

Thyroid Diseases in Pregnancy

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Abstract

Introduction: Changes in thyroid function in pregnancy encompass both hyper- and hypothyroidism. Failure to maintain euthyroidism may place both mother and foetus at higher risk of adverse obstetrical outcomes. This review examines the differences between physiological and pathological thyroid dysfunction during pregnancy and their management. **Methods:** Data were obtained from relevant clinical studies and review articles listed in MEDLINE. Additional cross-references from selected articles were identified. **Results:** In hyperthyroidism, the challenge lies in differentiating gestational transient thyrotoxicosis (GTT) from actual pathological states during the first trimester. GTT is thought to be due to elevation of isoforms of human chorionic gonadotropin (hCG) which may exert potent thyrotrophic effects. While thionamides are safe, the lowest possible dose should be used together with close monitoring of maternal thyroid function in order to avoid over-treatment. Surgery for thyroid nodules may be safely performed during the second trimester. Conversely, diagnosing hypothyroid states, particularly subclinical hypothyroidism and postpartum thyroiditis (PPT), require a high index of suspicion. High levels of thyroid peroxidase antibodies (TPOAb) and thyroid stimulating hormone (TSH) in early pregnancy may be predictive of PPT and subsequent permanent hypothyroidism. Clinicians must recognise the need to increase thyroxine replacement as maternal hypothyroidism may adversely affect the IQ scores of children. The association between thyroid autoimmunity and recurrent abortions remain unclear. **Conclusion:** Regardless of the aetiology of thyroid dysfunction, the key to management lies in individualised therapy in close collaboration with the obstetrician.

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Introduction

Abnormalities of thyroid function associated with pregnancy encompass both hyperthyroidism and hypothyroidism. These may have been present before the onset of pregnancy, or occurred only during or after pregnancy. Symptoms suggestive of thyroid disease are common in pregnant individuals. However, the diagnosis of actual thyroid dysfunction can be very difficult because hormonal changes occurring during pregnancy may alter the biochemical parameters of thyroid function significantly in normal women. The failure to treat pathological thyroid disease or the inappropriate treatment of normal patients may affect both mother and foetus adversely. In addition, therapeutic options may be further limited by concern for the well being of the foetus. These issues in the diagnosis and management of hyper- and hypothyroidism in pregnancy will be discussed in this review. Data extracted from relevant clinical studies and review articles appearing

in MEDLINE were studied. Additional cross-references were identified from selected articles.

Normal Physiological Changes in Thyroid Function in Pregnancy

The changes in thyroid function in pregnancy are extremely complex.¹ Levels of thyroid-binding globulin (TBG) begin to increase a few weeks into the first trimester, gradually reach a plateau during the second trimester and are then maintained at 2 to 3 times baseline value for the remainder of the gestational period. The current consensus is that the increase in TBG is due to both an increase in hepatic synthesis of TBG and an oestrogen-induced increase in sialylation which increases the half-life of TBG.^{1,2} The rise in TBG results in the elevation of both total thyroxine (total T4) and total triiodothyronine (total T3) since both these hormones are strongly TBG-bound. On the other hand, the free thyroxine (free T4) index tends to yield low

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values in pregnancy.³ Recently, using highly sensitive thyroid function tests, we have reported elevated levels of free T4, free T3, total T3 and suppressed thyroid stimulating hormone (TSH) in 14.8%, 3.3%, 26.4% and 33.0%, respectively, of 182 normal Singaporean pregnant women assessed between 8th and 14th weeks of pregnancy.⁴ This transient elevation of free thyroid hormone levels in early pregnancy is termed gestational transient thyrotoxicosis (GTT).

Human chorionic gonadotropin (hCG) is an important thyrotrophic stimulator. A study by Kraiem et al⁵ has demonstrated that hCG stimulates T3 secretion, iodide uptake and organification in cultured human thyrocytes. This is especially evident in our population between 8 and 11 weeks of gestation when hCG levels are at their peak.⁴ This phenomenon is explained by the structural homology between hCG and TSH molecules. The potency of hCG appears to be dependent on its circulating concentration as well as its isoforms.^{5,6} Human chorionic gonadotropin should not be viewed as a single molecule, but as a family of isoforms varying in its carbohydrate and polypeptide structures.⁵ Desialylated hCG, a truncated isoform produced during pregnancy, is more potent and is able to exert greater thyrotrophic effect. This is supported by *in vitro* experiments conducted by Hoermann and co-workers⁷ showing that desialylated hCG binds with greater affinity to TSH receptors compared to intact hCG. However, there is also evidence that acidic isoforms of hCG are implicated in hyperemesis gravidarum.⁸ At present, the exact molecular variants of hCG responsible for thyrotrophic effects are unclear.

