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Perinatal Thyroid Workshop Report – 2015

Oluş Api[1], Cihat Şen[2], Murat Yayla[3], Mertihan Kurdoğlu[4], Elif Gül Yapar Eyi[5], Mekin Sezik[6], Gökhan Göynümer[7], Özlem Moraloğlu Tekin[5]

[1]Perinatology Clinics, Faculty of Medicine, Yeditepe University, Istanbul, Turkey; [2]Perinatology Department, Faculty of Medicine, Istanbul University, Istanbul, Turkey; [3]Perinatology Clinics, Acıbadem Hospital, Istanbul, Turkey; [4]Department of Obstetrics and Gynecology, Faculty of Medicine, Gazi University, Ankara, Turkey; [5]Gynecology and Obstetrics Clinic, Zekai Tahir Burak Training and Research Hospital, Ankara, Turkey; [6]Department of Obstetrics and Gynecology, Faculty of Medicine, Süleyman Demirel University, Isparta, Turkey; [7]Gynecology and Obstetrics Clinic, Göztepe Training and Research Hospital, İstanbul, Turkey

Abstract

A Perinatal Thyroid Workshop has been carried out in order to determine scientific data and clarify confusions in clinical practices as a result of new findings and interpretations in pregnancy and thyroid recently. Since maternal oral L-thyroxine intake cannot treat fetal hypothyroidism in the intrauterine life, it is scientifically not right to say as a basic result that L-thyroxine treatment of a mother would also treat the possible hypothyroidism in fetus. Since the association of adverse gestational outcomes with overt hypothyroidism has been proven, the treatment should be initiated as soon as it is detected during pregnancy. It is known that subclinical hypothyroidism is more common than overt hypothyroidism. Although an association has been shown between subclinical hypothyroidism and adverse gestational outcomes, no such association was found in randomized controlled studies. Maternal oral L-thyroxine intake does not treat fetal hypothyroidism in the intrauterine life. While overt hyperthyroidism has many reasons, it occurs during pregnancy mostly associated with Graves' disease. Therefore, the treatment is initiated immediately as soon as it is detected during pregnancy, and it is aimed to keep mother in mild hyperthyroidism. The drug mostly preferred in the treatment is propylthiouracil (PTU) since it passes through placenta at minimal rates. In the beginning of the pregnancy, the screening requires to check only the levels of thyroid stimulating hormone (TSH). Free or total T4 measurement is required only when there is a change in TSH. Similarly, anti-thyroid antibodies during pregnancy are not recommended to use for routine screening since there is no evidence to make a recommendation in favor of or against screening. Considering the current literature, guides and expert opinions, it is not advisable to screen all pregnant women on a routine basis. Screening by TSH should be done only in high risk. In Turkey, scientific data seem insufficient for now to suggest routine iodine support for all pregnant women during antenatal care. However, large-scale and population-based studies are required immediately to detect the true prevalance of iodine deficiency in Turkey.

Keywords: Pregnancy, perinatal, thyroid.

Özet: Perinatal Tiroid Çalıştay Raporu – 2015

Gebelik ve tiroid konusunda son yıllarda yeni bulgular ve yorumların ortaya çıkması ve bunun sonucunda klinik uygulamada meydana gelen karışıklıkların açığa kavuşturulması ve bilimsel verilerin belirlenmesi amacı ile Perinatal Tiroid Çalıştayı gerçekleştirilmiştir. Temel sonuç, maternal oral L-tiroksin alımı intrauterin hayatta fetal hipotiroidiyi tedavi edemediğinden, L-tiroksin tedavisi almakta olan bir anneye, bu tedavinin fetüsteki olası bir hipotiroidiyi de tedavi edebileceğini söylemek bilimsel olarak doğru değildir. Aşikar hipotiroidinin kötü gebelik sonuçlarıyla ilişkisi kanıtlanmış olduğundan gebelik sırasında saptanır saptanmaz hemen tedaviye başlanmalıdır. Subklinik hipotiroidinin, aşikar hipotiroididen daha yaygın olarak görüldüğü bilinmektedir. Subklinik hipotiroidi ile olumsuz gebelik sonuçları arasında bir ilişki gösterilmiş olmasına karşın, randomize kontrollü çalışmalarda böyle bir ilişki ortaya konmamıştır. Maternal oral L-tiroksin alımı intrauterin hayatta fetal hipotiroidiyi tedavi etmemektedir. Aşikar hipertiroidizmin pek çok sebebi olmakla beraber, gebelikte en sık Graves hastalığına bağlı olarak ortaya çıkar. Bu nedenle, gebelik sırasında saptanır saptanmaz hemen tedaviye başlanarak annenin hafif hipertiroid durumda tutulması hedeflenir. Tedavide en sık tercih edilen ilaç, plasentayı minimal oranlarda geçtiğinden dolayı propiltiyourasildir (PTU). Gebeliğin başlangıcında tarama, sadece tiroid stimülan hormon (TSH) düzeylerinin ölçümünü gerektirir. Serbest veya total T4 ölçümü sadece TSH'da bir değişiklik olduğunda gereklidir. Benzer şekilde, gebelikte antitiroid antikorların, tarama lehine veya aleyhine öneride bulunmak için yeterli delil bulunmadığından, rutin olarak taramada kullanımı önerilmemektedir. Mevcut literatür, kılavuzlar ve uzman görüşleri genel olarak değerlendirildiğinde, tüm gebe kadınların ilk trimesterde TSH ile taranmasının uygun olmadığı ortaya çıkmaktadır. TSH ile tarama yalnızca riskli olgulara yapılmalıdır. Ülkemizde antenatal bakım sürecinde tüm gebelere rutin iyot desteğini önermek için bilimsel veriler şimdilik yetersiz görünmektedir. Ancak, ülkemizdeki gebelerde iyot eksikliği prevalansının belirlenmesi amacıyla yapılacak geniş ölçekli ve toplum temelli çalışmalara acil olarak ihtiyaç vardır.

Anahtar sözcükler: Gebelik, perinatal, tiroid.

Correspondence: Cihat Şen, MD. İ.Ü. Cerrahpaşa Tıp Fakültesi, Kadın Hastalıkları ve Doğum AD, Perinatoloji Bilim Dalı, İstanbul, Turkey. e-mail: csen@cihatsen.com

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Introduction

Purpose of the Workshop

With the Workshop, it was aimed to establish a guideline for a national practice association under the name of "Gestational Thyroid Screening and Diagnosis Guide" for the use of obstetricians and gynecologists during their obstetric follow-ups and to reveal scientific evidence levels related with:

- Physiological process related with maternal and fetal thyroid hormone syntheses,
- Proper clinical use of assessment criteria and tests used to evaluate gestational thyroid functions,
- Impacts of clinical and subclinical maternal thyroid dysfunctions on maternal and fetal heath, and clinical management of these dysfunctions

For that purpose, Perinatal Thyroid Workshop has been organized with the support of association member academicians working at Turkish universities and training and research hospitals. The participants prepared current literature about the topics they determined months ago, and presented and discussed them.

Perinatal Thyroid Workshop held in Afyon between November 8 and 9, 2013 had following program:

1. Discussing the importance of the topic
2. Talking about the current situation in Turkey and the world
3. Discussed questions
4. Discussed solution recommendations
5. Questions with no answer

The Result Report of Perinatal Thyroid Workshop was established with the consensus of report committee and completed on May 19, 2015 after the literature was reviewed through reporting and e-mail and re-evaluation by the group of the reports prepared by the participants.

Evidences

The evidences were included in the report in accordance with the criteria *(U.S. Preventive Services Task Force Ratings: Strength of Recommendations and Quality of Evidence. 2003 Guide to Clinical Preventive Services, Third Edition: Period Updates, 2000–2003)* presenting the net benefit (benefit-loss) and the power of evidence, and based on in the evaluations made pursuant to the "*Preventive Service Task Force*" and "*Grading of Recommendations, Assessment, Development and Evaluation (GRADE)*" of the USA in the literature previously. The evidences are considered as good, medium and poor, and the recommendations in the "Grade" system are expressed as "1" if they are good and as "2" if they are poor. Evidence values are also expressed with following symbols:

- Evidence of very poor quality: +
- Evidence of poor quality: ++
- Evidence of medium quality: +++
- Evidence of high quality: ++++

A. The service provides benefit in terms of health; benefits outweigh risks; clinicians are highly recommended to provide this service for appropriate patients.

B. There are partial evidences that the service provide benefit in terms of health; benefits outweigh risks; clinicians should provide this service for appropriate patients.

C. There are partial evidences that the service provide benefit in terms of health; benefit-risk evaluations are very close to make a general recommendation; therefore, clinician cannot be recommended either to provide or not to provide this service for appropriate patients.

D. There are partial evidences that the service does not provide benefit or it is ineffective in terms of health; risks outweigh benefits; it is not recommended to clinician to provide this service as a routine practice for appropriate patients.

I. (Insufficient) Evidences for the benefit or risk of service in terms of health are insufficient; benefits outweigh risks; clinician should provide this service for routine patients

Workshop results were addressed as main topics below and interpreted:

I. Gestational Thyroid Function: How to Interpret Tests Properly?

II. Iodine Status in Turkey and the World for Iodine Insufficiency

III. Impacts of Hypothyroidism on Pregnancy

IV. Pregnancy and Hypothyroidism

I. Gestational Thyroid Function: How to Interpret Tests Properly?

Thyroid stimulating hormone (TSH) and thyroid hormone levels vary during pregnancy. Normal reference values of non-pregnant women should not be considered as "normal" for pregnant women[1] ***(Evidence Level A, High ++++)***. Knowing and evaluating them are of particular importance.

