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THYROID FUNCTION IN PREGNANT WOMEN

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ABSTRACT

Two pregnancy-related hormones—human chorionic gonadotropin (hCG) and estrogen—cause increased thyroid hormone levels in the blood. Made by the placenta, hCG is similar to TSH and mildly stimulates the thyroid to produce more thyroid hormone. Increased estrogen produces higher levels of thyroid-binding globulin, also known as thyroxine-binding globulin, a protein that transports thyroid hormone in the blood. These normal hormonal changes can sometimes make thyroid function tests during pregnancy difficult to interpret. Thyroid hormone is critical to the normal development of the baby's brain and nervous system. During the first trimester, the fetus depends on the mother's supply of thyroid hormone, which comes through the placenta. At around 12 weeks, the baby's thyroid begins to function on its own. The thyroid enlarges slightly in healthy women during pregnancy, but not enough to be detected by a physical exam.

KEYWORDS: Thyroid, pregnant women.

INTRODUCTION

Pregnancy is a physiological state accompanied by a high-energy demand and an increased oxygen requirement which leads to a complex alteration in metabolic and hormonal changes in the physiology of maternal-fetal system and the request for thyroid hormones is increased during gestation.[1] Due to specific conditions related to the pregnancy period, There is various alteration accompanied by this phase of life. Because autoimmune thyroid disease is common in women during the childbearing period, it is important to understand both the expected changes in thyroid function in normal pregnancy and how pregnancy may affect pre-existing Graves' disease, hypothyroidism, and thyroiditis. Etc.[2] Thyroid disorders may affect both the pregnant woman and the developing fetus; where thyroid hormones having an

essential role in embryogenesis and fetal development. A fetus is completely dependent on the mother for thyroid hormone.[3]

Uncorrected thyroid dysfunction in gestation has adverse effects on fetal and maternal well-being (before and after delivery). The deleterious effects of thyroid dysfunction can also extend beyond pregnancy and delivery to affect neurointellectual development in the early life of the child[4], and also lead to maternal, fetal, and neonatal morbidity, and mortality. Maternal complications involve miscarriage, pregnancy-induced hypertension, placental abruption, preterm labor, heart failure, and thyroid storm. Fetal and neonatal complications include low birth weight, stillbirth, hyperthyroidism, goiter, and hypothyroidism.[5]

Autoimmune thyroid disease is common in gestation. and characterized by the presence of antithyroid antibodies, specifically anti-thyroglobulin (TG-abs), and anti-thyroid peroxidase (TPO -abs).[6]

Normal pregnancy results in a number of important physiological and hormonal changes altering thyroid function. In the last twenty years, a major expansion of our knowledge has taken place regarding the relationships between pregnancy and the thyroid hormones. The most important finding includes maternal thyroid hormones play a vital role in early fetal brain formation, and their deficiency may impair future neuropsychological development of the fetus.[7] Pregnancy is associated with certain physiological changes and the maternal thyroid gland has to adapt accordingly. The first factor is the adjustment of bound to free ratio of T4 and T3 against the marked increase in the circulating levels of thyroxin-binding globulin (TBG) levels due to enhanced estrogen production. The second factor is the direct stimulation of the thyroid gland by an elevated concentration of human chorionic gonadotropin (hCG). These two factors occur in the first trimester of pregnancy.[8]

The third factor is the increased enzymatic activity of type III monodeiodinase. It converts T4 to reverse T3 (rT3) and thus increases the turnover rate of maternal T4 at the placental level, operative in later stages of pregnancy. During pregnancy maternal iodine requirement increases which is further increased due to increased renal clearance of iodine. Moreover, a part of the available iodine from the maternal circulation is diverted to fetal thyroid gland which becomes progressively functional by the end of the first trimester.[9]

Thus, the regulation of maternal thyroid function is complex and varies with each stage of pregnancy. Moreover, human chronic gonadotropin (hCG) can stimulate the thyroid gland during the first trimester because of its structural similarity to thyrotropin (TSH). Both normal pregnancy, and pregnancy complicated by conditions like hyperemesis gravidarum (HG) that can be associated with thyroid function study changes, strongly suggestive of hyperthyroidism, in the absence of primary thyroid disease.[10] Thus, a local reference range for thyroid hormones in pregnant women is essential.[11] The availability of gestational age-dependent reference intervals for thyroid hormones for local population should help to avoid the underdiagnosis of hyperthyroidism or the overdiagnosis of hypothyroidism, with inadvertent use of thyroxine replacement in later pregnancy, also allowing an accurate interpretation of thyroid hormone results in complicated pregnancies, which may have abnormal thyroid function, such as pre-eclampsia and HG.[12]