On the other hand, it is well documented that free T4 and free T3 levels decline by about 10% to 25% during the second and third trimesters compared to the non-pregnant reference range. This is associated with TSH values that are correspondingly higher, although levels of free T4, free T3 and TSH still remain within the reference range. It was previously thought that this phenomenon was artefactual in nature due to the lowering of serum albumin concentration in late pregnancy that may, in turn, affect certain assays that are albumin-dependent. However, in a longitudinal study examining the relationship between free T4 and albumin in 25 healthy pregnant women using 3 different one-step direct assay methods, Ball et al⁹ demonstrated that this phenomenon was not attributed to albumin artefacts, but physiological in nature. A complex interaction between TSH, oestrogen and thyroid binding proteins is thought to be responsible for the observed phenomenon, although the exact mechanism remains elusive.⁶ The lowering of free thyroid hormones in late pregnancy has important implications for hypothyroid pregnant women who will then require higher doses of thyroxine replacement.

An appreciation of all these physiological changes is important so that thyroid function results may be interpreted correctly within the appropriate context.

Thyroid Hyperfunction in Pregnancy

The prevalence of GTT in our population appears to be 11.0% at 8 to 14 weeks of gestation while that of Graves' disease is 1.1%.⁴ This is significantly higher than in Europeans.⁶ Differentiating between these two conditions is important. While GTT may be expected to resolve spontaneously without intervention, untreated pathological hyperthyroidism may lead to adverse obstetrical outcomes. These include higher rates of maternal pre-eclampsia, maternal thyroid crises, first trimester spontaneous abortions, still births, premature delivery, intrauterine growth retardation, low-birth-weight infants and neonatal hyperthyroidism.¹⁰ Clinical diagnosis may be difficult because the usual signs of hyperthyroidism viz. goitre, tachycardia, palpitations, heat intolerance, emotional lability and diaphoresis may also be found in healthy pregnant women.

As the main differential diagnoses, besides Graves' disease and toxic nodular goitre, include pregnancy-specific conditions such as GTT and hyperemesis gravidarum, the evaluation should consist of a relevant history, physical examination as well as laboratory assays of TSH-receptor antibodies (TRAb), thyroid peroxidase (TPOAb) and thyroglobulin (TgAb) antibodies.

The presence of thyrotoxic symptoms before the onset of pregnancy usually excludes pregnancy-specific conditions. Similarly, the possibility of a toxic solitary nodule or multinodular goitre should be considered if they are found on physical examination.

On the other hand, Graves' disease is likely if the patient has a background history of autoimmune thyroid disease or a diffuse goitre or signs of dysthyroid eye disease. The diagnosis may be established if elevated levels of thyroid antibodies, especially TRAb, are present. The second generation TRAb assays has a sensitivity of around 99%.¹¹ In addition, TRAb levels carry prognostic value for foetal and neonatal thyrotoxicosis. This is because TRAb has the ability to cross the placenta and stimulates the foetal thyroid. In view of this, it is recommended that TRAb levels be assessed in early pregnancy and again in the last trimester.

In the absence of any thyroid antibodies, thyroid nodules, significant goitre or orbitopathy in a patient presenting in the first trimester, the diagnosis of GTT is highly likely. The terms GTT and hyperemesis gravidarum are sometimes used interchangeably. However, increasingly, GTT is used to refer to the transient elevation of free thyroid hormones in early pregnancy while hyperemesis gravidarum is characterised by severe nausea and vomiting beginning

between 6 and 9 weeks of pregnancy, to an extent requiring hospitalisation. Abnormal thyroid function tests, consisting of an elevated free T4 in association with a suppressed or undetectable TSH, are found in about 60% of women with hyperemesis gravidarum, which normalise after the cessation of vomiting by 16 to 20 weeks.¹² The conditions, therefore, often co-exist but are not synonymous. Ethnic differences in predisposition to GTT and hyperemesis gravidarum appear to exist with evidence that these conditions are more common in some non-European populations.¹³⁻¹⁵ Hyperemesis gravidarum and thyrotoxicosis due to a mutation in the extracellular domain of the TSH receptor have been reported.¹⁶ This mutation resulted in a receptor that is 30 times more sensitive than the wild-type receptor to hCG. However, we studied genomic DNA from 7 patients with elevated free T4 levels, normal or mild hCG elevations and a history of at least one other first degree relative with a history of hyperemesis gravidarum. Exon 7 of the TSH-R gene was amplified and the PCR fragment was then sequenced. In 2 patients, the entire TSH-R was sequenced. No mutations were detected in any patient, suggesting that it is unlikely that TSH-R polymorphisms are the primary reason for the increased prevalence of GTT in our population.⁴

