A REVIEW OF THYROID DISEASE IN PREGNANCY

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SUMMARY

Goitre is common and alterations in biochemical indices of thyroid function are invariable during pregannecy, but thyroid disease, of which hyperthyroidism is the most frequent (0,05% of 72,257 pregnancies at three Dublin Maternity Hospitals, 1979-81) is rare. Good results in terms of perinatal loss (4/112, 3.57%) has been achieved by one of us (MID) in 109 pregnancies using antithyroid drugs alone.

Neonatal thyrotoxicosis occurs in one to two percent of babies born to mothers with thyroid disease. The condition is usually transient but a prolonged course may occur in up to 20 percent.

Successful pregnancy is possible despite maternal hypothyroidism; three such pregnancies have been managed by one of us (MID).

Clinical hyperthyroidism due to trophoblastic disease is very rare and is cured by evacuation of molar tissue.

The course of thyroid cancer is not affected by pregnancy.

SYNOPSIS

The diagnosis and rational treatment of thyroid disease during pregnancy is based on a comprehensive knowledge of feto-maternal thyroid physiology. A critical review of thyroid disease in pregnancy which incorporates the personal experience of one of the authors is presented.

INTRODUCTION

During the past twenty years many advances were made in elucidating the complex changes in human feto-maternal thyroid physiology which make it difficult to assess thyroid function during pregnancy. Diagnosis of thyroid dysfunction at this time is especially important because of the risk of undiagnosed disease to mother and foetus. The mode of treatment is similarly complicated by foetal considerations. Despite these rapid advances in our understanding of thyroid physiology in the pregnant mother, foetus and new born, there are several important questions which remain unanswered. This review focuses on current knowledge of thyroid pathophysiology during pregnancy. The rational diagnosis and treatment of thyroid disorders based on this knowledge is discussed and the clinical experience of one of us (MID) is presented.

FETO-MATERNAL THYROID PHYSIOLOGY

Although the occurrence of thyroid enlargement during pregnancy has been known since antiquity, the aetiology is uncertain. Radioiodine uptake is increased during pregnancy ([1]) and the histological evidence of large follicles filled with colloid suggests active formation and secretion of thyroid hormone ([2]). Thyroid enlargement is associated with low levels of plasma inorganic iodide, a two-fold increase in renal clearance of iodide and a three-fold increase in thyroidal iodine

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clearance [3]. Relative iodine deficiency may act as a stimulus to growth of the thyroid gland. The goitrogenic action of placental thyrotropins is speculative. As criteria for the detection of goitre are subjective, the exact prevalence of pregnancy goitre is uncertain. Using subjective, but reproducible criteria it was noted that 74% of pregnant women in North-East Scotland had goitre [4]. A comparative study in an area of low iodine intake showed that the prevalence of goitre was no greater in pregnant women than in non-pregnant controls (20%) [5]. Using the same criteria, we found a goitre in 236 out of 406 (58%) Irish women attending for antenatal care at the National Maternity Hospital, Dublin (unpublished observation).

Although pregnant women are euthyroid numerous changes occur in laboratory tests of thyroid function. The 20% increase in basal metabolic rate (BMR) in normal pregnancy [6] is attributed to the increased respiration of the feto-maternal unit and increased maternal cardiac output [7]. Free thyroid hormone levels measured either directly or indirectly are essentially unchanged during pregnancy [8, 9], although there have been some minor discrepancies between results reported by different authors [10-14]. The most comprehensive study of free hormone levels in pregnancy has been performed by Souma *et al.* [15], who found that free thyroxine levels are slightly increased during the first trimester, returning to normal levels during the second and third trimesters. Small sample sizes and failure to relate results to trimester may account for the minor discrepancies between studies.

Thyroid hormones are more than 99% protein bound. By the eighteenth week increasing levels of oestrogen have caused a two-fold increase in thyroxine binding globulin [16-18]. Conversely, levels of the other two binding proteins, thyroxine binding albumin and prealbumin may fall [19]. The increase in TBG is responsible for the higher levels of protein bound iodine (PBI), total serum thyroxine (T4), triidothyronine (T3) and reverse (3, 3′, 5′) triiodothyronine (rT3). The increase in total thyroid hormone concentration is maximal in the second trimester and usually returns to normal during the puerperium [20]. The development *de novo*, of thyrotoxicosis or hypothyroidism, or its persistence post-partum, occurs most commonly against a background of autoimmune thyroid disease [21]. Steady state thyroxine turnover and urinary free T3 and T4 are unaltered during pregnancy [20]. Thyrotropin (TSH) levels are slightly raised during the first trimester [8], but revert to normal thereafter [2, 22]. Protein bound iodine, T4 and rT3 are readily detectable in amniotic fluid [23-25] while T3 and TSH are usually undetectable [24-26].