In the first trimester, TSH levels secondary to the increase of human chorionic gonadotropin (hCG) are suppressed. This is physiological, and therefore it should not be considered as pathology. With the stimulating effect of hCG hormone on thyroid gland, free thyroxin (sT4) levels during first trimester stay within normal ranges only with a slight increase, and TSH levels decrease (<0.1 mIU/L). In following trimesters, TSH reaches to normal levels. Therefore, in evaluating gestational thyroid functions, it is recommended to use TSH reference ranges specific to trimesters ***(Evidence Level B, Medium +++)***.

A significant problem in the changes of gestational thyroid functions is the difficulty of making pathology – physiology distinction. This distinction is possible by determining normal reference values specific to pregnancy. However, there is no full consensus on determining reference values. These values vary depending on the regional, ethnic and genetic characteristics[2-4] ***(Evidence Level B, Medium +++)***. Reference values also vary according to the week of gestation[3,5,6] ***(Evidence Level A, High ++++)***. Therefore, it is recommended to use 2.5 – 97.5 percentile value ranges instead of using absolute values.[5,6] The reference values found in the literature are close to each other, and there is no full consensus on these values.

In cases where percentile values specific to trimester cannot be established by laboratory, the upper limits for TSH provided in the **Table 1** can be used[2–8] ***(Evidence Level B, Medium +++)***.

The first step for evaluating gestational thyroid functions is the measurement of serum TSH levels ***(Evidence Level B, Medium +++)***. For TSH measurements, automated platforms such as "chemiluminescence" using "improved immunometric assay" methods are recommended.[3,8] Using 3rd or 4th generation (ultrasensitive) kits in these automated systems helps to detect even the slightest differences (<0.02 mU/L) in TSH values compared to the systems using ELISA techniques. Therefore, it is recommended to use TSH measurement by using sensitive "immunometric assay" as a screening test for evaluating thyroid function ***(Evidence Level B, Medium +++)***.

Table 1. Lower and upper limit values for serum TSH according to gestational trimesters.

- 0.1 – 2.5 mU/L for the first trimester
- 0.2 – 3.0 mU/L for the second trimester
- 0.3 – 3.0 mU/L for the third trimester

The production of thyroid-binding globulin (TBG) increases during pregnancy. Accordingly, total triiodothyronine (T3) and thyroxine (T4) levels increase about 1.5 times. Therefore, usually the measurements of free triiodothyronine (fT3) and free thyroxine (fT4) levels are preferred during pregnancy. However, just as in TSH, fT4 level exhibits physiological changes according to trimesters. In the first trimester, fT4 exceeds normal reference values, and decreases 30% below fT4 normal reference values. Therefore, it is recommended during pregnancy –as in TSH– trimester- that specific fT4 reference values should be determined by each laboratory or 150% of total T4 should be considered as the reference value. On the other hand, like TSH, there is no reference value specific to each trimester with a consensus achieved.

In the measurement of free T4, "immunoassays" are used widely. However, it should be remembered that the laboratory methods used and kit differences may provide misleading results for free hormone measurements[9,10] ***(Evidence Level A, High ++++)***. Especially, "*equilibrium*" dialysis or the method of isotope-dilution fluid chromatography-tandem mass spectrometry (LC-MS-MS) was considered to be more reliable and reproducible when evaluating serum fT4 levels in pregnant women[11,12] ***(Evidence Level A, High ++++)***. But this method is used in a limited way since it is performed in private laboratories and it is expensive. Therefore, similar to TSH measurements, it should be kept in mind that fT4 measurement during pregnancy is error-prone. For that reason, we recommend that each laboratory should calculate percentile values for their own gestational study population and report the studied results through percentile values.

As total T3 level is not a preliminary test for evaluating thyroid functions even in non-gestational cases, it

cannot be used also to evaluate thyroid dysfunctions during pregnancy. However, after hyperthyroidism is detected, it is recommended to use for follow-up purposes, in case of T3 toxicosis or in the differential diagnosis of hyperthyroidism.[13]

Last but not least, "hyperemesis gravidarum" is another significant clinical condition which may have misleading impacts on TSH and fT4. In hyperemesis gravidarum, fT4 levels may increase in 30–60% of pregnant women in addition to the physiologically suppressed TSH at first trimester. In such cases, it is recommended to evaluate TSH receptor stimulating antibody levels and to carry out differential diagnosis with Graves' disease. In case of hyperemesis gravidarum, TSH receptor stimulating antibodies are negative, hyperthyroidism findings do not occur in patients and fT4 levels returns to normal ranges between 15 and 18 weeks of gestation. In Graves' disease, TSH receptor stimulating antibody levels are determined especially at third trimester and hyperthyroidism risk in the newborn should be considered[14] ***(Evidence Level A, High ++++)***.

In conclusion

- In case of indication during pregnancy, 3rd or 4th generation (ultrasensitive) TSH measurement is recommended as thyroid screening test ***(Evidence Level B, Medium +++)***.
- When evaluating serum TSH during pregnancy, reference values of non-pregnant population should not be used ***(Evidence Level A, High ++++)***.
- In serum TSH evaluation during pregnancy, using percentile values or reference values specific to each trimester seems an appropriate clinical practice ***(Evidence Level A, High ++++)***. Our recommendation in accordance with literature evidences is to use TSH values provided in the **Table 2**.
- In cases where TSH levels are high or low during pregnancy, the first thing to do is laboratory test for free or total T4 measurement. Serum T3 level is not among the tests to be requested first.
- If total T4 is measured during pregnancy, the increase of 1.5 times in total T4 amount should be considered as pathological ***(Evidence Level B, Medium +++)***.
- For the evaluation of fT4 levels during pregnancy, "*equilibrium*" dialysis or the method of isotope-dilution fluid chromatography-tandem mass spectrometry (LC-MS-MS) is more reliable ***(Evidence Level A, High ++++)***. However, this method is used in a limited way since it is performed in private laboratories and it is expensive. Immunometric tests are used more widely to determine free T4 values during pregnancy in the laboratories in Turkey and the world.
- It should be kept in mind that immunometric fT4 measurement during pregnancy is error-prone as long as percentile values specific to the laboratory, in which the test is performed, is not used ***(Evidence Level A, High ++++)***. For that reason, we recommend that each laboratory should calculate fT4 percentile values for their own gestational study population and report the studied results through percentile values.

II. Iodine Status in Turkey and the World for Iodine Insufficiency

Iodine insufficiency is still a significant public health problem in the world.[15] It is estimated that 35% of the world population has insufficient iodine intake.[16] Daily iodine intake amounts determined by World Health Organization (WHO) are provided in the **Table 3**. Iodine amount in most of the natural foods are usually low and it varies depending on environmental factors

Table 2. Daily iodine intake recommendations of World Health Organization.[4]

Age	Iodine intake
<5 years old	90
6–12 years old	120
>12 years old	150
Pregnancy/Lactation	250

Table 3. Iodine insufficiency classification.[4]

Iodine insufficiency level	Urinary median iodine concentration (mcg/L)
Severe	<20
Medium	20–49
Mild	50–99
Sufficient intake	100–199
Sufficient intake of pregnant women	150–249

such as the iodine concentration in the soil and fertilizer use. Some of the iodine in the world is taken from the surface of the ground by snow and rain and moved to seas by winds and floods, and by being vaporized here, they return to the soil again through rain. As a result, especially the seaweeds and sea products are among the iodine-rich sources. However, iodine content may vary to a large extent in different fish species.

Yoghurt, cow milk, egg, strawberry and also fresh cheese types with less amounts of iodine are among other iodine-rich sources that we may recommend people to consume daily. On the other hand, processed foods including iodized salt and materials including iodate used to thicken dough are also among the iodine-rich nutritional sources. The efforts to make people consume iodized salt in order to increase daily iodine intake in many countries resulted in success. Similarly, Mother and Child Care and Family Planning Center of Turkish Ministry of Health and UNICEF initiated the "Program of Preventing Diseases Caused by Iodine Insufficiency and Iodizing Salt" in 1994.

In accordance with the Table Salt Communiqué of Turkish Food Codex published in the Official Gazette No. 23397 dated 09 July 1998, iodizing table salts became mandatory. Accordingly, it is mandatory to add 50–70 mg/kg potassium iodure or 25–40 mg/kg potassium iodate to table salts. Table salt is the refined or unrefined salt which is enriched by iodine, powderized and directly offered to consumers. In accordance with the provisions of the act, it was decided that Ministry of Agriculture and Rural Areas would be in charge during production process, and Ministry of Health would be in charge from production until delivered to consumers. However, another issue to highlight is that iodized salt is harmful for some thyroid patients such as those with Graves' disease, Hashimoto Thyroid and hot nodules. Therefore, with the "Communiqué Concerning Revision in the Table Salt Communiqué of Turkish Food Codex" published in the Official Gazette No. 24141 dated 15 August 2000, it was allowed to manufacture table salt without iodine in 250 g packages for such patients.

In the determination of iodine insufficiency, urinary iodine excretion is considered. Urinary iodine measurement is a cost-efficient and widely recognized test with easy applicability. As almost 90% of iodine taken is excreted with urine, urinary iodine level is accepted as a sensitive test to show current iodine intake. However, there is a significant point to highlight. In terms of urinary iodine excretion, it is known that the amount may vary day by day, even in the same day. Due to these variations, urinary iodine excretion to be used as a diagnostic test to show iodine intake may cause misleading evaluations and treatments.[17] Since urinary iodine values do not exhibit normal distribution, it is recommended to use this test in studies based on population and to use median values as mean value and percentiles instead of standard deviation values.[18]

The degree of iodine insufficiency is classified based on median urinary iodine concentration of the population studied (**Table 4**).