Therapeutic Options for Hyperthyroidism in Pregnancy

The choice of therapy depends on a number of factors, namely the exact underlying diagnosis, the presence of any compressive symptoms from a goitre, the managing physician's preference, drug allergies and, last but not least, the patient's personal wishes. Apart from rehydration and symptomatic relief, no specific anti-thyroid treatment is needed for GTT as spontaneous resolution is to be expected. In patients with Graves' disease—either diagnosed prior to or during pregnancy—the usual anti-thyroid drugs such as carbimazole and propylthiouracil have been shown to be safe with a low risk of complications, especially if low doses are used in conjunction with close monitoring of maternal thyroid function.¹⁷

Traditionally, propylthiouracil has been the preferred choice as its transplacental passage and secretion in breast milk are minimal and it also inhibits the peripheral conversion of T4 to T3. Moreover, it has not been associated with aplasia cutis, a teratogenic anomaly which had been reported with the usage of methimazole and, to a much lesser extent, carbimazole.^{18,19} However, propylthiouracil has not been proven to be more effective than carbimazole in reducing the risk of treatment-induced foetal hypothyroidism.²⁰ Women who are already taking carbimazole prior to pregnancy need not necessarily switch over to propylthiouracil during pregnancy.²¹ In an analysis of 643 neonates from mothers with Graves' disease, Momotani and colleagues²² were unable to demonstrate

any significant teratogenic effects in those whose mothers took methimazole. In fact, significant teratogenicity was only seen in the neonates of mothers with untreated, uncontrolled hyperthyroidism. The block-and-replace regimen should be avoided as thyroxine does not cross the placenta. The risk of neonatal thyrotoxicosis should be assessed by comparing maternal TRAb levels during the last trimester against its baseline value.² If TRAb levels remain elevated, neonatal thyroid function must be checked during birth (from cord blood) and again 4 to 7 days later to detect early and delayed hyperthyroidism.²³

The hyperthyroidism of Graves' disease usually improves or may even subside totally during the course of pregnancy for reasons that are still unclear. One possible explanation is the phenomenon of relative maternal immune suppression that may account for the absence of rejection of the foetus (which contains foreign paternal antigens) by the mother. This effect may spill over to any on-going autoimmune disease process in general, hence accounting for the favourable course of Graves' disease during pregnancy.²⁴ Similarly, the lack of immune suppression after delivery of the foetus may explain for the higher rate of recurrence of Graves' disease in the postpartum period. An alternative explanation proposed by Kung and Jones²⁵ is a change in the nature of TRAb from a stimulatory to a blocking function during pregnancy. A reciprocal change is later seen in those who suffer from a relapse of Graves' disease in the postpartum period.

As such, it is advisable to monitor maternal thyroid function frequently during pregnancy in order to avoid treatment-induced hypothyroidism, which may result in foetal hypothyroidism and goitre formation that may cause difficulties during labour. The aim should be to use the lowest possible dose of anti-thyroid drugs compatible with euthyroidism, maintaining maternal free T4 levels in the upper third of the normal reference range.²¹ In some instances, it may even be necessary to stop anti-thyroid medication. As the normalisation of free T4 precedes that of free T3 after the initiation of thionamide therapy, the former is better as a guide for the adjustment of anti-thyroid therapy.²¹ Maternal TSH may remain suppressed for weeks to months following the normalisation of free T4.

Beta-adrenergic blockers, often used to control hypermetabolic symptoms, are not contraindicated in pregnancy. However, a greater risk of miscarriage was found in 1 study of 33 pregnancies where β -blockers were used in conjunction with carbimazole.²⁶ In view of this, it is recommended that, if necessary, β -blockers should only be used for short durations until symptoms abate with anti-thyroid medication.

