Epidemiology and Prevention of Thyroid Disease in Pregnancy

John H. Lazarus

Pregnancy has variable effects on thyroid hormone concentrations throughout pregnancy as well as being associated with goiter. The latter is largely preventable by ensuring optimal iodine intake of at least 200 μg/d. Immunologic changes in pregnancy include a so-called TH2 shift that reverts to TH1 status around birth or early in the postpartum period. Hyperthyroidism during gestation, usually caused by Graves’ disease, is rare (0.2%) and is best managed medically with propylthiouracil; thyroid-stimulating antibodies should be measured. Prevention of the deleterious effects of Graves’ disease includes adequate preconception advice, adequate monitoring during pregnancy, and total avoidance of 131I therapy during pregnancy. Hypothyroidism during pregnancy has an incidence of 2.5% although there is a 10% incidence of thyroid peroxidase (TPO)-antibody positivity in early gestation. There are convincing epidemiologic data to show that suboptimal thyroid function in pregnancy is associated with impaired neurointellectual development (e.g., 19% with IQ < 85 compared to 5% in one study). Therefore, there is a case for screening for thyroid function in early pregnancy with thyroxine (T4) intervention therapy. Maintenance of optimal iodine intake is critical to prevent nonautoimmune gestational maternal hypothyroxinaemia. Postpartum thyroid dysfunction (PPTD) occurs in 5%–9% of women and in up to 50% of TPO-antibody positive women (as ascertained in early pregnancy). Prevention of PPTD at this time could only be achieved by pregestational ablation of the thyroid. Another approach is to at least improve the prediction of postpartum thyroid disease (PPT) because the TPO antibody has a sensitivity of only 50%.

Introduction

Evaluation of thyroid disease in pregnancy is important for gestational maternal health, obstetric outcome, and subsequent development of the child. This review will concentrate on epidemiological aspects which will document the high incidence of some thyroid abnormalities in pregnancy. It is often stated that the best treatment of disease is prevention. Our understanding of the pathogenesis of autoimmune thyroid disease has not allowed us to achieve this goal. However, strategies involving screening of pregnant women may be valuable and these will be discussed.

Thyroid Function During Pregnancy

Pregnancy has an appreciable effect on thyroid economy (1,2). There are significant changes in iodine metabolism characterized by increased excretion of iodine in the urine accounting for the increase in thyroid volume even in areas of moderate dietary iodine intake. Although thyroid size increases in areas of iodine deficiency it does not do so in those regions that are iodine sufficient (3). Iodine deficiency during pregnancy is associated with maternal goiter and reduced maternal thyroxine (T4) level (4). Even in moderate iodine-deficient regions, urinary iodine excretion is higher in all trimesters than in nonpregnant women and may be causative in maternal goiter formation as assessed by ultrasound. In iodine-deficient areas (including marginal iodine deficiency seen in many European countries) the pregnant woman may become significantly hypothyroxinaemic with preferential triiodothyronine (T3) secretion. The thyroidal stress is also evidenced by an increase in the median thyrotropin (TSH) and serum thyroglobulin. Gestational goitrogenesis is preventable by iodine supplementation not only in areas of severe iodine deficiency (24-hour urinary iodine less than 50 μg) but in areas such as Belgium and Denmark where trials have shown clear beneficial effects on maternal thyroid size (5). The goal of these studies was to increase the iodine supply to pregnant and lactating women to at least 200 μg/d.

Immunology of Normal Pregnancy

Pregnancy has a profound effect on the immune system, in order to maintain the fetal-maternal allograft, which is not rejected despite displaying paternal histocompatibility antigens (6). While there is no overall immunosuppression during pregnancy, dramatic clinical improvement usually occurs in patients with immunologic disorders such as...
rheumatoid arthritis (RA) when they become pregnant. Clinical improvement occurs as well in psoriatic arthritis and Graves’ disease. On the other hand, systemic lupus erythematosus (SLE) may flare during pregnancy. Although the distinction between T<sub>H1</sub> and T<sub>H2</sub> responses in humans remains less clear than in mice the general agreement is that in pregnancy there is a bias toward a T<sub>H2</sub> response. This seems to be achieved by the fetal/placental unit producing T<sub>H2</sub> cytokines, which inhibit T<sub>H1</sub>. T<sub>H1</sub> cytokines are potentially harmful to the fetus because interferon-α (IFN-α) is a known abortifacient.