It is a well-recognized fact that severe iodine sufficiency has negative impacts on the fetal development and neuro-cognitive functions in developing countries. Cretinism and mental retardation are the major adverse effects ***(Evidence Level A, High ++++)***. However, since the impacts of iodine on fetal brain developments have been understood well in recent years, the impacts of mild-medium iodine insufficiency

Table 4. Pregnant women recommended early TSH screening.

- Thyroid dysfunction / surgery underwent (since hypothyroid development rate is 33% after lobectomy)
- Thyroid disease history in the family
- Goiter presence
- Thyroid antibody positivity, especially thyroid peroxidase auto-antibodies (TPOAb increases hypothyroidism risk, and the probability increased 40% in those with TPOAb positivity compared to TPOAb negativity)
- Presence of clinical hypothyroidism findings/symptoms
- Type I diabetes (since hypothyroidism rate increases to 16%)
- Miscarriage and preterm labor
- Presence of vitiligo, adrenal failure, hypoparathyroidism, atrophic gastritis, pernicious anemia, systemic sclerosis, SLE, Sjögren's syndrome associated with autoimmune thyroid dysfunction
- Infertility presence (Although overt and subclinical hypothyroidism rates are as wide as 1–43%)
- Those who underwent head-neck irradiation (since hypothyroidism prevalence is 67% in the 8-year follow-up)
- Morbid obeses whose BMI (body mass index) is >40 (since hypothyroidism was found as 13–19.5%)
- Women over 35 years (The rate of Serum TSH value be ? 5 increases together with the age)
- Amiodarone treatment applications (14–18% hyperthyroidism-hypothyroidism)
- Lithium use (6–52 hypothyroidism)
- Exposure to iodinized contrast agents (until 6 weeks before pregnancy, thyroid dysfunction in 20% cases)
- Living in regions with medium level of iodine insufficiency

on fetal neurological development have been discussed and researched. Iodine requirement increases since thyroid hormone production in mother and fetus during pregnancy and renal iodine excretion increase ***(Evidence Level A, High ++++)***. In those with sufficient iodine intake before and during pregnancy, iodine stocks in thyroid gland can meet increased needs. Therefore, iodine amount does not change in those with sufficient iodine intake. However, the studies performed on pregnant women with mild-medium iodine insufficiency show that urinary iodine excretion decreases as an indication of decrease in body stocks towards the end of pregnancy.[19] On the other hand, the most significant source of iodine for newborn is breast milk. Thus, sufficient iodine intake of mother is essential in terms of the newborn development.[20] Important sources of iodine in the diet are sea products, egg, meat and chicken. Countries develop different strategies to prevent iodine deficiency.

In order to meet increased needs during pregnancy, iodine supplement is used during antenatal period in some countries. The daily amount recommended during pregnancy is 250 microgram according to WHO. Also, iodizing table salt is the most common practice to prevent iodine insufficiency including our country. However, even though table salt is iodized, conformity to the codex and standardization may cause problems.[18,21] Besides, humidity and heat (i.e. during cooking / by direct effect of sunlight), iodine amounts in the iodized salt decrease[22,23] ***(Evidence Level A, High ++++)***. On the other hand, all countries practice strategies to decrease daily salt consume to prevent hypertension. In Turkey, iodine supplement is not provided routinely to pregnant women during antenatal period and postpartum lactation period. Although it was found in small-scale studies that more than 80% of pregnant women in Turkey use iodized salt, it is not known if this rate is same for the entire country.[24,25]

New data shows that 85% of the households in Turkey use iodized salt.[26] Society-based studies in Turkey indicate that iodine insufficiency level has changed from "mild insufficiency" to "sufficient intake" within the last decade[27,28] ***(Evidence Level B, Medium +++)***. The number of the studies researching iodine insufficiency prevalence of pregnant women in Turkey is insufficient. Also, current studies including pregnant women mostly cover a single region and a limited number of pregnant women.[24,26,29–31] Therefore, large-scale and society-based studies are required. For that purpose, it has been decided to plan a prospective, multi-centered research project under the coordinatorship of Turkish Perinatology Society.

The short- and long-term impacts of mild iodine insufficiency during pregnancy on fetus and newborn are controversial; related small-scale cross-sectional studies showed that medium level iodine insufficiency may have negative impacts on neurological, behavioral and learning abilities in the short-term.[32] In 2013, two major studies were published which showed long-term negative impacts of mild iodine deficiency during pregnancy on neurocognitive functions during childhood.[32,33] It would be useful to take a look these studies. In the study of Bath et al. carried on approximately 1040 pregnant women and published in Lancet, urine samples of pregnant women were collected and kept at 10–13 weeks of gestation.[33] The IQ scores at 8-year-old of the children born from these pregnant women and their reading performances at 9-year-old were evaluated. In the urine samples maintained, median iodine concentrations were measured and it was determined if iodine intakes of pregnant women were sufficient or not, and pregnant women were separated into two groups (as those with median urinary iodine concentration <150 mcg/g and >150 mcg/g). According to the results of the study, both verbal IQ scores and reading-understanding abilities were found significantly low in those with mild-medium iodine insufficiency (median urinary iodine concentration <150 mcg/g).[33] In the sub-group analysis, the negative impact on IQ scores and reading abilities increased as iodine insufficiency increased. This study is very significant since it was conducted in a country where iodine intake was classified as sufficient, it showed that even mild-medium insufficiency may have impacts on neurological development and it has been the widest study so far.

Similarly, another longitudinal cohort study was performed in Australia in 2013.[34] In this study, pregnant women were separated into two groups as having median urinary iodine concentration <150 mcg/g and >150 mcg/g. Children born from these pregnancies were evaluated in terms of school performances (grammar, spelling, reading-writing) when they were 9 years old. According to the results of the study, the performances of grammar, spelling and reading-writing were signifi-

cantly lower in pregnant women with mild-medium iodine insufficiency (median urinary iodine concentration <150 mcg/g).

Although negative impacts of mild iodine insufficiency were found in these two studies, the cause-effect relationship of these impacts has not been established fully yet. Also, even such relationship is established, possible positive impacts of iodine supplement on fetal neurological development should be shown by randomized controlled studies.

Consequently

- Scientific data to recommend routine iodine support to all pregnant women during antenatal care seems insufficient for now ***(Evidence Level I, Low +++)***.
- Large-scale and society-based studies are required immediately to determine iodine sufficiency prevalence of pregnant women in Turkey.
- If the region that pregnant women live is known to have severe iodine insufficiency, iodine supplement should be recommended certainly during antenatal period ***(Evidence Level A, High ++++)***.
- Mild-medium iodine insufficiency during pregnancy was shown to have short- and long-term negative impacts on neurological, behavioral and learning abilities. However, the cause-effect relationship has not been established fully yet ***(Evidence Level B, Medium +++)***.

III. Impacts of Hypothyroidism on Pregnancy

Does overt (clinical) hypothyroidism have impacts on gestational outcomes?

Hypothyroidism may have negative impacts on gestational outcomes depending on the intensity of biochemical anomalies. High TSH and low free T4 levels and overt hypothyroidism complicating the pregnancy are seen rarely (0.3–0.5% of screened women). This is caused by two factors. First is that some of the hypothyroid women are anovulatory.[35] Other is that new or insufficiently treated hypothyroidism complicating pregnancy is associated with increased first trimester spontaneous abortion rate.[36–38] In the ongoing pregnancies, it was found that hypothyroidism is associated with increased risk for following complications:[39–44] preeclampsia and gestational hypertension, ablation placentae, unreliable fetal heart rate trace, preterm labor including very early delivery (before 32 weeks), low birth weight [this was explained in a study most likely due to preterm labor for preeclampsia,[45] but independent from preeclampsia in a second study where preeclampsia rate may be ignored[46]], increased cesarean rate,[46] perinatal morbidity and mortality, neuropsychological and cognitive disorder, postpartum hemorrhage. In the study of Matalon et al., it was shown that treated maternal hypothyroidism is not associated with adverse perinatal outcomes, but hypothyroidism is an independent risk factor for cesarean delivery.[47]

Does subclinical hypothyroidism has impacts on gestational outcomes?

The results of the studies performed on this matter are controversial. In brief, while cohort studies found an association between subclinical hypothyroidism and poor gestational outcomes, randomized controlled studied revealed no such association.