Thyroid surgery is rarely necessary during pregnancy. In

instances such as thyroid carcinoma, symptomatic compression due to a large goitre or florid Graves' disease where the patient is allergic to anti-thyroid medication, surgery may be safely performed during the second trimester.¹⁰ It is imperative that euthyroidism be achieved as quickly as possible after surgery to minimise maternal hypothyroidism.

Radioiodine is contraindicated in pregnancy. The main concerns are congenital hypothyroidism and congenital malformations, especially after the 12th week of gestation where the foetal thyroid is able to concentrate iodine.²¹ Miscarriages are also commoner in women who received radioiodine during the year of conception as well as the year preceding conception.²⁷ It is a good practice to screen for pregnancy in women of childbearing age who are due to receive radioiodine so as to avoid any inadvertent exposure.

Thyroid Hypofunction in Pregnancy

The incidence of hypothyroidism in pregnancy is unclear, although some authors have estimated it to be between 0.05% and 0.7%, while a prevalence rate of 0.3% has been reported in another study.^{1,28,29} It is thought that the association between hypothyroidism and subfertility in women, probably resulting in ovulatory disturbances, accounts for its lower incidence in pregnancy compared to the usual incidence of 0.6 and 1.4% in the general population.⁶ Most cases are due to previous thyroidectomy, pre-existing Hashimoto's thyroiditis or post-ablative Graves' disease entering into pregnancy, although Hashimoto's thyroiditis may also present afresh during pregnancy. Untreated hypothyroidism during pregnancy has been associated with pre-eclampsia, postpartum haemorrhage, abruptio placenta, intrauterine growth retardation, pre-term labour as well as low-birth-weight infants.^{2,30} In addition, Haddow and co-workers³¹ found that children born to mothers who had untreated hypothyroidism during pregnancy had significantly lower IQ scores compared to matched controls. About 20% of these children, aged between 7 and 9, had IQ scores of 85 or less compared to 5% in the control group, suggesting that untreated maternal hypothyroidism may have far-reaching effects long after pregnancy.

Of equal importance, perhaps, is the problem of subclinical hypothyroidism in pregnancy where TSH is elevated but free T4 is normal. While this condition is seldom detected as these patients are largely asymptomatic, the actual prevalence amongst pregnant women may be as high as 2.5%.²⁹ In a series of 41 such patients by Glinioer and co-workers, 40% were due to autoimmune thyroid disease while thyroid hypotrophy was found in the remaining subjects who did not carry thyroid antibodies. It is thought

that this subset of women has sufficient thyroidal functional reserve before pregnancy but which is inadequate to meet the demands of pregnancy. This hypothesis appears to be supported by observational data showing that thyroid function in these women reverted back to normal in the postpartum period even after thyroxine replacement had been stopped.⁶ The presence of TPOAb as well as a high-normal serum TSH level at the onset of pregnancy have also been shown to correlate positively with the risk of developing hypothyroidism during gestation. In a study of 1660 consecutive pregnancies without any history of thyroidal illness, 40% of those with thyroid antibodies had TSH levels exceeding 3 mU/L as well as a 30% reduction in free T4 levels at the time of delivery.³² Thyroid autoimmunity has been shown to be associated with a higher risk of spontaneous abortions, premature deliveries, maternal hypothyroidism during pregnancy and postpartum thyroiditis.⁶ Because of this, some authors are in favour of starting these women on thyroxine treatment during pregnancy, although data from randomised studies are needed to provide firmer evidence of benefit.³²

Levo-thyroxine is the drug of choice for thyroid replacement therapy. Emerging data from the last decade have confirmed that hypothyroid pregnant women who are already on thyroxine replacement actually require an upward adjustment of their daily thyroxine dosages in order to maintain euthyroidism. Studies by Mandel et al³³ and Kaplan³⁴ showed that the serum TSH of pregnant women who were already on thyroxine tended to rise if their thyroxine dosages remained unchanged during pregnancy, indicating under-treatment. The increase in requirement stems from the increase in serum TBG concentration as well as increased placental production of Type III deiodinases.^{2,10} Generally, an increment of 40% to 50% in dosage is required, although there is a great deal of inter-individual variation. As the increased need for T4 is already apparent in the first trimester, it is recommended that the dose adjustment be implemented in the early stages of pregnancy in order to avoid the potential problems of hypothyroidism.⁶ After delivery, thyroxine may be readjusted back to the pre-pregnancy dose.

