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Review

Thyroid diseases during pregnancy: A number of important issues

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ABSTRACT

The most common thyroid diseases during pregnancy are hyper- and hypothyroidism and their variants including isolated hypothyroxinemia (hypo-T_4), autoimmune thyroid disease (AITD) and different types of goiter. AITD represents the main cause of hypothyroidism during pregnancy ranging in prevalence between 5 and 20% with an average of 7.8%. The incidence of isolated hypo-T_4 is about 150 times higher compared to congenital hypothyroidism. Prevalence of Graves' disease (GD) ranges between 0.1% and 1% and the Transient Gestational Hyperthyroidism Syndrome between 1 and 3%. Thyroid stimulating hormone (TSH) is a sensitive marker of thyroid dysfunction during pregnancy. Normal values have been modified recently with a downward shift. Thus, the upper normal range is now considered to be 2.5 mUI/mL in the first trimester and 3.0 mUI/mL for the remainder of pregnancy. Most studies have shown that children born to women with hypothyroidism during gestation had significantly lower scores in neuropsychological tests related to intelligence, attention, language, reading ability, school performance and visual motor performance. However, some studies have not confirmed these findings. On the other hand, multiple retrospective studies have shown that the risks of maternal and fetal/neonatal complications are directly related to the duration and inadequate control of maternal thyrotoxicosis. The latter is associated with a risk of spontaneous abortion, congestive heart failure, thyrotoxic storm, preeclampsia, preterm delivery, low birth weight and stillbirth. Despite the lack of consensus among professional organizations, recent studies, which are based on sophisticated analyses, support universal screening in all pregnant women in the first trimester for thyroid diseases.

Key words: Autoimmune thyroiditis, Hyperthyroidism, Hypothyroidism, Pregnancy, Screening during pregnancy, Thyroid disease

INTRODUCTION

Numerous hormonal changes as well as alterations in metabolic demands occur during pregnancy, resulting in profound and complex effects on thyroid function. Because thyroid disorders are much more prevalent in women of childbearing age than in men of the same age group, it is not surprising that common thyroid disorders, such as chronic autoimmune thyroiditis, hypothyroidism, Graves' disease (GD), etc, are relatively frequently observed in pregnant women. The main change in thyroid function asso-

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ciated with the pregnant state is the requirement for an increased production of thyroid hormone which depends directly upon adequate availability of dietary iodine and a normal and functional thyroid gland. Indeed, the physiological adaptation to the pregnant state can only take place when the iodine intake is appropriate. When iodine intake is deficient, however, pregnancy can reveal an underlying iodine deficiency.[1] Iodine deficiency (ID) during pregnancy and infancy may impair growth and neurodevelopment of the offspring and increase infant mortality. It is noteworthy that assessment of iodine status in pregnancy is difficult. Meanwhile, it remains unclear whether iodine intakes are sufficient in this group, leading to calls for iodine supplementation during pregnancy in several industrialized countries.[2] The economy of the thyroid is modified by several complex physiological changes such as the marked increase in both serum thyroid binding globulin (TBG) concentrations and extrathyroidal thyroxine (T_4) distribution space that take place during the first half of gestation. To maintain the homeostasis of T_4 concentrations, the thyroid machinery must produce more T_4 until a new steady state is reached around mid-gestation. Thus, the main change in thyroid function associated with the pregnant state is the requirement of an increased production of thyroid hormone which, in turn, depends directly upon the adequate availability of dietary iodine and integrity of the thyroid gland. Therefore, any functional perturbation of normal thyroid function may have consequences for pregnancy outcome, and conversely, pregnancy by itself may affect the presentation and course of most thyroid disorders.[3-9]

THYROID FUNCTION TESTING DURING PREGNANCY

The normal reference range of serum thyroid stimulating hormone (TSH) is modified during pregnancy, implying the need to define trimester-specific normative TSH reference values. Of note, serum free T_4 (FT_4) estimates, as measured by most – if not all – commonly available FT_4 assays, are flawed during pregnancy.