The permeability of the placenta to thyroid hormones has been studied in detail in a variety of animal species, but there are few good studies. The animal work indicates that there are species differences in placental permeability. Thus transplacental transfer of T3 and T4 in early pregnancy in the rabbit is low, but improves in late pregnancy [27, 28]. There is very little transfer in sheep [29-31] whilst there is conflicting evidence on the permeability of the guinea pig placenta to thyroid hormones [32, 33]. In the rat there is indirect evidence of transfer of T4 and to a lesser extent T3 [34-36], but there is no evidence of transfer of intact hormones [36]. Most human studies show that the placenta is permeable to TRH and impermeable to TSH [38, 39] while transfer of T4 and T3 is limited. However, Man *et al.* [40] concluded from their study of butanol extractable iodine and serum precipitable iodine in maternal and neo-natal blood (measured at various times from day 4 to 52) that there was an equilibrium with respect to hormonal iodine across the placenta. Clinical evidence

supporting the notion of maternal-foetal transplacental passage of thyroid hormones is tenuous. Carr *et al.* [41] reported that in two mothers who had previously given birth to cretins a prescription of 150 microgrammes of l-thyroxine- daily during pregnancy resulted in two normal infants. Clinical evidence for reverse transfer i.e., from foetus to mother is provided by Kennedy and Montgomery [42] who reported an increase in maternal T4 and T3 and a decrease in maternal TSH, as pregnancy advanced in a mother with known hypothyroidism. Studies using radioine labelled T3 and T4 or large doses of unlabelled hormone have shown that transfer of exogenous hormone across the placenta during the first trimester and at term is limited [43-48]. Further evidence for the relative impermeability of the human placenta comes from the clear absence of a correlation between maternal and foetal serum concentrations of T4, T3, free T3 and TSH at any time during gestation [49-51].

The development of the foetal hypothalamo-pituitary-thyroid axis and the complex changes in perinatal thyroid physiology have been the subject of several recent reviews [52-54]. By the end of the first trimester the foetal thyroid gland can concentrate radioiodine, the foetal pituitary contains radioimmunoassayable TSH and TSH and T4 are measurable in foetal serum. Foetal serum T4 and free T4 levels increase progressively during the last trimester of pregnancy while serum TSH concentration remains unchanged. Serum T3 is unmeasurable in the human foetus until approximately 30 weeks gestation and remains considerably less than the maternal level antenatally. A surge of TSH occurs during the first 30 minutes after birth with a decline to adult values by 24 hours. At birth, values of T3 are approximately onethird of adult values while rT3 is elevated during the first four days of life. Serum thyroxine is similar in maternal and cord blood. After birth T4 and T3 levels increased with a peaking T4 at 24 hours and a peaking T3 at 2-4 hours and again at 24-36 hours. Values decrease slowly over the first weeks of life.

There is a marked scarcity of metabolic and histological data concerning the effects of fetal hypothyroidism on intrauterine neurological development in humans. Animal experiments have shown depressed RNA and protein synthesis and a deficit of myelin [55, 56]. Somatic growth does not appear to be hormone dependent because the birth weight and lengths of infants with congenital hypothyroidism are usually normal [57]. The postnatal importance of thyroid hormones for CNS development is not in doubt and the available evidence suggests that longterm prognosis for mental development is critically dependent on the duration of the interval between birth and initiation of thyroid replacement [58-60].

DIAGNOSIS AND TREATMENT OF HYPERTHYROIDISM DURING PREGNANCY

The reported frequency of hyperthyroidism complicating pregnancy has varied from 0.05% [61] to 3% [62]; the latter seems unlikely. During the years 1979-1981 37 hyperthyroid pregnancies were seen by one of us (MID) at three Dublin Maternity Hospitals (National Maternity, Coombe Lying-In Hospital, and Rotunda Hospitals), from a total of 72,257 pregnancies, giving a frequency of 0.05%.

The normal increase in maternal metabolic rate can mimic the signs of hyperthyroidism; pregnancy goitre is common (vide supra) and total T4 and T3 measurements are unreliable, but assays for free hormones are not yet routinely available. The free thyroxine index for T4 (FT4I) and T3 (FT3I) calculated as:

$$\text{FTI} = \text{total T4 or T3} \times \frac{\text{patient resin T3 uptake value}}{\text{mean normal resin T3 uptake value}}$$

allows indirect assessment of free hormone concentration and is the single most useful laboratory test for diagnosis of hyperthyroidism during pregnancy.

Untreated hyperthyroidism is associated with an increase in foetal loss [63], with premature labour [64] and with low birth weight [65]. There is some tenous evidence that thyrotoxicosis may be ameliorated by pregnancy per se [66, 67]. Radioactive iodine is contraindicated during pregnancy because it is concentrated in the foetal thyroid gland [68]. Iodides and potassium perchlorate are also contraindicated. Three groups of drugs have been used for treatment of maternal hyperthyroidism: thiouracils (methylthiouracil and prophylthiouracil), imidazoles (methimazole and carbimazole) and beta adrenergic blockers (propranolol). All of the antithyroid drugs used in pregnancy cross the placenta [69, 70], and interfere with foetal thyroid hormone synthesis with the potential consequences of foetal goitre and hypothyroidism. It has been suggested that the addition of l-thyroxine to an antithyroid drug might prevent foetal goitre and hypothyroidism. This remains unproven and in view of the limited permeability of the placenta to thyroid hormones it seems unlikely to be correct. A direct correlation between increasing dose of antithyroid drugs and foetal goitre has not been found [71]; goitre has occurred in babies born to mothers on combined treatment [43, 72, 75] and combined therapy does not prevent the as yet unknown proportion of foetal goitres which occur due to transplacental passage of thyroid stimulating immunoglobulins [76] nor does it prevent transient neonatal hypothyroxinemia [76].