Postpartum Thyroid Dysfunction

Postpartum thyroid dysfunction occurs within the first year after delivery and it also includes both hyper- and hypofunction. Hyperthyroidism in the postpartum period may be due to postpartum thyroiditis (PPT) or Graves' disease—either a relapse or a fresh case. PPT, the commonest cause of postpartum thyroid dysfunction, may also account for postpartum hypothyroidism although other possibilities include hypopituitarism due to Sheehan's syndrome as well as lymphocytic hypophysitis.²

PPT, which is a specific entity caused by destructive autoimmune thyroiditis affecting 3.7% to 5.9% of women in the first postpartum year,³⁵ is typically triphasic—being characterised by a brief hyperthyroid phase occurring within the first 3 months postpartum, followed by a transient hypothyroid phase 3 to 8 months postpartum after which full recovery is to be expected in more than 80% of patients 12 months after delivery.^{2,36} As the symptoms of PPT may be mild or non-specific, a high index of suspicion is required in any postpartum woman who presents with palpitations, fatigue or depression, with or without a goitre. The radionuclide thyroid scan is useful in differentiating between toxic Graves' disease from the hyperthyroid phase of PPT, as uptake is characteristically low in the latter. Apart from symptomatic treatment with β -blockers, there is no role for the usage of anti-thyroid drugs during the hyperthyroid phase of PPT as the condition is secondary to the leakage of pre-formed thyroid hormone from the damaged gland. Similarly, the usually mild and transient nature of the hypothyroid phase does not necessitate any thyroxine replacement.

About 25% to 30% of women with PPT go on to develop permanent hypothyroidism 3 to 5 years after delivery.³⁷ In a prospective, case-controlled study comparing 98 TPOAb-positive pregnant women (of whom 48 developed PPT and 50 without) against 70 TPOAb-negative women who were followed-up for 77 months, the risk factors which were identified to be predictive of future thyroid dysfunction included a hypothyroid form of PPT, TSH greater than 20 mU/L and high TPOAb levels. Women with hypothyroid PPT, high TPOAb and a hypoechogenic ultrasound pattern carried a relative risk of 32 for developing long-term hypothyroidism, compared with a relative risk of 12.9 for TPOAb-positive and PPT-positive women who remained euthyroid at the end of the first postpartum year, and 2.8 for TPOAb-positive but PPT-negative women.³⁷ Opinion is still divided as to whether or not pregnant women ought to be screened for PPT as its benefits and cost-effectiveness are not immediately clear.³⁸ Nevertheless, long-term surveillance of women who had PPT and who are TPOAb-positive is recommended. Serum TSH values should be monitored at yearly intervals or sooner if they become pregnant again or develop symptoms of thyroid dysfunction.²

Thyroid Nodules in Pregnancy

The incidence of thyroid nodules discovered during pregnancy is estimated to be about 10%, compared to a population incidence of between 4% and 7%.^{39,40} These may have been present before pregnancy—hitherto undiscovered—or arise only after its onset. It has been suggested that reproductive hormones as well as iodine

deficiency may contribute to the development of thyroid nodules in pregnancy, although evidence is lacking.^{40,41} The chief concern would be to exclude malignancy, where prevalence rates of 30% to 40% have been reported in pregnant women presenting with thyroid nodules, and to ascertain the thyroid status.^{42,43} It is not, however, clear if these high prevalence rates in fact represent skewed populations. While malignancy is less likely in the setting of hyperthyroidism, the likelihood is greater in patients with a history of neck irradiation, a family history of thyroid cancer, rapidly enlarging nodules or hoarseness of voice. To date, there is no evidence of pregnancy having any significant impact on the development of thyroid malignancy.³⁹

The diagnostic approach is similar to that in non-pregnant women, with the exception that radionuclide studies are contraindicated. Fine needle aspiration cytology (FNAC) remains the diagnostic tool of choice. If performed properly, this procedure is generally safe, well tolerated, inexpensive and reliable in the hands of experienced personnel. The concern that FNAC may suggest a follicular neoplasm because of generalised increase in follicular epithelium caused by pregnancy-induced follicular hyperplasia, when no distinct adenoma is present, has not been supported by clinical studies. In a review of 40 patients where the FNAC findings were compared with corresponding histology, those that were diagnosed to have follicular neoplasm on FNAC were indeed confirmed to be follicular adenomas on histology.⁴⁰ In another series of 97 FNAC findings from 57 pregnant women, Marley and Oertel⁴⁴ did not find any distinct cytologic features indicative or associated with pregnancy. Compared to FNAC, ultrasonography is less useful as it can neither diagnose nor exclude thyroid malignancy.