TSH is a sensitive marker of thyroid dysfunction during pregnancy.[10,11] This is true despite the significant effect of human chorionic gonadotropin (hCG) on TSH concentrations, especially in the first trimester. During the first trimester, hCG induces a decrease in circulating TSH and, as a consequence, reference values have been modified accordingly. As a result, utilizing normal values for the non-pregnant population leads to diagnostic errors. Due to the interference of pregnancy-modified plasma proteins, the measurement of maternal FT_4 with the usual techniques presents some difficulties. Certain FT_4 immunoassays have a high correlation with equilibrium dialysis, which is considered today as the gold standard for FT_4 measurement during pregnancy.[12,13]

The determination of total T_4 (TT_4) has also been proposed as an alternative method for evaluating thyroid function during pregnancy, as TT_4 measurements are performed by a more robust methodology than those used for FT_4. The increase in TT_4 due to the increase in placental hCG is more predictable and it appears that the reference values established in different populations are more comparable and probably more reliable than those obtained for FT_4. Of interest, it has recently been suggested that the normal levels for TT_4 may be reliably obtained by multiplying by 1.5 the reference values of non-pregnant women.[14] However, the validity of such a method has been questioned because of the close relationship between TT_4 and the variability of TBG.[15]

FT_4 index (FT_4I) which is based on two estimates, namely a measurement of T3 resin uptake and an immunoassay estimate of TT4, could still be a good method for situations when TBG concentrations are dynamically modified, as occurs during pregnancy.[16] However, FT_4I frequently fails to completely correct for the TBG-induced increase in TT_4.

The recent American Thyroid Association (ATA) guideline recommends that in the absence of local reference values and after taking into account the importance of potential variations between the technical methods of measurement, the upper normal value for TSH in pregnant women should be 2.5 mUI/mL in the first trimester and 3.0 mUI/mL in the second and third trimesters. This value of 2.5 mUI/mL was chosen not only because it is close to the 97.5 percentile but also because higher values are associated with higher fetal morbidity.[5,17] Figure 1 illustrates the downward shift of the TSH reference range according

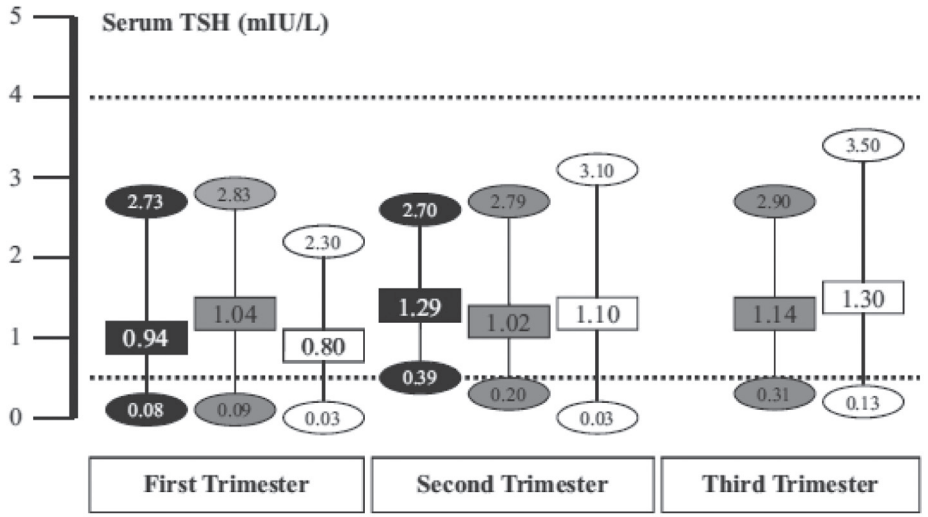

Figure 1. The figure illustrates the downward shift of the TSH reference range, according to trimesters of pregnancy. The graph shows the median TSH values (boxes) and the upper and lower reference limits of normal (ovals). The upper and lower limits show the 5th and 95th centiles. For the black set of symbols see ref. 30. For the grey set see ref. 72 and for the white set see ref. 73. The horizontal dotted lines show the non-pregnant serum TSH reference range (0.40–4.0 mIU/L). *Modified from ref. 4*

to the trimesters of pregnancy on the basis of data from three relevant publications.

THYROID DISEASES AND PREGNANCY

Thyroid dysfunction during pregnancy includes overt hypothyroidism (OH) and subclinical hypothyroidism (SCH), with a relative incidence of approximately 0.4% for OH and 3% for SCH, as well as overt and subclinical thyrotoxicosis, with relative incidences of approximately 0.2% for the former and 2.5% for the latter. Finally, concerning autoimmune thyroid disease (AITD), it was shown to range between 5 and 20%, with an average of 7.8%. AITD represents the main cause leading to hypothyroidism in pregnant women.