Hyperthyroidism in Pregnancy

Hyperthyroidism in pregnancy occurs in up to 0.2% of women and is mostly caused by Graves’ disease (7,8). Maternal complications include miscarriage, abruptio placenta, and preterm delivery. Congestive heart failure and thyroid storm may also occur and the risk of preeclampsia is significantly higher in women with poorly controlled hyperthyroidism.

Neonatal hyperthyroidism, prematurity, and intrauterine growth retardation may be observed. A retrospective survey documented a 5.6% incidence of fetal death or stillbirth in 249 pregnancies from hyperthyroid mothers and a further 5% of fetal and neonatal abnormalities. Gestational amelioration of Graves’ disease is often associated with a reduction in titer of TSH-receptor antibody and a change from stimulatory to blocking antibody activity. TSH-blocking antibodies have been shown to cause maternal hyperthyroidism, which developed during gestation. In addition thyroid-stimulating antibody (TSAb) can cross the placenta and be shown to be present in the fetus by cordocentesis.

Prevention of Deleterious Effects of Graves’ Disease on Maternal, Fetal, and Neonatal Status

Preconception

There is a good theoretical case for a preconception clinic for patients with Graves’ hyperthyroidism who wish to become pregnant. First, education about the effects of the disease on maternal health and fetal well-being can be given to allay fears that are commonly present in these women. The patient’s thyroid status should be checked frequently to minimize risk of miscarriage should the patient be hyperthyroid at the time of conception. At present there are no studies documenting the outcome of the strategy of a preconception clinic. If treatment had been commenced with methimazole or carbimazole a change to propylthiouracil (PTU) may be considered to reduce the admittedly rare occurrence of aplasia cutis reported after the administration of the former drugs although this is disputed.

Previously treated patients with Graves’ disease

These patients may have received antithyroid drugs, surgery, or radioiodine therapy and be euthyroid or hypothyroid on or off thyroxine therapy. The important concern here is that neonatal hyperthyroidism may still occur. Recent guidelines (Table 1) (9) state that if previous antithyroid drugs have been used there is no need to measure TSH-receptor antibodies because the maternal thyroid function provides a reliable estimate of fetal thyroid status and the risk of neonatal hyperthyroidism is low. TSH-receptor antibodies should be measured in a euthyroid pregnant woman previously treated by either of the other modalities early in pregnancy. If the level is high at this time the fetus should be evaluated carefully during gestation and the antibodies measured again in the last trimester.

Graves’ hyperthyroidism inadvertently treated with radioiodine in early gestation

In many clinics routine pregnancy testing is not performed before 131I administration. This simple test would have important preventive implications in relation to 131I administration.

Despite denial of pregnancy several reports of inappropriate radioiodine administration have highlighted the concern about the fetal radiation risk (10). Administration of up to 15 mCi (555 MBq) 131I for hyperthyroidism up to 10 weeks’ gestation does not compromise fetal thyroid function and the low fetal whole-body irradiation is not considered sufficient to justify termination of pregnancy although this is often per-

<table>
<thead>
<tr>
<th>Patient status</th>
<th>Measurement</th>
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<tbody>
<tr>
<td>1. Euthyroid—previous ATD only</td>
<td>Not necessary</td>
</tr>
<tr>
<td>2. Euthyroid/hypothyroid +/- T&lt;sub&gt;4&lt;/sub&gt; therapy previous 131I/surgery</td>
<td>Check in early pregnancy: if low or absent, no further testing if high, check fetus and check antibodies in last trimester&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>3. Receiving ATD during pregnancy</td>
<td>Measure in last trimester</td>
</tr>
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<sup>a</sup>TSH-receptor antibody assay normally measured by competitive inhibition (i.e., not indicating whether the antibodies are stimulating the thyroid)

<sup>b</sup>High ≥40 U/L.