Subclinical hypothyroidism (high TSH, normal free T4) is more common than overt hypothyroidism, it is seen in 2–2.5% of women screened in the regions of the USA with sufficient iodine.[48,49] Complication risk during pregnancy in women with subclinical hypothyroidism is lower than those associated with hypothyroidism. However, some studies reported that women with subclinical hypothyroidism had increased risk in terms of severe preeclampsia, preterm labor and/or pregnancy loss.[45,50,51]

In a prospective study performed on 17,298 pregnant women included for prenatal care, subclinical hypothyroidism defined by considering 97.5 percentile as the threshold (TSH range: 2.74–11 mU/L) was found 2.3% and preterm labor risk was 2 times higher and ablation placentae risk was 3 times higher in these cases.[50] In the same study, the rates of newborns of the cases with subclinical hypothyroidism for referral to newborn care unit and respiratory distress syndrome were found to be two times higher than normal ones. In the study of Wilson, general incidence was found 10.9% for all hypertensive diseases in pregnant women with subclinical hypothyroidism, but a significant risk increase was shown for only severe hypertension (OR=1.60, 95% CI 1.08–2.379).[51] In another study comparing gestational outcomes in women with negative antithyroid peroxidase, gestational loss was found higher In women with normal free T4 and first trimester serum TSH between 2.5 and 5.0 mU/L than

the women with TSH below 2.5 mU/L (6.1% vs. 3.6%).[52] However, no difference was observed in preterm labor rates. As not corresponding with these findings, the sub-group analysis of the results of prospective multi-centered FASTER study which evaluated Down syndrome risk in the obstetric population with singleton pregnancy did not show an association between maternal subclinical hypothyroidism and poor gestational outcomes (preterm labor, miscarriage, premature membrane rupture).[53] In a society-based prospective cohort study conducted in China, maternal thyroid function during first 20 weeks of gestation and development in following fetal and infantile periods were analyzed, and it was found that subclinical hypothyroidism is associated with increased fetal distress, preterm labor, sight impairment and neural growth retardation.[54] However, the reliability of the results of this study is controversial since the number of cases with subclinical hypothyroidism is only 41. In a meta-analysis published recently and analyzed many studies, it was shown that the risks for gestational diabetes mellitus, pregnancy-induced hypertension, cesarean labor and labor with low and high birth weight did not increase in cases with subclinical hypothyroidism compared to euthyroid controls, but preeclampsia, ablation placentae and perinatal mortality risks increased as OR=1.68, (95% CI 1.09–2.40), OR=1.68 (95% CI 1.09–2.60) and OR=2.73 (95% CI 1.59–4.70), respectively.[55] In conclusion, while cohort studies show an association between subclinical hypothyroidism and poor gestational outcomes, randomized controlled studies do not show such an association.

Does treatment in pregnant women diagnosed with clinical or subclinical hypothyroidism change gestational outcomes? Is treatment recommended?

In the lights of current data, there is an uncertainty about the potential benefits of treatment. Treating clinical hypothyroidism with levothyroxine during pregnancy has been adopted as a standard approach based on the benefits put forth by previous non-randomized studies.[56,57] Additionally, since maternal euthyroidism is potentially essential for normal fetal cognitive development, UpToDate[57] and Endocrine Society[58] recommend treating pregnant women with subclinical hypothyroidism irregardless of TPO antibody condition. The guide of American Thyroid Society recommends treating only pregnant women with subclinical hypothyroidism who are found to be positive for TPO antibody.[8] On the other hand, the same society stated that there is no sufficient evidence to oppose supporting treatment in cases with subclinical hypothyroidism who are negative for TPO antibodies. Therefore, there is an uncertainty in potential benefits of the treatment of those with TPO negative and especially with TSH between 2.5 and 3.0.[58] Besides, it was shown in a Cochrane compilation published in 2013 for gestational outcomes of women with overt or subclinical hypothyroidism who had treatment that there was a decrease in preterm labor and first trimester miscarriages.[56]

Does isolated hypothyroxinemia has any impact on gestational outcomes

No… Isolated hypothyroxinemia (low T4) is defined as the reference range of maternal free T4 concentration together with normal TSH between 5th or 10th percentile. Although the reason of isolated maternal hypothyroxinemia observed in 1–2% of pregnant women is not known clearly, it is considered that it may be associated with low iodine intake.[59] It is considered that this condition not accepted as an independent thyroid disorder in the clinical practice may also be caused by laboratory problems related with free T4 measurements. The impacts of isolated hypothyroxinemia on perinatal and neonatal outcomes are not clear.[43,60–63] In a study, maternal serum free T4 concentrations below 2.5 percentile with normal TSH were not found to be associated with poor gestational outcomes.[61] In FASTER study, increased risk was found for preterm labor (OR=1.62), macrosomy (OR=1.97) and gestational diabetes (OR=1.70); however, the results were determined as inconsistent.[53] Neuropsychological performance (mean intelligence, psychomotor or behavioral scores) in the children of mother with normal TSH together with low maternal free T4 between 12 and 20 weeks of gestation was found to be lower than the children of mothers with normal thyroid functions.[43,60,62,63] It was observed that fetal development was normal in those found to have isolated hypothyroxinemia at the first trimester but had normal values at second and third trimesters or those with normal values at the first trimester but poor values at second and third trimesters. There is no publication showing the gestational outcomes of L-thyroxine treatment during pregnancy and the benefits on the development of newborn.[59]

Do gestational outcomes get affected in pregnant women with positive thyroid antibody positivity without thyroid dysfunction?

There is no sufficient evidence to reach a certain conclusion. Autoimmune thyroid disorder is the most common autoimmune disease and it is the leading reason for hypothyroidism among women. It is asserted that autoimmunity may have impacts on pregnancy through two mechanisms. The first one is the interaction of increased demand on thyroid with adaptive mechanisms, and the second one is the direct impacts on placenta and fetus as a result of general activation of immune system together with autoimmune environment.[59,64–66] According to this hypothesis, autoimmunity prevents adaptive thyroid reaction towards high demand, and it results in even lower thyroid hormone levels. As a result, mechanisms of the harms towards pregnancy are based on the direct impact of hormones on different areas of maternal-fetal unit. There are evidences showing that thyroid hormones regulate cytokine production with angiogenic growth factors as well as the development of trophoblastic proliferation and placenta and decidua.[67,68] In a meta-analysis published in 2011, five cohort studies analyzing the impact of autoimmune thyroid disease on premature labor in pregnancies with preserved thyroid functions were evaluated and it was shown that all studies had a positive association (OR=2.07, 95% CI 1.17–3.68). Subsequently, in another meta-analysis carried out in 2012 on studies excluding cases with thyroid dysfunction, general combined relative risk (RR) was found to be significantly high in terms of preterm labor for pregnant women with thyroid antibodies and positive TPO antibody (for thyroid antibodies, RR=1.98, 95% CI 1.29–3.04; P=0.002; for TPO-antibodies, RR=1.8, 95% CI 1.29–3.04; P=0.002). No such evaluation was made for women with positive TG-antibody, because there is no study conducted in this context.[69]

In the meta-analysis published in 2011, 31 studies, which evaluated the low risk of autoimmune thyroid disease together with normal thyroid function together with normal thyroid function, were included. However, these studies had differences on many aspects. While some of them were cohort studies,[70–88] others were "case control" studies.[89–94] These studies also had differences among themselves since they also included diseases with different characteristics (infertile patients, patients with repeating pregnancy losses and pregnant women). Total analysis showed a positive relationship for autoimmune thyroid disorder together with abortion risk and normal thyroid risk as OR=3.9 (2.4–6.1; p<0.01) for cohort and OR=1.80 (95% CI 1.25–2.60; p=0.002) for "case control". In this study, it was also observed that autoimmune thyroid disorder accompanied increased TSH levels. In another study, TSH levels were found higher in pregnant women who were positive for TPO antibody (3 vs. 1 mIU/l; p<0.01).[95]

In the prospective study of Negro et al. published in 2006, TPO antibody positivity was found as 11.7% in a population of 984 pregnant women. It was shown that euthyroid pregnant women who were positive for TPO antibody developed degenerated thyroid function and it was associated with increased miscarriage and premature labor risks.[96]

Should pregnant women with thyroid antibody positivity be treated without thyroid dysfunction?

No… Although a positive association was shown between the presence of thyroid antibodies and pregnancy loss, it is not recommended currently to screen and treat antithyroid antibodies routinely in all pregnant women. However, under the light of current data, it has been shown in the Cochrane database that treatment of euthyroid women with TPO antibody positivity by levothyroxine has decreased preterm labor risk significantly at a rate of 72% (RR=0.28, 95% CI 0.10–0.80).[56] The study based on in this compilation is the prospective study of Negro et al. published in 2006.[96] In another retrospective study, it is recommended to administer levothyroxine if serum TSH values are not below 1 mIU/l and are above 3 mIU/l in pregnant women with TPO antibody positivity, since these patients tend to exhibit subclinical hypothyroidism and this condition is not anticipated in the first trimester.[95] As women with high anti-TPO antibodies are under increased risk in terms of miscarriage, preterm labor and hypothyroidism progression, if detected, it is recommended to evaluate these women before pregnancy and also during first and second trimesters in terms of thyroid functions.[97]

Are gestational outcomes affected in first trimester pregnant women whose TSH values are between 2.5 and 5 mIU/L and negative for thyroid antibody?

There is no sufficient evidence to reach a certain conclusion on this matter. According to current literature, we can say that it is expected to have more loss rates in first trimester pregnancies with TSH values between 2.5 and 5 mIU/L and negative for thyroid antibody.

However, there is no study evaluating the efficiency of treatment in these cases.

The study of Negro et al. which is the only prospective study on this matter, pregnancy loss rate was found higher in first trimester pregnant women whose TSH values were between 2.5 and 5 mIU/L and negative for thyroid antibody compared to the first trimester pregnant women whose TSH values were below 2.5 mIU/L and negative for thyroid antibody (6.1% vs. 3.6%, respectively, P<0.006).[52] On the other hand, there was no significant difference between these groups in terms of preterm labor rates.

Maternal thyroid screening: for everyone?

