysis was performed using a well-established and widely used analyser (Advia Centaur, Siemens). Apparently, the recommended cut-off at 2.5 mU/L would lead to large numbers of positive pregnant women during screening.

The part of women who screened positive ( $n=822$ ) were invited to a follow-up study 1–3 years after delivery. In order to gain as complete their clinical state and history as possible, they were asked to fill out a detailed internet-based questionnaire concerning their personal, family, and gynaecological history. Furthermore, these women were invited for a blood test control, including an analysis of TSH, FT4, and TPOAb. The two main aims of the study were: a) to assess the prevalence of high risk-profile women in this group; and b) to evaluate the postpartum thyroid function in this group, with regard to the adequacy of treatment. Of the 822 women invited, 237 (28.8%) joined the postpartum evaluation study; their average age was 31 years (89). The use of the new guidelines of the American Thyroid Association (61) for identification of high-risk women substantially increased the proportion of high-risk women among those who screened positive. We also tried to identify the most important risk factors,

in order to simplify the decision process of which women should be screened. We found that four risk factors could identify 82% of the high-risk women: age >30 years (in our analysis, 31 years and more), a personal or family history of thyroid disease, and the presence of goitre. Based on these preliminary results, we performed an analysis showing that although age is not a risk factor for AITD in pregnancy, the inclusion of age  $\geq 30$  criterion substantially improves the proportion of hypothyroid women identified in a case-finding screening (up to 85%) due to a larger number of women screened (90).

Forty percent of the initially euthyroid pregnant women, positive for TPOAb, had thyroid dysfunction more than 1 year after delivery. There is a strong agreement that after delivery TPOAb positive women should be closely monitored, even if they are euthyroid during pregnancy (89). TPOAb positivity carries a high risk of developing hypothyroidism up to 1 year postpartum. Our findings are in concordance with Stagnaro-Green, who found that 50% of women with postpartum thyroiditis were hypothyroid 1 year after delivery (61).

A worsening of the child's mental development, due to suboptimal maternal thyroid function, and resulting in poor learning performance, as well as worsen professional employment all have their negative economic consequences. Two studies have dealt with the cost-effectiveness of universal screening for thyroid disorders in pregnancy, and both found it cost-effective under the circumstance that subclinical hypothyroidism decreases IQ of the offspring (91, 92).

The early diagnosis of thyroid disorders based on correct reference interval of analytes and treatment during pregnancy not only prevent complications during the pregnancy, but also can prevent possible problems in the development of

the embryo's brain, as well as the risk of poor neuropsychological development of their offspring.

## Conclusions

Prenatal screening should be offered universally to all women who desire to know the health status of the children they bear. Therefore, all women have to be made aware of the available screening tests, and the purpose of each test. There also must be a clear explanation and an understanding of the difference between a screening test and a diagnostic test.

Today, there is a variety of accepted screening protocols for DS. These choices can be confusing, both to patients and clinicians. The fully integrated test or the sequential integrated test is the safest and most cost-effective test currently available. If a NT measurement is not available, then the serum-integrated test is best. First trimester combined screening is better than second trimester screening; both step-wise sequential screening and fully integrated screening have higher rates of detection of DS, with low rates of false positives. It has become apparent that most major aneuploidies can be identified at the 11th to the 13th weeks of gestation by a combination of maternal characteristics, ultrasound findings, and biochemical tests of the maternal blood. However, the decision to screen, and to perform invasive confirmatory testing, is a personal one that may be influenced by the presence (or absence) of a family history of aneuploidy or genetic disorders, as well as by the woman's obstetrical and medical history.

The prevalence of thyroid disorders is relatively high among pregnant Czech women, compared with other developed iodine-sufficient countries. About 11% of pregnant women are TPOAb positive, and more than 5% have subclinical or overt hypothyroidism in the first trimester of pregnancy.

One-third of all initially euthyroid TPOAb-positive pregnant women have TSH out of the reference interval 1½ years after delivery. This was due to postpartum thyroiditis. Both TSH and TPOAb measurement should be included in screening programmes. In the Czech Republic, a targeted case-finding screening programme would miss one half of pregnant women with thyroid disease. These findings change substantially if age  $\geq 30$  is included among the criteria used for identification of women who should be screened.

In conclusion, our data provide a contribution to the guidelines previously published for the management of thyroid disease in pregnancy; plus additionally lending support to the implementation of general screening for thyroid disorders in pregnant women, as well as the close follow-up (for a prolonged period after delivery) in those women who screen positive.

Quality information and counselling are important prior to antenatal screening (and related interventions) in order to prepare women for the possible results, to explain all of the options, and enable families to access support when it is required. The screening scheme needs to include effective cooperation between experts. The new, safer and less invasive screening methods improve the possibilities of prenatal care for a better future world.

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