BACKGROUND

Historically, there has been a widely held belief that the thyroid increases in size during pregnancy, as depicted in hieroglyphics in Ancient Egypt and in paintings, such as Saint Luke Painting the Virgin by Roger van der Weyden (Alte Pinakothek, Munich, Germany). According to the older literature, the thyroid gland shows some degree of enlargement during gestation, notably in areas of low environmental iodine.[13]

Marine & Kimball, in 1921, considered the goiter of pregnancy to be a form of work hypertrophy due to iodine deficiency and concluded that the enlargement could be prevented by iodide therapy.[14] However, there is still confusion among clinicians about the entity ‘goiter of pregnancy’. Moreover, the question of whether a goiter of pregnancy is solely prevalent in areas of iodine deficiency is not settled.[15]

hyroid function during pregnancy

Rasmussen et al.[16] found no change in thyrotropin (TSH) levels during pregnancy, as compared with 12 months postpartum. Romano et al. reported TSH levels within the normal range with no difference between the iodine-treated and control groups. Pedersen et al.[17] observed a fall in free thyroxine (FT4) levels in both control and iodine-treated groups but a rise in plasma TSH in the control group only. In the study of Glinoer et al.[18] plasma FT4 as well as FT3 decreased during pregnancy (cross-sectional data), whereas TSH levels increased, in negative correlation with plasma human choriogonadotropin (hCG) levels. In the second study by Glinoer et al.[19], on subjects selected by the criteria of low FT4 levels, a

high T3/T4 ratio and a high thyroglobulin concentration comprising less than 10% of a large cohort, a decrease in FT4 was observed in the untreated control group and again a rise in TSH in the third trimester. An analysis of papers with a longitudinal study design, the exclusion of subjects with thyroid disease, medication interfering with thyroid hormone regulation or metabolism and complicated pregnancy, and the measurement of FT4 by a valid assay, as judged by a minimal decrease in FT4 on dilution of the serum sample[20], reveals that FT4 significantly decreases by about 30% to low normal values in the second and third trimester of pregnancy[21] in both iodine-depleted and -replete areas. The vast majority of the transversal studies published after 1980 employing free hormone immunoassays also indicate a fall in serum FT4. FT4 values in the second and third trimester are generally lower than outside pregnancy.

However, a small transient increase in FT4 in the first trimester was observed in three studies that subdivided the first trimester into weeks. The two prospective studies, i.e. with FT4 values from the same females measured before pregnancy[22], did not find a difference between pre-pregnancy and first-trimester values, but the sampling time during the first trimester was not indicated in these studies. The decrease in serum FT4 in pregnancy cannot be explained by changes in plasma volume or concentrations of albumin, thyroxine-binding globulin and free fatty acids in the serum. There are at present no data indicating that thyroid hormone production is increased during pregnancy in order to meet increased maternal and fetal demands. Although renal iodine clearance is increased during pregnancy, probably by increased glomerular filtration rate, absolute thyroidal iodine uptake remains unchanged.[23] Moreover, relative iodine deficiency cannot fully explain the decrease in FT4, because it is observed in iodine-deficient as well as iodine-replete areas. The decrease in FT4 is associated with a similar decrease in FT3, which also argues against an iodine-related phenomenon, since, in iodine deficiency, T3 values are normal or even increased. Lastly, net T4 turnover and presumably also thyroid hormone requirements are unaltered in human pregnancy, i.e. 90 mg per day in non-pregnant women vs 97 mg per day in pregnant women.[24]

Our understanding of the appreciable effects of pregnancy on thyroid economy has had notable advances in the last 20 years. Pregnancy determines an increase of urinary iodine excretion and thyroxine-binding globulin (TBG) levels and a rise in thyroid hormone degradation by placental type III deiodinase; furthermore, the fetus utilizes maternal thyroid

hormones. Thus, the demands on maternal thyroid axis are increased, and as a consequence, the maternal thyroid hormone production rise.

This scenario induces compensatory mechanisms such as an increased thyroidal production of free-thyroxine (FT4) and free triiodothyronine (FT3) triggered by the placental secretion of human chorionic gonadotrophin (hCG). Furthermore, it is well known that pregnancy induces a condition of general immunosuppression for all its duration.[25] As a consequence, the activity of autoimmune disorders is reduced during gestation, including thyroid autoimmunity and leading to additional changes in thyroid hormones levels.