OH is defined as a low serum FT_4 with elevated serum TSH concentration. With regard to SCH in pregnancy, the upper normal limit of serum TSH values is shifted downward because of the indirect dampening effect of elevated serum hCG levels of TSH secretion, hCG acting as a TSH-like agonist on the thyroid gland. Due to the downward shifting of TSH, a significant proportion of pregnant women with only slight serum TSH elevations may not be diagnosed.[4,8]

Besides the classical presentations of maternal thyroid failure as OH and SCH, another condition has been reported specifically in the context of pregnancy, namely isolated hypothyroxinemia (hypo-T_4), which is defined as a lowering in serum FT_4 without concomitant serum TSH elevation. This biochemical condition was first described in pregnant women residing in areas with mild to moderate ID, which is today believed to possibly be responsible for relative hypo-T_4 with normal TSH.[18] However, the causes of the latter currently remain not well understood and even somewhat enigmatic.

The incidence of isolated hypo-T4 is about 150 times more frequent than congenital hypothyroidism.[19]

Regarding hyperthyroidism, prevalence of GD with ranges between 0.1% and 1%[20] and transient gestational hyperthyroidism syndrome, with ranges between 1 and 3%, have been reported.[21] Multiple retrospective studies have shown that adverse outcomes of pregnancy, namely risks of maternal and fetal/neonatal complications, were directly related to the duration and inadequate control of maternal thyrotoxicosis.[22-28] Poor control of thyrotoxicosis is associated with a risk of spontaneous abortion, congestive heart failure, thyrotoxic storm, preeclampsia, preterm delivery, low birth weight and stillbirth. In a study from Australia by Smith et al,[29] the outcome of pregnancy was evaluated in women with undiagnosed

GD. Results demonstrated severe prematurity (mean delivery time, 30 wks) associated with very low birth weight (<2 kg) and neonatal hyperthyroidism requiring antithyroid drugs (ATDs) treatment. In contrast, pregnancy outcome was excellent for women with GD in whom diagnosis was made early and ATD treatment was started promptly.[29]

The overall goal of therapy is to control maternal thyrotoxicosis as early as possible. With the use of ATDs, which constitute the first-line therapy option for GD in pregnancy, women should be maintained at a high euthyroid or borderline hyperthyroid level.[24,30,31] Because all ATDs cross the placenta, it is recommended to use the smallest possible ATD dose that will allow for controlling maternal thyrotoxicosis without the risk of harming the fetus because ATDs also inhibit fetal thyroid function. Combined administration of ATD and levothyroxine (LT_4) to the mother should be avoided because the transplacental passage of ATD is high, whereas it is negligible for thyroid hormones; hence, addition of LT_4 will not protect the fetus from ATD-induced hypothyroidism. ATDs belong to the thionamide drug family, the compounds prescribed being propylthiouracil (PTU), methimazole (MTZ) or carbimazol (CMZ), the pharmacological precursor of MTZ.[31-33] MTZ has been reported to be the cause of congenital abnormalities, so called "MTZ embryopathy", which includes aplasia cutis and choanal or esophageal atresia.[34-36] Aplasia cutis, which is the absence of skin and accessory structures over the scalp, has so far not been reported in mothers exposed to PTU. Skin defects are estimated to occur in one of approximately 4,000–10,000 pregnancies and, from the scarce data available, it is considered that this incidence does not exceed background incidence in pregnant women who have received MTZ.[37] Choanal or esophageal atresia is a severe congenital anomaly requiring major surgery to repair and is considered to have a higher incidence than expected in fetuses exposed to MTZ in the first trimester.[38] The relative risk of choanal atresia in pregnant women receiving MTZ was estimated to be approximately 17-fold greater than in the general population, although it should be noted that such congenital birth defects could also be attributed to thyrotoxicosis *per se* rather than to the administration of MTZ.[39]