There is no global practice recognized widely in the world for this matter. In accordance with the current data about pregnancy and thyroid screening, a consensus report comes into prominence which has been published recently and presented with a large-scale literature review.[98] This consensus report is the collaborative work between the Study Group of Iodine Insufficiency Diseases and Thyroid Dysfunction of Spanish Endocrinology and Nourishment Society and Spanish Gynecology and Obstetrics Society. The recommendations offered in the conclusion part of the report are as follow:

1. The benefit of the screening for thyroid dysfunction in the pregnant population has been proved to determine clinical hypothyroidism and to initiate treatment early (<10 weeks). This screening should be carried out before conception preferably or in the onset of the pregnancy if possible.
2. The benefit of screening to determine subclinical hypothyroidism or isolated hypothyroidism has not been proven; because there is no data available showing the benefits of subsequent thyroxine treatment.
3. Sufficient amounts of iodine intake should be assured for entire population, especially fertile women and pregnant and breastfeeding women. Recommended iodine intake in pregnant and breastfeeding women is 250 mcg/day. In societies with iodine insufficiency, iodine supplement about 150–200 mcg will help to receive recommended intake. Ideally, it should be ensured that sufficient iodine intake is provided before conception.
4. Screening at the onset of pregnancy just requires the measurement of TSH levels. The tests to be carried out for free or total T4 are only required when there is a change in TSH.
5. Reference values of these values to be measured by routine laboratory procedures for each trimester and each society should be available.
6. Since it is difficult to interpret the results of thyroid hormone tests, it would be useful to organize trainings to train primary care physicians, obstetricians, internal disease and endocrinology specialists who are not familiar with gestational thyroid dysfunctions. In this way, it should also be highlighted to avoid therapeutic interventions in cases proceeding with unproven pathological values.

In summary, Study Group of Iodine Insufficiency Diseases and Thyroid Dysfunction of Spanish Endocrinology and Nourishment Society and Spanish Gynecology and Obstetrics Society recommend evaluate thyroid function in all pregnant women at early period (before 10 weeks of gestation) routinely with TSH.

However, the recommendations offered in the guide published by American Thyroid Society in 2011 did not provide such certain messages for routine screening.[8] The Society made following recommendations for the screening:

1. There is no sufficient evidence to make recommendation for or against routine TSH screening in the first trimester visit.
2. Since the benefit of the treatment for isolated maternal hypothyroxinemia has not been shown in the studies so far, it is not recommended to screen pregnant women with routine free T4.
3. There is no sufficient evidence to make recommendation for or against screening with preconceptional TSH test in women under high risk for hypothyroidism.
4. All pregnant women should be screened in the first prenatal visit in terms of any thyroid dysfunction and/or thyroid hormone use or anti-thyroid drug use.
5. Serum TSH values should be obtained in the early weeks of gestation for the following women with high risk of overt hypothyroidism:
   - History of thyroid dysfunction or previous thyroid surgery
   - >35-year-old
   - Symptoms of thyroid dysfunction or presence of goiter
   - TPO antibody positivity
   - Type 1 diabetes or other autoimmune diseases

- History of miscarriage or preterm labor
- History of radiation at head or neck regions
- Family history of thyroid dysfunction
- Morbid obesity (BMI ≥40 kg/m^2)
- Use of amiodarone or lithium or recent use of iodized radiological contrast
- Living in a region with middle or serious iodine insufficiency

6. There is no sufficient evidence to make recommendation for or against screening for antithyroid antibodies at the first trimester of pregnancy in all women.
7. There is no sufficient evidence to make recommendation for or against screening for antithyroid antibodies at the first trimester of pregnancy in women with the history of sporadic or repeating miscarriage.
8. There is no sufficient evidence to make recommendation for or against screening for antithyroid antibodies at the first trimester of pregnancy in order to prevent preterm labor.

American College of Obstetricians and Gynecologists (ACOG) also has reported that there is no sufficient evidence to support routine screening in pregnant women who are asymptomatic for hypothyroidism, and that it will be convenient to carry out thyroid tests only in those with personal thyroid disease history or thyroid disease symptoms. It was stated that there is no sufficient evidence to carry out thyroid function tests even in asymptomatic pregnant women with mildly grown thyroid, but those with severe goiter or isolated nodules should be evaluated as any other patient.[99] In the committee opinion of ACOG published in October 2007, an approach against the routine screening of all pregnant women was asserted.[100] However, it was shown that these recommendations are quite old and testing pregnant women routinely for thyroid dysfunctions is a screening tool with cost-benefit balance.[101,102]

In the compilation of Bailey Spitzer,[103] it was reported that TSH is sufficient as a screening test in both pregnant and non-pregnant populations with low risk. It was recommended to screen women under high risk (autoimmune disease, thyroid nodules and goiter in physical examination, radiation exposure or personal or family history of thyroid cancer) with both TSH and thyroid peroxidase (TPO) antibodies. It was highlighted that all women with TSH values >5 should be evaluated in terms of TPO antibody positivity. It was stated that thyroid replacement is required for increasing TSH in the TPO antibody positivity while antibodies should be re-screened 3 month later in case of negativity.

According to the results of a study conducted on 4800 pregnant women in China, thyroid hormone insufficiency screening to be carried out by using reference values specific to gestational age before 8 weeks of gestation is supported.[104] The authors reported that TSH and free T4, which can be applied easily in many clinics for hypothyroid screening, were considered as good tests.

In another study carried out on 592 pregnant women in Czech Republic and published recently, it was reported that the diagnosis of new thyroid pathology is established in 7.6% of women who have no risk factor.[105] Based on this result, the authors indicated that a simple routine screening would be appropriate in pregnant women. They asserted that the evaluation of TSH and free T4 levels between 5 and 10 weeks of gestation is a requirement to analyze thyroid function.

They reported that 1.9% of autoimmune thyroidism with pathological sonography cannot be recognized in cases where TPO is not evaluated.

The Endocrine Society, established in 1916 and recognized as a significant authority for endocrinology, offered following recommendations in their guide, which was renewed in 2012, for the thyroid screening during pregnancy:[58]

1. Before and during pregnancy, routine screening is not recommended for the presence of anti-TPO antibodies.
2. Women with high anti-TPO antibodies have increased risks for miscarriage, preterm labor, hypothyroidism progression and postpartum thyroidism. Therefore, if detected, these women should be screened in terms of serum TSH anomalies before the pregnancy and at first and second trimesters of pregnancy.
3. The committee could not reach a consensus in terms of screening recommendations for all new pregnant women. Therefore, they offered two versions:
   - Some members recommended screening all pregnant women in terms of serum TSH anomalies at 9 weeks of gestation or their first visits.
   - Some members did not express any opinion for or against routine screening of all pregnant women at their first visits in terms of in terms of serum TSH anomalies.

In the compilation of Springer et al.,[106] it was decided to support a general screening in pregnant women for thyroid diseases. It was also recommended to follow those with positive screening results for a long time after delivery.

Miller et al. interpreted in their compilation published in 2011[107] that the test considered for routine screening should fulfill some certain criteria. These are:

1. The incidence of the disease should be as high as to justify screening. The prevalence of subclinical hypothyroidism during early pregnancy reported in the literature fulfills this condition.
2. The cost-efficiency balance of screening should be convenient. If it assumed that the treatment will improve neurological development in children of women who have subclinical hypothyroidism, it can be said that the screening to be carried out for subclinical hypothyroidism has this balance.
3. Poor outcomes should be associated with disease condition. There are some inconsistencies in the literature about the association between subclinical hypothyroidism and poor gestational outcomes. Additionally, the data about the association of subclinical hypothyroidism or isolated hypothyroxinemia with delayed neurocognitive development are insufficient.
4. There should be evidences that the intervention will improve the outcomes. It is impossible to say it with the current literature.

In the light of these data, Miller et al.[107] concluded that, until such data are obtained, there is no sufficient evidence for recommending a routine screening for thyroid disease during pregnancy or for the treatment of subclinical hypothyroidism or hypothyroxinemia even they are detected by chance.

According to the guide of American Association of Clinical Endocrinologists, screening with TSH should be a routine before pregnancy or in the first trimester of pregnancy.[108] What the specialists in perinatology field think about it? They commented about this issue as follows:[109] John H. Lazarus believes that thyroid screening should be applied to all women during early pregnancy since thyroid dysfunction is common during pregnancy. He stated that 65% of women with abnormal test results would be overlooked if these criteria are applied even current guides say that some criteria (autoimmune disease history, previous radiation exposure on neck region etc.) are required for the test. However, he said that there is a single randomized study evaluating the impact of T4 implementation on childhood IQ but it provides no benefit for this implementation.[110] He expresses that measuring TSH in all pregnant women in first trimester will be useful currently, and T4 should be checked if it is >2.5 mIU/L. John H. Lazarus states that TPO antibody should be checked if TSH is >5 mIU/L, and alternatively, if laboratory provides a gestational reference range for TSH, then TSH should be considered as abnormal if it is above 97.5 percentile. He recommends that threshold value of T4 should be minimum 2.5 percentile and threshold value should be determined according to the specific test used.

Sarah Kilpatrik thinks that some criteria should be fulfilled for any screening test, for example, the incidence of the disease should be as high as to justify screening and a known effective treatment decreases poor outcomes of screened diseases. She expresses that the incidence of gestational hyperthyroidism is <0.5% and therefore hyperthyroidism screening is not required. She states that (clinical and subclinical) hypothyroidism incidence is about 3% in routine screening studies, and this is as high as to justify screening. She asserted that, crucially, most of these women had subclinical hypothyroidism and as stated above, there is no data proving that the treatment will eliminate potential poor perinatal or childhood outcomes associated with maternal subclinical hypothyroidism.