During gestation, plasma volume and glomerular filtration rate increase significantly, with consequent augmented excretion of iodine in the urine.[26] Thus, the reduced serum iodine concentration exacerbates iodine deficiency and may be causative of goiter and reduced levels of maternal thyroxine (T4), especially in areas of endemic cretinism.[27]

An augmented thyroid volume has been observed even in areas of mild-moderate iodine deficiency, but not in iodine-sufficient regions.[28] This is of particular relevance to the UK which is iodine deficient[29] and data from the UK has shown mild-moderate iodine deficiency in pregnancy is associated with a lower child IQ.[30] A daily iodine intake of 250 µg in pregnancy is recommended by several different authorities[31], however, it is not always achieved even in developed parts of the world (9,21). Endocrine disruptors may exacerbate iodine deficiency and may also have a deleterious effect on offspring neurodevelopment.

Thus, to prevent fetal brain damage additional iodine supplementation in pregnancy may be required in areas of suboptimal iodine nutrition. Ideally, iodine sufficiency should be attained prior to conception by either universal salt iodization or targeting women of child-bearing age.[32]

During pregnancy, the levels of thyroid hormone transport proteins rise, especially TBG, due to estrogen-induced increase in TBG sialylation with consequently reduced degradation and increased half-life, as well as enhanced hepatic synthesis. As a consequence, total T4 and total T3 levels rise. The hCG glycoprotein hormone shares a common alpha subunit with thyroid stimulating hormone (TSH) but has a unique beta subunit, which confers specificity; the amount and type of hCG secretion by placenta seems to be somewhat dependent on ethnicity.

In vitro studies on thyroid tissue and on eukaryotic cells stably expressing the human TSH receptor (TSHR) showed that hCG acts as a TSH agonist; however, others showed limitations of such in vitro assays, therefore this topic is still objected of controversy. The incidence of gestational transient hyperthyroxinemia caused by elevated hCG levels and therefore not treated was 0.285% in a study screening more than 23,000 pregnant women.

There is good evidence that hyperemesis gravidarum (severe nausea and vomiting), which sometimes requires hospitalization for the management of its potential complications including dehydration and ketosis, may be associated with hyperthyroidism due to excess hCG stimulation. Furthermore, both the hCG secreted in the first trimester of pregnancy and that produced by hydatidiform mole tissue, have a high thyroid stimulating specific activity.[33]

The sensitivity of TSHR to hCG has also been demonstrated by a few isolated case reports of familial gestational hyperthyroidism caused by mutant TSHR (missense mutation) which was more sensitive to hCG than the wild type receptor.[34] Recent data suggest that women with positive autoantibodies to thyroid peroxidase (TPOAb) may have an impaired response to hCG[35] and therefore may not be able to meet the extra demands placed on the thyroid. This may be a key factor in why TPOAb positivity is associated with adverse outcomes. In this complex scenario the precise mechanisms leading to a decline in free thyroid hormones have not been elucidated, however, the interaction of estrogens, hCG, TSH, and thyroid binding proteins is crucial. In iodine-deficient areas (including marginal iodine deficiency) the pregnant woman may become significantly hypothyroxinaemia with preferential T3 secretion, especially if iron deficient.[36] As a general rule, FT4 transiently rises in the first trimester due to the relatively high circulating hCG concentration, while FT4 decreases in the second and third trimester, albeit still within the normal reference range.[37] Changes in FT3 concentration are also seen in which they broadly parallel the FT4, again within the normal range.[38] The thyroidal ‘stress’ is also evidenced by a rise in the median TSH and serum thyroglobulin; in particular, TSH levels have a specular trend compared with hCG, therefore lower in the first trimester and higher in the second and third trimesters.[39]

Table 1 Physiologic changes in pregnancy that influence thyroid function

Physiologic change	Impact on thyroid economy
↑Thyroid binding globulin (TBG)	↑Serum total T4 and T3 concentration
↑hCG levels (1st trimester)	↑Free T4 and ↓TSH (thyroidal hCG response may be impaired in TPOAb positive women)
↑Plasma volume	↑T4 and T3 pool size
↑Type III iodothyronine-deiodinase activity (inner ring deiodination) from placenta	↑T4 and T3 degradation consequent ↑demand on thyroid gland for increased hormone production
Thyroid gland enlargement (in some women)	↑Serum thyroglobulin
↑Renal iodine clearance	↑Iodine requirements; ↓hormone production in iodine deficient areas