With regard to PTU, a controversy has recently come to light after the alarming report that the use of PTU for treatment of pediatric GD was associated with a significant and therefore unacceptable risk of liver failure.[40-42] Soon thereafter, The Endocrine Society alerted its members about the risk of hepatotoxicity and recommended that PTU use be stopped in the pediatric population.[43] An additional concern is that liver failure related to PTU administration is idiosyncratic and, therefore, no biomarkers can be used to predict liver toxicity.[44] In the specific context of the first trimester of pregnancy, however, PTU remains the drug of choice because of the potential adverse effects of MTZ on the fetus, described above.[45,46] Although there have been a few isolated reports of maternal liver injury associated with the use of PTU in pregnancy, there are presently no clear data that would allow to us evaluate the relative risks of MTZ-induced fetal anomalies *vs* PTU-associated liver failure. A possible modification of currently available recommendations could be to limit the use of PTU to the first trimester of gestation –during which time completion of organogenesis takes place– and possibly to switch women with active GD to MTZ treatment thereafter. Finally, pregnant women under PTU should report any new symptom (such as anorexia, nausea, etc.) to their physician and, although liver toxicity may appear abruptly, it seems reasonable to recommend monitoring of liver function tests.

Guidelines for GD treatment in pregnancy are depicted in Table 1.

Recently, Bulmus et al[47] conducted a prospective clinical study with 998 pregnant women between the ages of 17–48 years. In the first step, a detailed medical history was obtained and a detailed thyroid gland examination was performed in all subjects (n=998). In pregnant women diagnosed with thyroid disease (TD) or considered to have TD with these results (n=107), TD was evaluated via thyroid function tests and imaging methods. In the second step, TSH, FT_4 and free triiodothyronine (FT_3) were measured in the first antenatal examination of the pregnant cases considered not to have TD after medical history and examinations (n=891). Thyroid antibodies (Abs) were measured in cases with abnormal thyroid indices. It was found that the incidence of hyper- and hypothyroidism during pregnancy in the whole study group came to 71 cases, 67 of whom had TD before

TABLE 1. Guidelines for the Medical Treatment of Graves' Disease in Pregnancy

1	Monitor clinical signs (heart rate, weight gain, thyroid size, etc.) and serum free T4 and T3, TSH every 2-4 weeks.
2	Use the lowest dose of ATD to maintain the patient in a euthyroid or mildly hyperthyroid state. ATD dosage can usually be lowered after the first trimester and often discontinued during the last trimester.
3	Do not attempt to normalize serum TSH. Serum TSH concentrations between 0.1 and 0.4 mIU/L are appropriate. Lower – or undetectable – TSH levels are acceptable if the patient's clinical condition remains satisfactory.
4	Concerning the choice of ATD, the use of PTU is preferable during the first trimester (remember the potential risk of liver injury).
5	With PTU (or its equivalent dosage for MTZ/CMZ), doses as low as 100-200 mg/d may still affect fetal thyroid function. However, there are many reports of PTU dosages as high as 400 mg/d in the literature (without serious side effects).
6	Consider thyroidectomy (in the second trimester) if the patient is non-compliant or cannot tolerate the administration of ATD, or when persistently elevated doses of ATD are required (PTU >600 mg/d or MTZ >40 mg/d).
7	When ATD have been withdrawn in the last weeks of gestation, keep in mind that a rebound of thyrotoxicosis may occur in early postpartum with the need to reinstitute (or increase) ATD dosage after delivery.

pregnancy. They concluded that detailed medical history and family history obtained during the first trimester of pregnancy helped them to identify 67/71 cases who had TD before pregnancy.

The authors emphasize the importance of detailed first prenatal examination regarding the thyroid.

MATERNAL THYROID DISEASES AND THEIR ASSOCIATION WITH MATERNAL, FETAL, NEONATAL AND INFANT DISTURBANCES

Several studies have shown an association between abnormal thyroid status and different diseases which would support the recommendation of universal screening for TD in pregnancy.