She expresses that these facts explain why routine screening is not indicated; however, screening women at high risk for thyroid disease is very significant since there are evidences justifying that treating women with over thyroid disease has benefits both for mother and baby. She says that those with thyroid disease history, those with strong family history for thyroid disease, those exposed to radiation on neck region, those who have goiter, or those who have known antithyroid antibodies or other autoimmune diseases or type 1 diabetes should be tested. According to her, TSH should be checked in the first prenatal visit of these women; if TSH is high, then free T4 or free thyroxine index and TPO antibodies should be measured. She states that in case of overt hypothyroidism, the disease should be treated by thyroid hormone as keeping within TSH reference range. She believes that subclinical hypothy-

roidism should be treated if TPO antibodies are positive. Sarah Kilpatrik highlights that patient should be evaluated in terms of any hyperthyroidism disease finding if TSH is suppressed, and if they are unavailable and patient is in the first trimester when TSH is measured, then TSH should repeat together with free T4 at mid-second trimester, and treatment can be recommended if they are concordant with hyperthyroidism. She also warns that it should be well known that subclinical or clinical hypothyroidism may be seen in women if TSH is temporarily suppressed by human chorionic gonadotropin from first trimester up to mid-second trimester of the pregnancy. She adds that this does not cause any morbidity and it spontaneously recover, therefore treatment is not required.

Roberto Negro is also among those supporting routine screening in the beginning of the pregnancy. He says, "mean first gestational age is 25–30 in the western countries, and there are data showing that 15% of women above 25 years old may have thyroid anomalies, and there is a consensus that it is required to treat overt thyroid dysfunction and especially overt hypothyroidism". The study of Dosiou et al. published recently[110] reports that routine screening displays more cost-effective benefit not only against non-screening but also against screening women with high risk for only thyroid dysfunction. Robert Negro, noteworthily, highlights that the authors of this analysis assume women with any level of hypothyroidism are treated, but only women with overt hypothyroidism benefit from the treatment. In his personal opinion, he believes that, especially in countries with high quality healthcare system, a woman about 25–30 years old in her first pregnancy should have the right to know if she is hypothyroidic or not, if she has any risk to develop hypothyroidism or postpartum hypothyroidism. Robert Negro thinks that TSH and TPO antibodies should be the first tests to screen a woman in terms of thyroid dysfunction and TSH concentrations >2.5 mIU/L in the first trimester and >3.0 mIU/L in the second and third trimesters should be considered as pathological.

James Haddow also thinks that all women should be screened with TSH measurement during pregnancy and this service should be provided in a programmed framework under the guidance of current prenatal screening models. Haddow, stating that TSH is currently the most reliable marker of thyroid dysfunction, argues that a reasonable TSH threshold, a reference range appropriate for gestational age could be 97.5th or 98th percentile. Haddow states that the discussions for and against screening in the recent years especially focused on fetal well-being, but maternal health should be taken into consideration before proving fetal morbidity which may be associated with subclinical hypothyroidism. He says that his observational studies reveal that about 3 out of each 1000 pregnant women have non-diagnosed overt hypothyroidism in addition to the cases with subclinical hypothyroidism, and there is a common opinion that these cases require treatment. He states that two third of these women are permanently hypothyroidic, and approximately 5 years passes before establishing any diagnosis clinically, and 4 of 32 hypothyroidic women in his studies could not get any diagnosis until their TSH levels are checked in the follow-up 10 years later.

In accordance with these findings, the recommendations of Turkish Perinatology Society are as follow:

Maternal thyroid hormones ensuring fetal brain development during pregnancy, and subsequently, presence of convincing evidences for the requirement in terms of neuropsychic development in the child and the opinion that risk factors cannot be determined directly may indicate that maternal thyroid screening should carry out on all cases. On the other hand, applicability of screening programs is determined according to following matters:

- The disease to be screened should be seen frequently and cause significant health problems. The incidence should be above 5% in the society screened.
- By the screening, it should be possible to detect diseases at an early period, it should be acceptable by patients and it should have general clinical practicality.
- The diseases should have a treatment.
- The treatment carried out by diagnosing after screening should be superior to the treatment carried out by diagnosing with known methods.
- The potential benefit of the screening should be higher than its potential harms and screening costs.

In terms of these aspects:

Thyroid disease screening in all pregnant women cannot fulfill all conditions required to be in screening

program for today. Therefore, it is controversial if screening is required for all pregnant women to determine thyroid dysfunction and to carry out its treatment when prevalence and complications, diagnostic accuracy and practicality, potential benefits, potential harms and screening costs of the disease are evaluated.

In conclusion, serum TSH measurement is required before pregnancy and during early pregnancy in the group with high risk for overt hypothyroidism. Pregnant women recommended early TSH screening are given in the **Table 4**.

Does oral L-thyroxine administered to mother also treat possible hypothyroidism in fetus?

No… Oral L-thyroxine administered to mother does not treat fetus. Because, under normal conditions, thyroxine does not pass through placenta; however, in case of fetal hypothyroidism, a small amount of maternal thyroxine may pass through placenta. Yet, this amount is not sufficient to treat fetal pathology.[111] In cases where there are large goiters as preventing swallowing functions, L-tyroxine was administered with intramuscular injections without any apparent evidence that it has any benefit.[112] Weekly administration of L-thyroxine through intraamniotic way was considered as a treatment option for congenital hypothyroidism and its application was supported.

Basic benefits of intraamniotic way were shown as low complication rates and relatively long periods between injections. However, there is no consensus on the intraamniotic dosage of L-thyroxine, it is required to be adjusted according to the size of goiter, current period for treatment until delivery and respond to the treatment.[111,113]

Does Subclinical Hypothyroidism Cause Fetal Hypothyroidism?

No… Maternal subclinical hypothyroidism does not cause fetal hypothyroidism. In the study of Yuan et al. published recently, it was found that the TSH levels of newborns of women with subclinical hypothyroidism were higher than the newborns of women with normal thyroid functions ($p<0.05$).[114] In the same study, it was shown that neonatal TSH has generally a low correlation with maternal TSH. However, as case number was low, the clinical significance could not be established clearly. In the study, only one or two newborns had high TSH among the newborns delivered by women with high TSH levels. Therefore, it is not possible to generalize that if mothers have high TSH levels, then their babies will have high TSH levels, too. All of 20 newborns found to have TSH levels over threshold values had temporary hypothyroidism.

Is it necessary to add iodine to the levothyroxine replacement as a routine practice in hypothyroidism treatment?

No… Levothyroxine is a synthetic version of T4 and it is used to treat cases with hypothyroidism specific to any reason. Levothyroxine can be converted to T3 in the body and it is sufficient to take a single form, which is levothyroxine, as a supplement for both hormones. As levothyroxine already includes iodine, it is not required to take additional iodine to treat hypothyroidism. If extra iodine is taken, they will not be added into new thyroid hormones since the functions of thyroid are fulfilled and undertaken by levothyroxine.[115] In fact, according to the results of a paper published in 1992, additional iodine taken as supplement is excreted by urine, feces and sweat.[116]

Can patient be without symptom when TSH value is between 2.5 and 10 mIU/L and T4 at normal ranges?

Yes… About 28.6% of cases with hypothyroidism can be without any symptom.[117] In the study of Rosario and Calsolari published recently, 252 women with TSH levels ≤10 mIU/L, who were established with the diagnosis of subclinical hypothyroidism, were evaluated.[117] In 180 (71.4%) of these women, at least one symptom or finding of hypothyroidism was observed which cannot be explained by any other condition; in the remaining cases, no symptom was observed.

Is it appropriate to carry out only antibody screening during pregnancy?

No… In the current literature, there is no study researching or comparing best screening strategy as only TSH, only anti-TPO antibody or anti-TPO antibody together with TSH in different populations characterized with various nutritional iodine conditions.[65]

In the guides published by American Thyroid Society in 2011 and by The Endocrine Society (which is recognized as a significant authority for endocrinology) in 2012, we see following recommendations about this matter.[8,58]

Both guides do not recommend screening all pregnant women for thyroid antibodies in the first trimester in order to prevent preterm labor. This also applies for those with sporadic or repeating miscarriages or undergoing IVF treatment. It was also not recommended screening all women in the first trimester in order to prevent spontaneous abortions or miscarriages. However, when it is detected, it is recommended by American Thyroid Society to evaluate serum TSH levels once in every four weeks during the first half of pregnancy and at least once between 26 and 32 weeks of gestation. The Endocrine Society recommends screening patients, who were found to have thyroid antibody, before pregnancy and at first and second trimesters in terms of TSH anomalies.

Does iodine insufficiency cause fetal hypothyroidism?