Thyroid function assessment during pregnancy

Clinical relevance

The profound changes that occur during pregnancy have consequences for thyroid hormone serum concentrations and the assessment of thyroid function. There is a significant overlap between the signs and symptoms of the hypermetabolic state typical of normal euthyroid pregnant women and those due to thyroid dysfunction. Therefore, a differential diagnosis can be challenging to make, and the availability of reliable accurate tests for gestational thyroid function is crucial to this purpose. However, the notable underlying physiological changes occurring during pregnancy also cause many difficulties with the laboratory measurements of thyroid function.[40]

The diagnosis of maternal gestational thyroid dysfunction is of clinical importance for both maternal and fetal health[41], and therefore requires:

(I) Specialized assays measuring thyroid hormones with high specificity and sensitivity;

(II) Normal and reliable intervals for comparison during pregnancy;

(III) And an appropriate treatment regimen.

To this purpose dedicated guidelines have been published by several organizations.[42] Several factors influence thyroid status in pregnancy, including iodine status, hCG levels, ethnicity, body mass index,[43] parity, and male fetal sex.[44] A population of pregnant women not biased by such key factors is required to calculate more precise gestational-related reference ranges for thyroid hormones, essential to make a correct diagnosis.

Therefore, centers should assess their normal thyroid reference-range excluding women with thyroid dysfunction and/or positivity for TPOAb, using medications altering thyroid function,

resident in areas of iodine deficiency. Equally, women who have undergone in vitro fertilization or are expecting twins, since both conditions are characterized by higher hCG levels.[45]

The current American Thyroid Association guidelines recommend the use of pregnancy-specific, local population-based reference ranges where possible. Furthermore, normal thyroid status changes over pregnancy, therefore the accurate assessment of thyroid function in pregnant women requires the use of different gestational age (trimester-specific) reference intervals. Two guidelines provided by the Endocrine Society and the National Academy of Clinical Biochemistry[46] detailed the strengths and limitations of currently available thyroid function tests. TSH has been traditionally the primary marker of thyroid status during pregnancy, however, the measurement of T4 levels is essential in differentiating between overt and subclinical thyroid disease, and the assessment of thyroid hormones during pregnancy has several weaknesses. In particular, the free hormone assays based on measuring the concentrations of thyroid hormone binding-proteins are known to be method-dependent and therefore are at risk of providing inaccurate FT4 and FT3 values during gestation. Direct FT4/FT3 assays based on equilibrium dialysis are more reliable however less available since expensive and time-consuming.[47]

Finally, most laboratories still do not use pregnancy-specific reference intervals for thyroid function tests. In some cases, serum TPOAb and autoantibodies to thyroglobulin (TgAb) and/or to TSHR (TRAb) can provide other information. TPOAb can predict the risk of hypothyroidism; low TSH levels in pregnant women are accompanied by TRAb in 60–70% of the cases and need to be monitored since may cause fetal and neonatal hyperthyroidism.[48]

TSH measurement

Since TSH and FT4 are linked by a log-linear relationship, very small changes in T4 levels will determine a much larger variation in serum TSH concentrations.[49] For this reason, serum TSH levels represent the first biochemical indicator checked in the suspect of thyroid dysfunction. However, during gestation thyroid and pituitary functions undergo notable variations; for example, during early pregnancy, the significant rise in hCG concentrations determines a suppression of TSH levels by 20–50% by week 10.[50]

Therefore, the measurement of only serum TSH in women treated for thyroid dysfunction during gestation has several limitations since can result in maternal under replacement with

levothyroxine, or overtreatment with anti-thyroid drugs (ATD), both scenarios causing maternal hypothyroidism with consequent increased risk for impaired fetal brain development. The biochemical evaluation of the hypermetabolic symptoms presented by women with reduced TSH but still normal FT4 levels may include the measurement of FT3 and FT3 index (FT3I). Total and free thyroid hormone measurements T4 and T3 circulates >99% bound to plasma transport proteins, mainly to TBG and to a lesser extent to transthyretin and albumin; the free- and protein-bound hormones are at equilibrium.[51]

The highly concentrated (nanomolar) protein-bound hormone fractions act as a storage reservoir and prevent thyroid hormones from entering cells where they exert their biological effects. The biologically active form of thyroid hormones is free from protein-binding and present at much lower concentrations (picomolar).[52] Assays for total thyroid hormones have been much easier to develop compared with their free component, due to their increased serum concentrations, and are considered more accurate and valid compared with free hormone assays. In particular total T4 assays generally, agree quite well, and are characterized by better-defined reference intervals in adults.