It is preferable to perform surgery for benign nodules as well as those with low malignant potential, such as Hurthle cell lesions, after the patient has delivered so as to avoid unnecessary surgical risks to the foetus. On the other hand, surgery for malignant nodules, or those that are suspicious of malignancy, may be safely carried out during the second trimester. However, it will be necessary to delay postoperative radionuclide scans and ablative therapy until after delivery.

Thyroid Antibodies and Foetal Loss

The last decade has seen increasing interest amongst investigators concerning the possible association between thyroid autoimmunity and recurrent abortion, defined as three or more consecutive spontaneous miscarriages, in euthyroid women. Initial reports by Stagnaro-Green et al⁴⁵ and Glinioer et al⁴⁶ pointed to a strong correlation between the presence of thyroid antibodies—TPOAb, TgAb or

both—and first trimester pregnancy loss. Since then, several studies have shown that the incidence of thyroid antibodies in euthyroid women with habitual abortions are significantly higher compared to matched controls without previous abortions.⁴⁷⁻⁴⁹ Of particular interest is the study by Pratt et al.⁴⁷ which enrolled 42 euthyroid women with a history of recurrent abortions who were planning to conceive again, where the detection of thyroid antibodies before conception carried an increased risk of pregnancy loss in the next pregnancy (64% versus 14%). On the other hand, another study involving 74 subjects, with corresponding controls, failed to demonstrate an association between thyroid autoimmunity and pregnancy loss.⁵⁰ The mechanism underlying such an association, if any, is unclear. Several hypotheses have been offered, including “mild thyroid hypofunction” as well as abnormal T-lymphocyte function, where thyroid antibodies may represent a marker of impaired maternal immune system regulation.

Conclusion

The physiological changes of pregnancy may affect the interpretation of thyroid function tests in these women. It is important to determine whether hyperthyroidism in pregnant women is pregnancy-related or due to Graves' disease as this has important therapeutic implications. In hypothyroidism, clinicians must recognise the need to step up thyroxine replacement during pregnancy. Regardless of the underlying cause of thyroid dysfunction, individualised therapy coupled with close monitoring of patients, in collaboration with their obstetricians, are essential in order to avoid over- or under-treatment and to minimise both maternal and foetal complications.