No… The iodine insufficiency of mother does not cause fetal hypothyroidism. Almost 50 years ago, it was set forth that the first respond of thyroid gland against decreased iodine levels initiated very effective autoregulatory mechanisms. Among such mechanisms, there are the increases in thyroid vascularity, iodine intake, acinar cell sizes, hyperplasia, and serum T3/T4 rates. It was shown in human studies as well as animal studies that such changes occurred independent from TSH.[118] Synthesis and secretion of thyroid hormones due to the decreased iodine supplement shows a change on behalf of T3 where less iodine is used instead of T4.[119] As a result, no decrease is observed in T3 when T4 decreases.[120–122] For that reason, increase of serum TSH is observed rarely in cases with goiter living in regions where only iodine insufficiency exists. Increased thyroglobuline concentrations are seen more frequently in the mild and medium level of iodine insufficiency.[123] It was shown that these mechanisms work similarly in pregnant women. It was revealed that TSH levels in pregnant women in a population with medium level of iodine insufficiency did not increase even in women with the lowest first trimester free T4 levels, but T3/T4 rates and serum thyroglobuline levels were found high all along. It was observed that TSH values started to increase together with the third trimester; yet, they were mostly within normal ranges.[69,124,125]

The idea which is general but not right, is that iodine insufficiency does not only decrease T4 production but also increases TSH in the circulation. However, the findings underlying this misconception were obtained from the studies carried out in the regions with insufficient iodine together with further factors (guatrogens, selenium insufficiency etc.) inhibiting the adaptation with autoregulatory mechanisms by causing mostly functional thyroid tissue loss and even glandular atrophy.[126]

Iodine insufficiency is also associated with the clinical findings of hypothyroidism defectively. Such an association can be valid only in iodine insufficiency goiter endemia accompanying myxedema where TSH increased.[123] Individuals living regions which allow the adaptation of autoregulatory mechanism to insufficient iodine intake are clinically euthyroid. This also applies for sever iodine insufficiency due to normal or increased T3 in circulation.[120]

Iodine supplement studies carried out on pregnant women in Europe present findings supporting that it is also observed in pregnant women.[125,127–131] In these studies, it was shown that maternal thyroid is capable of adapting enough to fulfill increased gestational thyroid hormone needs in regions with mild-middle iodine sufficiency. While it was introduced that this support is usually effective to decrease the increase in the size of thyroid during the pregnancy, only two of these six studies showed that maternal TSH was lower (within normal reference limits). None of the showed any clear impact of iodine supplement on maternal and newborn total or free thyroid concentrations. Considering that the thyroid hormone concentrations may be the best biochemical marker for health fetal development, the results of these studies are reassuring. However, it should be remembered that none of these studies evaluated long-term clinical outcomes such as maternal goiter or newborn developments.[132]

Yet, autoregulatory mechanisms which are possible for mother are not in question for fetus. The reason is that fetal thyroid gland is not fully maturated. As a result, decreased synthesis and secretion of T4 and T3 in fetus cause an increase in TSH concentration and this results with both clinical and biochemical fetal hypothyroidism.[133] It can be said that cretinism and mental retardation which may occur due to the intrauterine influence of fetus can only be associated with severe iodine insufficiency during pregnancy, and that there is no sufficient study data for slighter conditions.[134]

Summary Management

- As in non-pregnant women, high TSH blood levels make established primary hypothyroidism diagnosis in pregnant women. In the first trimester of pregnancy, there is no sufficient evidence to support a routine screening with only thyroid autoantibodies, so it is not recommended ***(Evidence Level C, Medium 2 +)***.
- In the current literature, it is not clarified which is the best screening strategy among screening only TSH, only anti-TPO antibody or anti-TPO antibody together with TSH.
- The ranges determined for each trimester of pregnancy as the upper threshold of TSH should be taken into consideration. Ideally, it is required to know reference value range specific to trimesters for each population. When high TSH is identified, free T4 should be measured to classify hypothyroidism as either clinical (overt) or subclinical. In cases where percentile value of population studied is not known, it is recommended to consider following references for definitions:
- TSH >2.5–10.0 mU/L together with normal free T4 level: Subclinical hypothyroidism
- TSH >2.5–10.0 mU/L together with low free T4 level: Clinical (overt) hypothyroidism
- TSH ≥10.0 mU/L, without considering free T4 level: Clinical (overt) hypothyroidism
- However, it should be careful when interpreting free T4 levels during pregnancy, and ranges specific to trimester determined by each laboratory should be referred, or instead, in second and third trimesters, new reference ranges obtained by multiplying pregestational total T4 reference ranges by 1.5 can be used. Free T4 index can also be used as an alternative reference value to be used during pregnancy ***(Evidence Level B, Medium 2 ++)***.
- Since the association of overt hypothyroidism with poor gestational outcomes was proven, maternal hypothyroidism should be avoided by initiating treatment as soon as identified during pregnancy ***(Evidence Level A, Good 1 +++)***.
- All pregnant women newly diagnosed with overt hypothyroidism should be treated with thyroid hormone (thyroxine, T4). T4 dose should be adjusted as keeping TSH below 2.5 mIU/L in first trimester and below 3 mIU/L in second and third trimesters (or within TSH ranges specific to trimester). Thyroid function tests should be evaluated within 30–40 days after the onset of treatment and once every 4–6 weeks subsequently ***(Evidence Level A, Good 1 +++)***.
- When using levothyroxine to treat cases with hypothyroidism associated with any reason, it is not required to include routine iodine supplement additionally ***(Evidence Level A, Good 1 +++)***.
- Since there is no study for the gestational outcomes of euthyroid pregnant women with positive TG-antibody, it is not recommended to treat such patients with levothyroxine ***(Evidence Level C, Medium 2 +)***.
- If hypothyroidism diagnosis is established before pregnancy, T4 dose should be arranged as keeping TSH below 2.5 mIU/L ***(Evidence Level C, Poor 2 +)***.
- After delivery, the dose administered during pregnancy of most of the hypothyroid women should be decreased to pregestational dose ***(Evidence Level A, Good 1 +++)***.
- As we do not have sufficient evidence about its activities and due to the inconsistencies in free T4 measurement, it is currently not recommended to treat isolated hypothyroxinemia ***(Evidence Level I, Weak 2 +)***.
- If there is more demand for thyroid during pregnancy and evidences are available showing that euthyroid women, which have autoimmune thyroid disease at the early periods of gestation, have more risk for subclinical hypothyroidism or overt hypothyroidism in the advanced weeks of gestation, it is required to monitorize TSH once every 4–6 weeks in these women ***(Evidence Level A, Medium 1 +++)***.
- Although current literature data are limited, gestational loss is higher in first trimester pregnant women whose thyroid antibody is negative and TSH value is between 2.5 and 5 mIU/L compared to first trimester pregnant women whose TSH value is below 2.5 mIU/L. However, since the efficiency of treatment cannot be suggested, levothyroxine treatment is controversial. Studies evaluating treatment efficiency are required for these cases ***(Evidence Level I, Weak 2 +)***.
- Considering the current literature, guides and expert opinions generally, it is seen that screening all preg-

nant women with TSH in the first trimester is not convenient. Screening with TSH should be carried out for risky cases ***(Evidence Level I, Weak 2 +)***.

- Since maternal oral L-thyroxine intake cannot treat fetal hypothyroidism, it is scientifically not right to say that L-thyroxine treatment of a mother due to any thyroid dysfunction would also treat the possible hypothyroidism in fetus ***(Evidence Level A, Medium 1 +++)***.

IV. Pregnancy and Hyperthyroidism

While overt hyperthyroidism has many reasons, it is mostly occur associated with Graves' disease during pregnancy (0.1–1%).[135] Hyperthyroidism during pregnancy may cause abortion of mother, hypertension associated with pregnancy, preterm labor, anemia, arrhythmias and coronary failure in more advanced cases and thyroid crisis. In term of fetus, intrauterine growth retardation, stillbirth and prematurity are possible undesired problems. The diagnosis is established when TSH and free T4 level over 95th percentile or when total T4 level exceeds upper limit which is considered to be 1.5 times of normal value.[135,136] In addition, it should be remembered that low TSH level in the first trimester of normal pregnancy is an expected finding. Small doses of propylthiouracil (PTU) are preferred in the treatment. The purpose is to keep patient in mild hyperthyroid condition. Although it does not cause any certain contraindication, methimazole (MMI) is not used much during pregnancy since it passes through placenta easily and its reported maternal and fetal side effect profile.[8,137]

Hyperthyroidism during pregnancy is the hyperthyroidism which is seen more common than Graves' disease and associated with hCG.[138] Hyperthyroidism associated with hCG courses slighter than Graves' disease. While the incidence of Graves' disease during pregnancy is 0.1–1%, the incidence of hyperthyroidism associated with hCG is 1–3%.[139,140] Hyperthyroidism associated with hCG is seen temporarily in the first half of pregnancy. Gestational temporary thyrotoxicosis, hyperemesis gravidarum, trophoblastic hyperthyroidism, familial gestational hyperthyroidism and multiple pregnancies are among its reasons.[141–146] When serum hCG concentration peaks in the 10–12 weeks of gestation, total serum T4 and T3 concentrations also increase, free values do not change much, but serum TSH decreases. This temporary and usually subclinical hyperthyroidism should be evaluated as a normal physiological finding.[14] In the following weeks, together with the decrease of hCG, serum free T3 and T4 levels also decrease and TSH concentration returns to normal ranges. If TSH is low and free T4 and T3 levels are within normal ranges in the following weeks (also persisting after first 12 weeks), subclinical hyperthyroidism diagnosis is established. One of the most common conditions is "hyperemesis gravidarum". In hyperemesis gravidarum, free T4 level can be found increased in about 30–60% of these pregnant women in addition to TSH suppressed physiologically in the first trimester. What should be done here is to do differential diagnosis with Graves' disease by checking TSH receptor stimulating antibodies. In the hyperemesis gravidarum condition, TSH receptor stimulating antibodies are negative and no hyperthyroidism finding occur in these patients, and free T4 values return to normal at 15–18 weeks of gestation without any treatment. In case of Graves' disease, the levels of TSH receptor stimulating antibodies should be identified especially in the third trimester, and it should be prepared against hyperthyroidism risk of newborn.[14]

How subclinical hyperthyroidism diagnosis is established in the pregnancy? What impacts does it have on gestational outcomes?