However, in pregnancy estrogens cause an increase of TBG levels and therefore a consequent increase of total T4 concentrations (up to 1.5-fold in the second trimester), thus gestation-specific reference intervals for total thyroid hormones are necessary for accuracy (6). Due to the influence of thyroid hormone binding proteins, in most clinical laboratories FT4 assays have replaced the total T4 testing. The measurement of the free quote of thyroid hormones allows taking into account the biologically active form only, and this is a clear advantage. However, this approach has significant challenges compared with the total thyroid hormone assays due to:

(I) the lower concentration of the analyte;
(II) the risk to disturb the equilibrium between the free and protein-bound hormone quotes;
(III) the potential interference of the much higher concentrations of the protein-bound hormone quote. In fact, due to the changes in the TBG concentrations during pregnancy, concern has been raised regarding the accuracy of FT4 assays.

It has to be noted that such interference is maximum in the third trimester, while minimal in the first trimester, which is the most important time-point for thyroid dysfunction screening. Furthermore, variation in FT4 as opposed to T4 levels is more robustly associated with adverse obstetric and offspring outcomes.[53] The first step in the measurement of the free

hormones is their physical separation from the protein bound hormones by specific techniques (i.e., equilibrium dialysis or ultrafiltration), followed by immunoassay, or more recently using isotope dilution mass spectrometry (MS).[54]

The immunoassay methodologies are more prone to interference by thyroxine binding protein abnormalities or immunoglobulins (i.e., heterophilic antibodies and antibodies to thyroid hormones).[55] Possible strategies to overcome this limitation are:

(I) To measure the total hormone concentrations (T3 and T4) correcting for the increased binding proteins, i.e., directly measuring the TBG levels to provide T4/TBG or T3/TBG ratios;

(II) To perform a T3 or T4 uptake test to estimate free thyroid hormone indices.[56]

More recently free thyroid hormones have been measured by tandem MS which provides more accurate, specific, fast and simple measurements. Further development was achieved coupling MS with high-performance liquid chromatography.[57]

These assays are complex and laborious, therefore often not routinely employed in clinical practice and limited to specialized laboratories. In fact, clinical laboratories prefer to use commercially available immunoassays for FT4 and FT3 only estimating the concentration of the free thyroid hormone quote, since not physical separating that from the protein-bound hormone quote.[58]

Surprisingly, one of the commercially available FT4 assays resulted to correlate more closely to total T4 assays than to FT4 measured following physical separation of the free-quote from binding proteins. However, the physiological increase in TBG levels occurring during gestation has been showed to influence at various extents the results obtained with commercial FT4 immunoassays.[59]

This explains why a significant method-dependent variation exists when measuring gestational FT4 levels, with different groups reporting serum concentration of thyroid hormones to be decreased, increased or unchanged during pregnancy depending on the assays used; thus, it is challenging to establish universal gestation-related FT4 reference intervals.[60] Considering the differences in thyroid hormones related to the laboratory method used and the gestation period, the use of method- and gestation-specific reference intervals are recommended for the correct interpretation of thyroid function in pregnant women.

Method- and gestation-specific reference intervals for FT4 should be derived in the appropriate reference populations. To this purpose both the iodine and thyroid autoimmunity status should be evaluated when selecting the reference population; only iodine sufficient subjects should be taken into account.[61] Unfortunately, very few FT4 immunoassay manufacturers include appropriate method-specific normal pregnancy-related reference intervals, and most clinical laboratory reports only provide reference intervals not adjusted for gestation, making challenging the interpretation of laboratory results during pregnancy. In cases where a clear diagnosis is difficult to reach, the integration of both free and total thyroid hormone assays, and/or reanalysis of the samples on a different platform are possible options to consider.[62]

Table 2 Physiology of thyroid hormone availability to foetal brain

(A) Before onset of foetal thyroid function (1st trimester)
T4 and T3 are present in embryonic and foetal fluids and tissues
T4 and T3 are of maternal origin
Nuclear receptors are present and occupied by T3
D2 and D3 are expressed in brain
(B) Between onset of foetal thyroid function and birth (2nd–3rd trimesters)
Maternal transfer of T4 and T3 continues
Brain T3 is dependent on T4 and D2 and not on systemic T3
Normal maternal T4 protects foetal brain from T3 deficiency
Normal T3 in low T4 mother does not prevent cerebral T3 deficiency