REFERENCES

- Glinoe D. What happens to the normal thyroid during pregnancy? *Thyroid* 1999; 9:631-5.
- Frantz C R, Dagogo-Jack S, Ladenson J H, Gronowski A M. Thyroid function during pregnancy. *Clin Chem* 1999; 45:2250-8.
- Nelson J C, Weiss R M, Wilcox R B. Underestimates of serum free thyroxine (T4) concentrations by free T4 immunoassays. *J Clin Endocrinol Metab* 1994; 79:76-9.
- Yeo C P, Khoo D H C, Eng P H K, Tan H K, Yo S L, Jacob E. Prevalence of gestational thyrotoxicosis in Asian women evaluated in the 8th-14th weeks of pregnancy—correlations with total and free beta human chorionic gonadotrophin. *Clin Endocrinol* 2001; 55:391-8.
- Kraiem Z, Sadeh O, Blithe D L, Nisula B C. Human chorionic gonadotropin stimulates thyroid hormone secretion, iodide uptake, organification, and adenosine 3',5'-monophosphate formation in cultured human thyrocytes. *J Clin Endocrinol Metab* 1994; 79:595-9.
- Glinoe D. The regulation of thyroid function in pregnancy: Pathways of endocrine adaptation from physiology to pathology. *Endocr Rev* 1997; 18:404-33.
- Hoermann R, Broecker M, Grossman M, Mann K, Derwahl M. Interaction of human chorionic gonadotropin (hCG) and asialo-hCG with recombinant human thyrotropin receptor. *J Clin Endocrinol Metab* 1994; 78:933-8.
- Jordan V, Grebe S K, Cooke R R, Ford H C, Larsen P D, Stone P R, et al. Acidic isoforms of chorionic gonadotropin in European and Samoan women are associated with hyperemesis gravidarum and may be thyrotrophic. *Clin Endocrinol (Oxf)* 1999; 50:619-27.
- Ball R, Freedman D B, Holmes J C, Midgley J E M, Sheehan C P. Low-normal concentrations of free thyroxine in serum in late pregnancy: Physiological fact, not technical artefact. *Clin Chem* 1989; 35:1891-6.
- Mestman J, Goodwin T M, Montoro M M. Thyroid disorders of pregnancy. *Endocrinol Metab Clin North Am* 1995; 24:41-71.
- Costagliola S, Morgenthaler N G, Hoermann R, Badenhop K, Struck J, Freitag D, et al. Second generation assay for thyrotropin receptor antibodies has superior diagnostic sensitivity for Graves' disease. *J Clin Endocrinol Metab* 1999; 84:90-7.
- Goodwin T M, Montoro M, Mestman J H. Transient hyperthyroidism and hyperemesis gravidarum: Clinical aspects. *Am J Obstet Gynecol* 1992; 167:648-52.
- Price A, Davies R, Heller S R, Milford-Ward A, Weetman A P. Asian women are at increased risk of gestational thyrotoxicosis. *J Clin Endocrinol Metab* 1996; 81:1160-3.
- Jordan V, MacDonald J, Crichton S, Stone P, Ford H. The incidence of hyperemesis gravidarum is increased among Pacific Islanders living in Wellington. *N Z Med J* 1995; 108:342-4.
- Vangen S, Stoltenberg C, Stray-Pedersen B. Complaints and complications in pregnancy: a study of ethnic Norwegian and ethnic Pakistani women in Oslo. *Ethn Health* 1999; 4:19-28.
- Rodien P, Bremont C, Sanson M L, Parma J, van Sande J, Costagliola S, et al. Familial gestational hyperthyroidism caused by a mutant thyrotropin receptor hypersensitive to human chorionic gonadotropin. *N Engl J Med* 1998; 339:1823-6.
- Wing D A, Millar L K, Koonings P P, Montoro M N, Mestman J H. A comparison of propylthiouracil versus methimazole in the treatment of hyperthyroidism in pregnancy. *Am J Obstet Gynecol* 1994; 170:90-5.
- Mandel S J, Brent G A, Larsen P R. Review of antithyroid drug use in pregnancy and report of a case of aplasia cutis. *Thyroid* 1994; 4:129-33.
- Dutertre J P, Jonville A P, Moraine C, Autret E. Aplasia cutis after exposure to carbimazole in utero. *J Gynecol Obstet Biol Reprod (Paris)* 1991; 20:865-6.
- Momotani N, Yoshimura J, Ishikawa N, Ito K. Effects of propylthiouracil and methimazole on foetal thyroid status in mothers with Graves' hyperthyroidism. *J Clin Endocrinol Metab* 1997; 82:3633-6.
- Mestman J H. Hyperthyroidism in pregnancy. *Endocrinol Metab Clin North Am* 1998; 27:127-47.
- Momotani N, Ito K, Hamada N, Ban Y, Nishikawa Y, Mimura T. Maternal hyperthyroidism and congenital malformation in the offspring. *Clin Endocrinol* 1984; 20:695-700.
- Laurberg P, Nygaard B, Glinoe D, Grussendorf M, Orgiazzi J. Guidelines for TSH-receptor antibody measurements in pregnancy: results of an evidence-based symposium organised by the European Thyroid Association. *Eur J Endocrinol* 1998; 139:584-6.
- Formby B. Immunologic response in pregnancy: its role in endocrine disorders of pregnancy and influence on the course of maternal autoimmune diseases. *Endocrinol Metab Clin North Am* 1995; 24:187-205.
- Kung A W C, Jones B M. A change from stimulatory to blocking antibody activity in Graves' disease during pregnancy. *J Clin Endocrinol Metab* 1998; 83:514-8.
- Sherif I H, Oyan W T, Bosairi S, Carrascal S M. Treatment of hyperthyroidism in pregnancy. *Acta Obstet Gynecol Scand* 1991; 70:461-3.
- Scumberger M, De Vathaire F, Ceccarelli C, Delisle M J, Francese C,