Subclinical hyperthyroidism is defined as the low serum TSH levels below reference values while serum fT4 and fT3 levels are within reference values.[147]

With third generation TSH kits, levels as low as 0.01 – 0.02 mIU/L can be detected. Subclinical hyperthyroidism is evaluated in two categories: subclinical hyperthyroidism proceeding with detectable low TSH levels (0.1–0.4 mIU/L) and subclinical hyperthyroidism proceeding with suppressed TSH levels (<0.1 mIU/L).[147]

In studies analyzing the prevalence of subclinical hyperthyroidism, different rates were reported according to the threshold value of TSH. In a study carried out in the USA, the prevalence was found as 0.7% when TSH value was considered below 0.1 mIU/L, and as 3.2% when TSH value was considered below 0.4 mIU/L.[148] While subclinical hyperthyroidism may be associated with endogenous reasons such as Graves' disease, toxic adenoma, toxic multinodular goiter, it may also be associated with exogenous reasons such as iodine insufficiency or high dose administration of thy-

roid hormone treatment of those undergo hypothyroidism treatment.[149]

In the literature, unlike the findings of overt hyperthyroidism, it was not shown that subclinical hyperthyroidism is associated with poor gestational outcomes. Ohashi et al. screened thyroid dysfunctions in 392 risk pregnant women, and found a total of 26 subclinical hyperthyroidism cases. As a result, they highlighted that gestational complications such as IUGR (intrauterine growth retardation), diabetes mellitus, hypertension, intrauterine fetal death and ablatio placentae are more associated with hypothyroidism than hyperthyroidism.[150] Su et al. investigated the impacts of maternal thyroid dysfunction on fetus and newborn in their study and found that subclinical hyperthyroidism had no impact.[54] In their study, Wilson et al. showed that subclinical hyperthyroidism had no impact on gestational hypertension compared to subclinical hypothyroidism.[51] Bunevicius et al. reported that subclinical hyperthyroidism is associated with late gestational depression.[151]

The widest study carried out for subclinical hyperthyroidism frequency in pregnant women was done by Casey et al.[152] In their study, they performed TSH screening on 25,765 women and established subclinical hyperthyroidism diagnosis to 433 (1.7%) pregnant women. The subclinical hyperthyroidism diagnosis was established by identifying TSH levels as ≤2.5 percentile and free T4 levels as ≤1.75 ng/ml.

When impacts of subclinical hyperthyroidism on gestational outcomes researched, it was found that gestational hypertension problem was seen less in women with subclinical hyperthyroidism (adjusted OR=0.66, 95% CI 0.44–0.98; p=0.04), and no significant difference was observed in terms of severe preeclampsia, diabetes, ablatio placenta, preterm labor and delivery by cesarean.

Similarly, it was stated that subclinical hyperthyroidism did not increase the rates of low birth weight, hospitalization to intense care unit, low Apgar score, respiratory distress syndrome, necrotizing enterocolitis, intraventricular hemorrhage, major malformations, fetal/neonatal death and perinatal mortality. According to the results of this study, the authors highlighted that it is not required to treat subclinical hyperthyroidism with antithyroid drugs and even such drugs can be harmful since they cause suppression in fetal thyroid gland due to transition through transplacental fetus.

In Summary

- Hyperthyroidism treatment should be initiated in women with symptomatic and/or medium or advanced hyperthyroidism associated with Graves' disease or gestational trophoblastic disease ***(Evidence Level A, Good 1 +++)***.
- hCG-dependent hyperthyroidism (gestational temporary thyrotoxicosis) is temporary and does not require treatment. Similarly, treatment is not required in women with thyroid hyperfunction associated with hyperemesis gravidarum because it usually courses slightly and the symptoms regress together with the decrease in hCG production (at 14–18 weeks of gestation). In sever hyperemesis cases, hospitalization and supportive treatments such as treatment of dehydration with parenteral fluids may be required ***(Evidence Level A, Good 1 +++)***.
- Pregnant women with subclinical hyperthyroidism (decreased TSH, normal or minimal increased trimester specific fT4) and medium level asymptomatic hyperthyroidism associated with Graves' disease can be followed up without treatment. In the follow-up of these women, it is recommended measuring TSH, fT4 and/or total T4 or total T3 in the serum once in every 4–6 weeks ***(Evidence Level A, Medium +++)***.
- There is no evidence showing that subclinical hyperthyroidism treatment has positive impact on the pregnancy progress, and it should be remembered that the treatment may have potential side effects on fetus ***(Evidence Level I, Weak +)***.

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- Prof. Dr. Tayfun ALPER, Department of Obstetrics and Gynecology, Faculty of Medicine, Ondokuz Mayıs University, Samsun, Turkey
- Assoc. Prof. Dr. Oluş APİ, Department of Obstetrics and Gynecology, Faculty of Medicine, Yeditepe University, İstanbul, Turkey
- Assoc. Prof. Dr. Deniz ARIKAN, Department of Obstetrics and Gynecology, Faculty of Medicine, Kahramanmaraş Sütçü İmam University, Kahramanmaraş, Turkey

- Dr. Resul ARISOY, Perinatology Clinic, Zeynep Kamil Training and Research Hospital, İstanbul, Turkey
- Dr. Eftal AVCI, Perinatology Clinic, Kanuni Sultan Süleyman Training and Research Hospital, İstanbul, Turkey
- Assoc. Prof. Dr. Alev AYDIN, Perinatology Clinic, Kanuni Sultan Süleyman Training and Research Hospital, İstanbul, Turkey
- Dr. Barış BÜKE, Perinatology Department, Ege University, Faculty of Medicine, İzmir, Turkey
- Assoc. Prof. Dr. Eray ÇALIŞKAN, Department of Obstetrics and Gynecology, Faculty of Medicine, Kocaeli University, Kocaeli, Turkey
- Assoc. Prof. Dr. Bülent ÇAKMAK, Department of Obstetrics and Gynecology, Faculty of Medicine, Gaziosmanpaşa University, Tokat, Turkey
- Assoc. Prof. Dr. Filiz ÇAYAN, Department of Obstetrics and Gynecology, Faculty of Medicine, Mersin University, Mersin, Turkey
- Prof. Dr. Umut Kutlu DİLEK, Department of Obstetrics and Gynecology, Faculty of Medicine, Mersin University, Mersin, Turkey
- Dr. Emre ERDOĞDU, Perinatology Clinic, Zeynep Kamil Training and Research Hospital, İstanbul, Turkey
- Assoc. Prof. Dr. Elif Gül YAPAR EYİ, Gynecology and Obstetrics Clinic, Zekai Tahir Burak Training and Research Hospital, Ankara, Turkey
- Assoc. Prof. Dr. Ali GEDİKBAŞI, Perinatology Clinic, Kanuni Sultan Süleyman Training and Research Hospital, İstanbul, Turkey
- Assoc. Prof. Dr. Gökhan GÖYNÜMER, Gynecology and Obstetrics Clinic, Göztepe Training and Research Hospital, İstanbul, Turkey
- Assoc. Prof. Dr. Ömer KANDEMİR, Perinatology Clinic, Etlik Zübeyde Hanım Gynecology Training and Research Hospital, Ankara, Turkey
- Assoc. Prof. Dr. Burçin KAVAK, Department of Obstetrics and Gynecology, Faculty of Medicine, Fırat University, Elazığ, Turkey
- Assoc. Prof. Dr. Mertihan KURDOĞLU, Department of Obstetrics and Gynecology, Faculty of Medicine, Gazi University, Ankara, Turkey
- Prof. Dr. Selahattin KUMRU, Department of Obstetrics and Gynecology, Faculty of Medicine, Düzce University, Bolu, Turkey
- Prof. Dr. M. Faik KOYUNCU, Perinatology Department, Faculty of Medicine, Celal Bayar University, Manisa, Turkey
- Dr. Soner Recai ÖNER, İzmir, Turkey
- Prof. Dr. Selçuk ÖZDEN, Department of Obstetrics and Gynecology, Faculty of Medicine, Sakarya University, Sakarya, Turkey
- Prof. Dr. Mehmet ÖZEREN, Gynecology and Obstetrics Clinic, Tepecik Training and Research Hospital, İzmir, Turkey
- Prof. Dr. Okan ÖZKAYA, Department of Obstetrics and Gynecology, Faculty of Medicine, Süleyman Demirel University, Isparta, Turkey
- Assoc. Prof. Dr. Murat MUHCU, Perinatology Clinic, GATA Haydarpaşa Hospital, and Perinatology Clinic, Zeynep Kamil Training and Research Hospital, İstanbul, Turkey
- Dr. İbrahim POLAT, Perinatology Clinic, Kanuni Sultan Süleyman Training and Research Hospital, İstanbul, Turkey
- Assoc. Prof. Dr. Mekin SEZİK, Department of Obstetrics and Gynecology, Faculty of Medicine, Süleyman Demirel University, Isparta, Turkey
- Prof. Dr. Cihat ŞEN, Perinatology Clinic, Department of Obstetrics and Gynecology, Cerrahpaşa Faculty of Medicine, İstanbul University İstanbul, Turkey
- Prof. Dr. Turgay ŞENER, Eskişehir Acıbadem Hospital, Eskişehir, Turkey
- Assoc. Prof. Dr. Cüneyt E. TANER, Gynecology and Obstetrics Clinic, Tepecik Training and Research Hospital, İzmir, Turkey
- Prof. Dr. Alper TANRIVERDİ, Department of Obstetrics and Gynecology, Faculty of Medicine, Aydın University, Aydın, Turkey
- Assoc. Prof. Dr. Özlem MORALOĞLU TEKİN, Gynecology and Obstetrics Clinic, Zekai Tahir Burak Training and Research Hospital, Ankara, Turkey
- Prof. Dr. Ahmet YALINKAYA, Faculty of Medicine, Dicle University, Diyarbakır, Turkey
- Prof. Dr. Murat YAYLA, Acıbadem Hospital, İstanbul, Turkey

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