Although no randomized controlled trials of levothyroxine for overt hypothyroidism in pregnancy have been conducted, the wealth of data regarding the adverse consequences of overt hypothyroidism with pregnancy effects mean performing such studies would be unethical. However, all endocrine and obstetric society guidelines recommend treatment of overt hypothyroidism in pregnancy; in women established on levothyroxine prior to pregnancy, dose adjustments are often needed to cope with the increased thyroidal demand.[63]

Despite this, many women on levothyroxine have suboptimal thyroid function during pregnancy and in those with TSH levels,>4.5 mU/L an increased risk of fetal loss has been

described.[64] The "U" shaped response seen with maternal thyroid function and IQ (7) and the CATS II study also shows that caution should be taken in not overtreating patients with hypothyroidism or Scipio. This is particularly important in treating women with milder thyroid abnormalities as the residual function in the thyroid gland may be readily responsive to hCG resulting in over-treatment if injudicious doses of levothyroxine are given.[65]

Box 1 Management of hypothyroidism in pregnancy

Preconception: optimize levothyroxine therapy in patients with pre-existing disease, warning them of the need to increase dose over pregnancy and the need for closer monitoring

On confirmation of pregnancy, increase dose by 30–50% of preconception dose. Dose requirement is often higher in post-ablative and post-surgical hypothyroidism

If newly diagnosed overt hypothyroidism in pregnancy, start pregnancy-specific body weight-based dose: 2 mcg/kg/day

Be aware of drug interactions:

(I) Drugs which impair thyroxine absorption: iron supplements, cholestyramine, calcium carbonate, soy milk

(II) Drugs which increase thyroxine clearance: carbamazepine, rifampicin, valproate

Check thyroid function early in first trimester and every 4–6 weeks

Aim for TSH <2.5 mU/L in the first trimester and <3 mU/L in later pregnancy. Take care to avoid a T4 level that is too high—aim for upper half of the reference-range

After delivery reduce levothyroxine to preconception dose

Recheck thyroid function at 6 weeks postpartum

CONCLUSION

In the last decade, in particular, our knowledge regarding the diagnosis and treatment of thyroid disease in pregnancy has been revolutionized by substantial advances. In particular, we reached a better understanding of the thyroid hormone physiology during pregnancy and the gestational derived stress on the thyroid, which is exacerbated in areas of iodine deficiency. Furthermore, new developments have been achieved in the technology for thyroid hormone analysis, and progress has been made in defining pregnancy-specific reference intervals for thyroid hormones. In fact, the variation in assay methodology, and other determinants of thyroid function, indicated the necessity of establishing normative gestational-related (trimester-specific) reference ranges for thyroid hormones which are locally derived, namely method- and instrument-specific for the particular laboratory where samples were tested, and generated in iodine sufficient populations excluding women positive for TPOAb.

This is crucial to prevent misinterpretation of thyroid function test results during pregnancy. There is growing evidence that TPOAb positivity and higher TSH levels synergistically interact to increase the risk of adverse pregnancy outcomes. Even modest abnormalities in

FT4 levels as seen in IH are also associated with adverse neurological development in offspring further supporting the role of thyroid hormone in fetal neurodevelopment. These findings would support the use of thyroid screening in pregnancy, although more data are needed. Hypothyroidism is common in pregnancy and should be appropriately treated to reduce obstetric and fetal complications. Given fetal brain development requires adequate thyroxine delivery to fetal neurons, it also seems reasonable to treat mothers with hypothyroidism with levothyroxine to prevent IQ decrement as well as for obstetric reasons. Women already receiving levothyroxine require an increase in dose during gestation aiming for the top of the FT4 reference-range, however, caution is needed to avoid over-treatment and potentially modest deleterious effects on behavior. Hyperthyroidism in pregnancy, usually due to Graves' disease, is uncommon but has deleterious effects on mother and fetus and requires therapy. Especially in early pregnancy treatment with ATD may increase the risk of fetal abnormalities, although treatment is safer than uncontrolled thyrotoxicosis. Use of the lowest dose of ATD possible, including consideration of temporary cessation of treatment during critical periods of organogenesis with close monitoring, will mitigate this risk. Subclinical and mild forms of hyperthyroidism are usually caused by gestational thyrotoxicosis, a non-pathological condition usually self-limiting and not requiring treatment with ATD. Further prospective trials of early screening of thyroid function in pregnancy with both obstetric and developmental outcomes are still required to clarify whether universal thyroid screening in pregnancy is necessary. In the meantime, the correction of worldwide iodine deficiency continues to be required and monitored, and the impact of endocrine disruptors needs further exploration.

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