TSH, thyrotropin; ATD, antithyroid drugs; T<sub>4</sub>, thyroxine.
formed. Limited clinical data suggests that $^{131}$I given after 10 to 12 weeks results in biochemical hypothyroidism and even cretinism in the neonate. In these circumstances termination of pregnancy may be advised but dosimetry studies should be performed (11). The neonate should be evaluated at birth specifically for hypothyroidism and for malformations, which are more common with higher doses of radiation.

Patients found to have hyperthyroidism during pregnancy

Medical therapy is preferred by most clinicians because radioiodine is contraindicated and surgery requires pre-treatment with antithyroid drugs to render the patient euthyroid (Table 2). PTU should be given in a dose of 100 to 150 mg three times daily until the patient becomes euthyroid, at which time the dose should be reduced to the lowest amount to maintain the euthyroid state with serum $T_4$ at the upper end of normal and possibly continued up to and through labor if necessary (13). The so-called “block and replace” regime in which $T_4$ is given with antithyroid drug should be used with caution because the dose of antithyroid drug might be too high and cause fetal goiter and hypothyroidism. It has been reported that $T_4$ administration to pregnant women with Graves’ hyperthyroidism during pregnancy and after delivery, together with methimazole, was effective in reducing the incidence of postpartum recurrence of hyperthyroidism (vide infra) (14) but these results have not been confirmed. PTU has a shorter half-life than methimazole and is not present in as high a concentration in breast milk. Hence, women receiving PTU can breastfeed without significant risk to the neonate.

There is no significant effect of antithyroid drugs in utero on the long-term health of the neonate or child assuming the dose during gestation does not cause iatrogenic fetal hypothyroidism. $\beta$-Adrenergic blocking agents such as propranolol may be used for a few weeks to ameliorate the peripheral sympathomimetic actions of excess thyroid hormone but prolonged use can result in retarded fetal growth, impaired response to anoxic stress together with postnatal bradycardia and hypoglycemia. These drugs will need to be used in the uncommon instance of intolerance to both of the available thionamide drugs.

Subtotal thyroidectomy is indicated if control of the hyperthyroidism is poor on account of poor compliance or inability to take drugs. Patients with a large goiter may also require surgery because of pressure symptoms. Surgery is preferred in the second trimester because there is a higher risk of associated abortion at an earlier stage of gestation. In general, surgery should be avoided if it is considered that medical therapy has a reasonable chance of success.

Hypothyroidism in Pregnancy

The incidence of hypothyroidism during pregnancy is approximately 2.5%. Most patients are asymptomatic but have been found to have a high TSH on screening. Previous studies have documented the deleterious effects of hypothyroidism on maternal and fetal well-being, drawing attention to increased incidence of abortion, obstetric complications, and fetal abnormalities in untreated women. Women already receiving $T_4$ for hypothyroidism require an increased dose during gestation. This is critical to ensure adequate maternal $T_4$ levels for delivery to the fetus especially during the first trimester. The dose should normally be increased by 50 to 100 $\mu g$/d.