- Couette J E, et al. Exposure to radioactive iodine-131 for scintigraphy or therapy does not preclude pregnancy in thyroid cancer patients. *J Nucl Med* 1996; 37:606-12.
28. Buckshee K, Kriplani A, Kapil A, Bhargava V L, Takkar D. Hypothyroidism complicating pregnancy. *Aust N Z J Obstet Gynecol* 1992; 32:240-2.
 29. Klein R Z, Haddow J E, Faix J D, Brown R S, Hermos R J, Pulkkinen A, et al. Prevalence of thyroid deficiency in pregnant women. *Clin Endocrinol (Oxf)* 1991; 35:41-6.
 30. Leung A S, Millar L K, Koonings P P, Montoro M N, Mestman J H. Perinatal outcome in hypothyroid pregnancies. *Obstet Gynecol* 1993; 81:349-53.
 31. Haddow J E, Palomaki G E, Allan W C, Williams J R, Knight G J, Gagnon J, et al. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. *N Engl J Med* 1999; 341:549-55.
 32. Glinioer D, Rihai M, Grun J P, Kinthaert J. Risk of subclinical hypothyroidism in pregnant women with asymptomatic autoimmune thyroid disorders. *J Clin Endocrinol Metab* 1994; 79:197-204.
 33. Mandel S J, Larsen P R, Seely E W, Brent G A. Increased need for thyroxine during pregnancy in women with primary hypothyroidism. *N Engl J Med* 1990; 323:91-6.
 34. Kaplan M M. Monitoring thyroxine treatment during pregnancy. *Thyroid* 1992; 2:147-52.
 35. Gerstein H C. How common is postpartum thyroiditis? *Arch Intern Med* 1990; 150:1387-400.
 36. Lervang H H, Pryds O, Kristensen H P. Thyroid dysfunction after delivery: incidence and clinical course. *Acta Med Scand* 1987; 222: 369-74.
 37. Premawardhana L D K E, Parkes A B, Ammari F, John R, Darke C, Adams H, et al. Postpartum thyroiditis and long-term thyroid status: Prognostic influence of thyroid peroxidase antibodies and ultrasound echogenicity. *J Clin Endocrinol Metab* 2000; 85:71-5.
 38. Amino N, Tada H, Hidaka Y, Crapo L M, Stagnaro-Green A. Screening for postpartum thyroiditis. *J Clin Endocrinol Metab* 1999; 84:1813-21.
 39. Lazarus J H, Kokandi A. Thyroid disease in relation to pregnancy: A decade of change. *Clin Endocrinol* 2000; 53:265-78.
 40. Tan G H, Gharib H, Goellner J R, van Heerden J A, Bahn R S. Management of thyroid nodules in pregnancy. *Arch Intern Med* 1996; 156:2317-20.
 41. Struve C W, Haupt S, Ohlen S. Influence of frequency of previous pregnancies on the prevalence of thyroid nodules in women without clinical evidence of thyroid disease. *Thyroid* 1993; 3:7-9.
 42. Doherty C M, Shindo M L, Rice D H, Montero M, Mestman J H. Management of thyroid nodules during pregnancy. *Laryngoscope* 1995; 105:251-5.
 43. Hay I. Nodular thyroid disease diagnosed during pregnancy: How and when to treat. *Thyroid* 1999; 9:667-70.
 44. Marley E F, Oertel Y C. Fine-needle aspiration of thyroid lesions in 57 pregnant and postpartum women. *Diagn Cytopathol* 1997; 16: 122-5.
 45. Stagnaro-Green A, Roman S H, Cobin R H, El-Harazy E, Alvary Marfany M, Davies T F. Detection of at-risk pregnancy by means of a highly sensitive assay for thyroid antibodies. *JAMA* 1990; 264:1422-5.
 46. Glinioer D, Soto M F, Bourdoux P, Lejeune B, Delange F, Lemone M, et al. Pregnancy in patients with mild thyroid abnormalities: maternal and neonatal repercussions. *J Clin Endocrinol Metab* 1991; 73:421-7.
 47. Pratt D E, Kaberlein G, Dudkiewicz A, Karande V, Gleicher N. The association of antithyroid antibodies in euthyroid nonpregnant women with recurrent first trimester abortions in the next pregnancy. *Fertil Steril* 1993; 60:1001-5.
 48. Bussen S, Steck T. Thyroid autoantibodies in euthyroid non-pregnant women with recurrent spontaneous abortions. *Hum Reprod* 1995; 10:2938-40.
 49. Dendrinis S, Papasteriades C, Tarassi K, Christodoulakos G, Prasinos G, Creatsas G. Thyroid autoimmunity in patients with recurrent spontaneous miscarriages. *Gynecol Endocrinol* 2000; 14:270-4.
 50. Esplin S M, Branch W D, Silver R, Stagnaro-Green A. Thyroid autoantibodies are not associated with recurrent pregnancy loss. *Am J Obstet Gynecol* 1998; 179:1583-6.