The generation R study[48] investigated 5153 pregnant women in early pregnancy. Serum TSH, FT_4 and thyroid peroxidase (TPO) Abs levels were determined, while the association of thyroid function with the risk of hypertensive disorders was studied. The authors demonstrated that biochemical hyperthyroidism and also high-normal FT_4 levels during early pregnancy are associated with an increased risk of hypertensive disorders. These associations are even seen for a mild variation in thyroid function within the normal range.[48]

A prospective population based cohort study in China[49] investigated the association between thyroid abnormalities in pregnancy and subsequent fetal and infant development. They investigated 1017 women with singleton pregnancies. Maternal serum samples in the first 20 wks of pregnancy were tested for TSH and FT_4. Pregnant women were classified by hormone status into percentile categories based on laboratory assay and were compared accordingly. The authors found that OH was associated with increased fetal loss, low birth weight and congenital circulation system malformations. SCH was associated with increased fetal distress, preterm delivery, poor vision development and neurodevelopmental delay. Isolated hyperthyroxinemia was related to fetal distress, small-for-gestational-age and musculoskeletal malformations. Isolated hyperthyroxinemia was associated with spontaneous abortion. Finally, clinical hyperthyroidism was associated with hearing dysplasia. The conclusion is that thyroid dysfunction in the first 20 wks of pregnancy may result in fetal loss and dysplasia and some congenital malformations.

Ashoor and his group[50] investigated 102 singleton pregnancies that subsequently developed preeclampsia (PE) and compared the FT_4 and TSH results to the values of 4318 normal pregnancies. They found that in late-PE (delivery after 34 wks) pregnancies, the median TSH was significantly increased and the median FT_4 was decreased. Logistic regression analysis demonstrated that TSH provided a significant contribution to the prediction of late-PE.

In a study from the United Arab Emirates by Agarwal et al,[51] the aim of which was to determine the prevalence of abnormal thyroid function and antithyroid antibodies during early pregnancy in a population at high risk for Gestational Diabetes Mellitus (GDM), the authors investigated, by measuring FT_3, FT_4 and TSH, 301 pregnant women who underwent routine

"universal screening" for GDM. In 255 of the above women TPO Abs were also measured. GDM was confirmed in 80 of these women. No difference was found between the 80 women with and the 221 women without GDM for any of the above thyroid function tests. In the cohort tested for antiTPO Abs, the 51 (20%) women with positive Abs had higher mean TSH than negative women ($p < 0.001$). Seventeen women had low FT_4, while 12 women had high TSH. Twenty-eight women had low serum TSH, among whom three also had high FT_4. The authors concluded that higher prevalence of hypo-T_4 and TPO Abs titers than generally reported warrants routine screening for thyroid abnormalities. This screening would result in improved obstetric care.

In a study from Crete, Greece, the objective of which was to examine the association of thyroid function and autoimmunity in early pregnancy with adverse pregnancy and birth outcomes, Karakosta et al[52] investigated a total of 1170 women with singleton pregnancies. They measured serum FT_4, FT_3, TSH and thyroid Abs in the first trimester of pregnancy. The main outcome measures included gestational diabetes, gestational hypertension/preeclampsia, cesarean section, preterm delivery, low birth weight and small-for-gestational-age neonates.

They found that the combination of high TSH and thyroid autoimmunity in early pregnancy was associated with a 4-fold increased risk for gestational diabetes and a 3-fold increased risk for low birth weight neonates after adjustment for several confounders. Women positive for thyroid Abs without elevated TSH levels in early pregnancy were at high risk for spontaneous preterm delivery, whereas the combined effect of high TSH and positive thyroid Abs did not show an association with preterm birth. They concluded that high TSH levels and thyroid autoimmunity in early pregnancy may detrimentally affect pregnancy and birth outcomes.

Haddow et al[53] observed that at 9 years of age, children of women with undiagnosed hypothyroidism (TSH >98th percentile) during pregnancy had significantly lower scores in neuropsychologic tests related to intelligence, attention, language, reading ability, school performance and visual motor performance. Other studies linked SCH, AITD or hypo-T_4 in the mothers with poorer results on tests of intelligence and motor skills in their children.[54] The effect of maternal hypo-T_4 has generated an extensive debate about its causal involvement in impaired neuropsychological development of the progeny. Although several authors[55-59] have shown that maternal hypo-T_4, defined as FT_4 <10th percentile with a normal TSH, during the first trimester of gestation is associated with decreased neuropsychological development of the children, a recent study by Craig et al[60] has not confirmed these findings. However, it has to be remembered that Morreale de Escobar et al[61] already in 2000 presented epidemiological and experimental data strongly suggesting that hypo-T_4 detected during the first trimester, irrespective of whether TSH was normal or elevated, was associated with a higher risk of poor neuropsychological development of the offspring, mostly due to a decreased availability of T_4 to the developing fetal brain tissues.[61]

In 2009, Berbel et al,[62] using Stringent selection criteria for the assessment of neuropsychological parameters in their cohort of patients, clearly demonstrated the relationship between hypo-T_4 and impaired functional brain maturation.