Maternal Thyroid Disease in Pregnancy: Effect on Child Development

Recent work has raised concern that in an iodine-sufficient area maternal thyroid dysfunction (hypothyroidism or subclinical hypothyroidism) during pregnancy results in neurointellectual impairment of the child. Studies have shown that low thyroid hormone concentrations in early gestation can be associated with significant decrements of IQ of the children when tested at 7 years and 10 months, respectively (15,16). A significant decrement in IQ in children 5 years of age whose mothers were known to have circulating anti-TPO antibodies at 32 weeks’ gestation and were biochemically euthyroid has also been shown (17). Moreover, the 7-year-old children of hypothyroid women retrospectively diagnosed by noting high TSH concentrations in second trimester sera, also showed impaired psychological development compared to carefully matched control children. The neurodevelopmental impairment is similar to that seen in iodine-deficient areas and implies that iodine status should be normalized in regions of deficiency. However, much of the United States and parts of Europe are not iodine deficient that raises the

<table>
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<th>Table 2. Management of Graves’ Hyperthyroidism in Pregnancy</th>
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<tr>
<td>Confirm diagnosis</td>
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<tr>
<td>Start propylthiouracil</td>
</tr>
<tr>
<td>Render patient euthyroid—continue with low-dose ATD up to and during labor</td>
</tr>
<tr>
<td>Monitor thyroid function regularly throughout gestation (4–6 times per week)—adjust ATD if necessary to maintain $T_4$ at upper level of normal</td>
</tr>
<tr>
<td>Check TSAb at 36 weeks</td>
</tr>
<tr>
<td>Discuss treatment with patient</td>
</tr>
<tr>
<td>—effect on patient</td>
</tr>
<tr>
<td>—effect on fetus</td>
</tr>
<tr>
<td>—breast feeding</td>
</tr>
<tr>
<td>Inform obstetrician and pediatric</td>
</tr>
<tr>
<td>Review postpartum—check for exacerbation</td>
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</tbody>
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ATD, antithyroid drugs; $T_4$, thyroxine; TSAb, thyroid-stimulating antibodies.

<table>
<thead>
<tr>
<th>Table 3. Intervention Strategies to Reduce T-Helper Subset in Graves’ Disease</th>
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<tbody>
<tr>
<td>Generalized immune diversion away from $T_{H1}$ cells</td>
</tr>
<tr>
<td>Administration of IL-4, IL-10, or both</td>
</tr>
<tr>
<td>Agents against interferon- $\gamma$ or IL-12 (cytokine antagonists)</td>
</tr>
<tr>
<td>Use of $T_{H2}$-inducing compounds</td>
</tr>
<tr>
<td>Autoantigen-specific immune diversion away from $T_{H1}$ cells</td>
</tr>
<tr>
<td>Immunization without autoantigens in presence of IL4—oraly</td>
</tr>
<tr>
<td>—injection</td>
</tr>
<tr>
<td>Administration of peptide analogues of autoantigens</td>
</tr>
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Adapted from Liblau et al. (21).
IL, interleukin.
question of routine screening of thyroid function during early pregnancy or even at preconception. Another reason for screening could be to focus on the risk for postpartum thyroiditis. The following numerical issues should be considered in relation to such a strategy: the incidence of an elevated TSH in pregnancy is approximately 2.5%; the prevalence of anti-TPO antibodies is 10% as ascertained at a routine antenatal booking clinic; the incidence of thyroid dysfunction observed in anti-TPO positive pregnancies is up to 15%. Although these numbers are impressive, the question as to whether there is any effective intervention must be addressed. To date, there are no randomized trials examining, for example, the effect of T₄ intervention therapy given to susceptible women on subsequent child development. These considerations emphasize that it is important to ensure an adequate thyroid hormone supply to the developing fetus in all areas of the world whether iodine deficient or not. An adequate iodine intake (200 µg/d) is mandatory. In addition, pregnant hypothyroid women need to optimize their replacement T₄ therapy by increasing the dose by 50 to 100 µg daily. Further studies in this area are required to answer questions relating to thyroid function screening before and during pregnancy.

Postpartum Thyroid Disease

It is known that autoimmune thyroid disease may be exacerbated postpartum (18). The totality of this is characterized by Graves’ disease (approximately 10%), postpartum thyroiditis (PPT) with hyperthyroidism (25%), PPT with hyperthyroidism/hypothyroidism (20%), and PPT with hypothyroidism (45%) (19).