Mannisto et al[63] recently reported that hyper- or hypothyroidism in pregnant mothers was associated with multiple adverse outcomes in the offspring, like sepsis, respiration distress syndrome, transient tachepnea, tachycardia and apnea. Changes in TSH levels in the children of mothers with TD have also been described, as children of hypothyroid mothers show significantly higher TSH levels than controls and children of hyperthyroid mothers have lower levels of TSH. It is unknown if these alterations may in the long term increase the risk of TD in these children.

An important study was published recently which provides robust data regarding the above issue. Lazarus et al[64] conducted a randomized trial in which 21,846 pregnant women at 15 weeks 6 days or less gestation provided blood samples for TSH and T_4 measurements. The women were assigned to a screening group (in which measurements were obtained immediately) or a control group (in which serum was stored and measurements were obtained shortly after delivery). TSH levels >97.5th percentile, FT_4 <2.5th percentile or both were considered a positive screening result.

Women with positive results in the screening group were assigned to 150 μg LT_4 per day. The primary outcome was IQ at 3 years of age in children of women with positive results, as measured by psychologists who were unaware of the group of assignments. They concluded that antenatal screening (at a median gestational age of 12 weeks 3 days) and maternal treatment for hypothyroidism did not result in improved cognitive function in children of 3 years of age. This study supports the current ATA guidelines, which do not recommend routine antenatal screening for hypothyroidism in pregnancy.[65]

SCREENING FOR THYROID DISEASES: A PERMANENT CONFRONTATION BETWEEN EXPERTS

A question which is invariably raised at different meetings regarding this important issue is whether thyroid function should be screened in all pregnant women. Many major scientific societies have considered this issue. The American Association of Clinical Endocrinologists has recommended routine TSH measurements during the first trimester (or before pregnancy) in all women.[66]

The American Endocrine Society and all four world thyroid associations have endorsed the international guidelines recommending screening of pregnant women, especially those in high-risk groups.[5]

The "middle-way" position taken by the endocrine and thyroid societies resulted from a compromise within the ad hoc committee that prepared the guidelines, mainly to satisfy the opposite views held by our Ob-Gyn colleagues. In the end, the American College of Obstetricians and Gynecologists did not endorse the guidelines, considering that routine screening of thyroid function in pregnant women could not be recommended because of the lack of studies showing a proven benefit, even if asymptomatic women with SCH were identified and treated.[67]

The American Endocrine Society guidelines are considering high-risk categories of women justifying screening, especially those with a personal or family history of TD, symptoms of thyroid dysfunction, history of other autoimmune diseases, infertility, type 1 diabetes, history of head and neck radiation, and obviously also women with positive thyroid Abs.[5] However, the study by Vaidya et al[68] has shown that targeting high-risk groups is not a panacea because in the experience of these authors, targeted screening would still have missed about one third of all pregnant women with hypothyroidism.

To the question "Should women be screened for TPO antibodies before or during pregnancy with the goal of treating TPO Ab+ euthyroid women with LT_4 to decrease the rate of spontaneous miscarriage", the ATA Taskforce on Thyroid Disease during Pregnancy and Postpartum points out that there is insufficient data for or against screening all women for thyroid antibodies in the first trimester of pregnancy.[65]

To the question "Should women with recurrent abortion be screened for thyroid antibodies before or during pregnancy with the goal of treating TPO Abs + euthyroid women with LT4 or intravenous immunoglobulin therapy (IVIG) to decrease the rate of recurrent spontaneous abortion", the answer is that there is also insufficient evidence to recommend for or against screening for thyroid antibodies, or treating in the first trimester of pregnancy with LT4 or IVIG, in euthyroid women with sporadic or recurrent abortion or in women undergoing in vitro fertilization (IVF).[65]

To the question "Should women undergoing IVF be screened for TPO antibodies before or during pregnancy", the answer is that there is still no universal agreement regarding the mandatory screening for thyroid abnormality in pregnant women. However, there is a general agreement regarding thyroid screening in pregnant women who belong to high-risk groups.[65]

Most of the above statements which do not recommend universal antenatal screening for TD are based on the high cost of the programme. However, only a few studies up to now have investigated this issue in depth.