Prevention of Postpartum Graves’ Disease

Graves’ disease is an autoimmune disorder that involves the cellular and humoral arms of the immune system. Because the details of the disease process are incompletely understood it is difficult to provide any rational immunologically based therapy, which makes preventative strategies even more elusive. However, because it is possible to ablate the thyroid with radiiodine therapy it has been suggested that this treatment is appropriate to prevent any further episode of the disease occurring during pregnancy or presumably in the postpartum period (20). T₁₉₁ cells are central to the pathogenesis of organ specific autoimmune disease, while T₁₉₂ cells may be protective (21). Whether clonal diversification might have therapeutic implications, as has been proposed for other diseases (Table 3) remains to be tested.

While some of these maneuvers have been successfully carried out in mice, their feasibility in humans is still remote. Furthermore such treatment is effective only when administered at the time of priming. Extended treatment may be required and the promotion of a T₁₉₂ response may result in decreased immunity against intracellular organisms and may also predispose to allergic reactions. In addition, it will be very difficult to contemplate such therapy during gestation on account of safety considerations (22).

Postpartum Thyroid Disease

A variable incidence (from 3%–17%) has been reported worldwide because of wide variations in the number of women studied, the frequency of thyroid assessment post-partum, diagnostic criteria used, and differences in hormone assay methodology. However, there is a general consensus that the disease occurs in 5%–9% of unselected postpartum women. Women with type 1 diabetes have a threefold incidence of PPT compared to those without diabetes and in these cases there is a strong association with thyroid antibodies. The presence of TPO antibodies in early gestation has a high specificity (95%) but only a moderate sensitivity (50%). PPTD is also more likely to occur in a woman who has had a previous episode (23).

PPTD is characterized by the development of transient hyperthyroidism and/or hypothyroidism or both during the first 6 months of the postpartum period. Hypothyroidism is permanent in up to 25%–30% of women. The transient hyperthyroidism presents at about 14 weeks’ postpartum followed by transient hypothyroidism at a median of 19 weeks but may occur as late as 36 to 40 weeks (24). Occasionally the hypothyroid state is seen before the hyperthyroidism. PPTD occurs in 50% of thyroid peroxidase (TPO)-antibody–positive women (isolated anti-thyroglobulin-antibody occurs in only approximately 5%) of whom 19% are hyperthyroid alone, 49% hypothyroid alone, and the remaining 32% hyperthyroidism followed by hypothyroidism.

An increase of mild to moderate depression in antibody-positive women irrespective of thyroid status has been confirmed (30% in TPO-antibody–positive women independent of thyroid status compared to 20% in control antibody-negative women). A randomized double-blind placebo-controlled trial designed to attempt to prevent depressive symptomatology in anti-TPO-antibody positive women by administration of 0.1 mg T₄ for 18 weeks postpartum was unsuccessful (25).

The prevention of PPT is not possible but the prediction and therefore the early recognition of the syndrome is certainly feasible. As mentioned, TPO antibody presence in early gestation is the best marker but with only a 50% predictive value. Nevertheless, screening for TPO antibodies at 12 weeks’ gestation has been proposed (26) although the cost benefit is debated (27). It is possible that the predictive power of TPO antibodies could be improved if serum thyroglobulin, thyroid ultrasound morphology, and TPO-mediated complement activity were to be measured at 6 weeks postpartum but these data are not yet available.

Preventive Screening for Thyroid Disorder During Gestation

Consideration of the relatively high incidence of gestational hypothyroidism with its deleterious consequences for mother and neonate together with the high prevalence of thyroid antibodies in early pregnancy suggests that screening may be beneficial. As with the development of screening strategies for neonatal hypothyroidism over the last 30 years the precise testing schedule may vary. Further support will come from carefully performed randomized outcome studies in addition to a reduction in laboratory costs for high-volume automated assays and, significantly, from patient demand.

References


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