Dosiou et al,[69] in their first report on the issue, developed a state-transition Markov model and performed a cost-effectiveness analysis of screening pregnant women for AITD. Three strategies were compared: 1) no screening, 2) one-time screening using antiTPO Abs and 3) one-time screening using TSH. Screening tests were added to the laboratory tests of the first prenatal visit. Abnormal screening tests were followed

by further testing and subsequent thyroxine treatment of hypothyroid women. They found that screening pregnant women in the first trimester using TSH was cost-saving compared with no screening. Screening antiTPO Abs was cost-effective compared with TSH screening with an incremental cost-effectiveness ratio of $15.182 per quality-adjusted life-year. Screening using TSH remained cost-saving across a wide range of ages regarding screening, costs of treatment and probabilities of adverse outcomes.

The cost-effectiveness of antiTPO screening compared with TSH screening was mostly influenced by the probability of diagnosing hypothyroidism in unscreened subjects or subjects with a normal screening test. Screening remained highly cost-effective in scenarios where they assumed no improvement of child IQ outcomes by thyroxine treatment.

They concluded that screening all pregnant women for AITD in the first trimester is cost-effective compared with no screening.

A few years later the same first author, with different collaborators,[70] published a more sophisticated report on the same issue.

The objective of the study was to compare the cost-effectiveness of universal screening of pregnant women for AITD with screening only high-risk women and with no screening.

A decision-analytic model compared the incremental cost per quality-adjusted life-year (QALY) gained among the following: 1) universal screening, 2) high-risk screening and 3) no screening. Screening consisted of a first-trimester TSH and TPO Abs measurements. Women with abnormal results underwent further testing and, when indicated, LT_4 therapy. Randomized controlled trials provided probabilities for adverse obstetrical outcomes. The model accounted for the development of postpartum thyroiditis and OH. Additional scenarios in which therapy prevented cases of decreased child intelligence quotient were explored.

The results indicated that risk-based screening and universal screening were both cost-effective relative to no screening, with incremental cost-effectiveness ratios (ICERs) of $6,753/QALY and $7,138/QALY, respectively. Universal screening was cost-effective compared with risk-based screening, with an ICER of $7,258/QALY. Screening remained cost-effective in various clinical scenarios, including when only OH was assumed to have adverse obstetrical outcomes. Universal screening was cost-saving in the scenario of untreated maternal hypothyroidism resulting in decreased child intelligence, with LT_4 therapy being preventive. They concluded that universal screening of pregnant women in the first trimester for AITD is cost-effective, not only compared with no screening but also compared with screening of high-risk women.

SUMMARY

TDs during pregnancy includes mainly hyper- and hypothyroidism and their variants, isolated hypo-T_4, AITD and different types of goiter. AITD represents the main cause and ranges between 5 and 20% with an average of 7.8%.

TSH is a very sensitive marker of thyroid dysfunction during pregnancy. Normal values have been modified during gestation with a downward shift. The ATA recommends the upper normal range for TSH to be 2.5 mUI/ml in the first trimester and 3.0 mUI/ml for the remainder of pregnancy. Most of the studies have shown that children of pregnant women with hypothyroidism during pregnancy had significantly lower scores in neuropsychological tests related to intelligence, attention, language, reading ability, school performance and visual motor performance. However, some studies have not confirmed these findings. On the other hand, poor control of thyrotoxicosis is associated with a risk of spontaneous abortion, congestive heart failure, thyrotoxic storm, preeclampsia, preterm delivery, low birth weight and stillbirth.

An important question is whether universal screening for TD is justified or not. Despite the lack of consensus among professional organizations, recent studies which have been performed on the basis of sophisticated analyses have found that screening all pregnant women for AITD in the first trimester is cost-effective compared with no screening or with screening of high-risk women. This is in line with the everyday experience of most physicians who deal with such cases. For example, in the USA, and specifically in the area of Maine, it has been found that 76% of urban obstetric practices are investigated via TSH testing.[71]

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