Propranolol antagonizes sympathomimetic effects of thyroid hormones and diverts T4 to rT3 synthesis. There are only two reports on the use of propranolol in the treatment of six hyperthyroid pregnancies [77, 78]. All six ended in normal births. There are anecdotal reports of foetal bradycardia, intrauterine growth retardation, neonatal hypoglycaemia and depressed respiration associated with maternal ingestion of propranolol [79-81]. Small amounts of drug are excreted in breast milk. We feel that its use should be reserved for treatment of thyroid crises.

Thiouracils prevent iodine binding to thyroid hormone percursors. In addition the drugs decrease conversion of T4 to T3 and promote peripheral conversion of T4 to rT3. The usual daily dose schedule is 200-300 mg in three divided doses reducing thereafter to 50-150 mg daily. Side effects include gastrointestinal upset, skin rashes and bone marrow depression. Excretion in breast milk occurs, albeit to a lesser extent that with imidazoles [82-84] (vide infra).

Imidazole derivatives are concentrated in the thyroid gland and prevent iodine binding to thyroid hormone precursors. They may also inhibit the production of thyroid autoantibodies [85]. The initial daily dose is 40-60 mg in four divided doses, reducing after 4-6 weeks to a maintenance dose of 5-15 mg. Imidazoles are excreted in breast milk. Breast feeding should be avoided although its interdiction need not be absolute provided careful watch is kept on neonatal thyroid and haematological status.

Our policy is to treat maternal hyperthyroidism with carbimazole alone in the minimum effective dose; treatment is routinely discontinued at 37 to 38 weeks and resumed immediately following delivery [86]. Patients on treatment before conception are maintained on their usual maintenance dose of 5-10 mg carbimazole daily. Patients diagnosed for the first time during pregnancy are treated initially with carbimazole 60 mg daily in four divided doses with stepwise reduction after 4 weeks to the standard daily maintenance dose. Control of hyperthyroidism is assessed clinically and biochemically in view of pregnancy induced al-

Table 1. — *Treatment of hyperthyroidism complicating 109 pregnancies (112 infants).*

Method of treatment	Number of pregnancies	Time at which treatment was begun	
		Before conception	During pregnancy
Carbimazole	105	86	19
Carbimazole and l-thyroxine	1	1	
Methylthiouracil	1		1
Prophylthiouracil	1	1	
Lugol's iodine and phenobarbitone	1		1
Total	109	88	21

terations in metabolic rate and gland size and patients are seen regularly by the physician and obstetrician at a joint clinic. Since 1960, 109 pregnancies (88 mothers), complicated by maternal hyperthyroidism have been managed by one of us (MID). Five patients had coexistent diabetes mellitus and pregnancy was successful in each. One hundred and five pregnancies were managed by carbimazole alone and of these 86 were on treatment before conception; the remaining four patients had been started on alternative treatments elsewhere before referral to MID.

The *overall* foetal loss was 13.37 percent. There were four perinatal deaths (3.56 percent) 3 of which occurred in mothers treated by carbimazole alone (table 2). During the years of the study the average perinatal loss for all patients in the three hospitals concerned was 2.8 percent. Four infants (3.5 percent) had goitre: details of these cases have been published previously ([86, 87]).

Eighteen deliveries occurred whilst the patient was still taking carbimazole; foetal goitre did not occur in this group. There were 7 (6.6 percent) preterm deliveries of which three occurred among the 21 mothers started on antithyroid medication after conception. The mean birth weight in babies born to mothers who started treatment during pregnancy was 3.51 ± 0.65 kg. Among mothers in whom treatment was begun *during pregnancy* there was one stillbirth, one abortion at 27 weeks, three premature labours and two congenital malformations (one Down's syndrome – trisomy 21 : 1 cleft lip). Interpretation of these differences is difficult, but it may be that the less favourable outcome among the mothers in whom treatment was begun after conception is a consequence of suboptimal control of maternal hyperthyroidism.

Controlled comparison of the various therapies for hyperthyroidism during pregnancy has never been performed and valid retrospective comparison between series is difficult because of marked variation in dosage schedules, patient numbers and disease severity. Moreover, the usual criterion for assessing treatment outcome, namely foetal and perinatal loss is an extremely difficult parameter to interpret because of the multitude of factors independent of maternal disease which affect these figures. In most reported series the necessary careful developmental assessment and evaluation of thyroid function in children born to treated hyperthyroid mothers has not been performed. The thyroid status and physical and psychological development of 43 children born to mothers on antithyroid drugs alone has been assessed at follow-up periods ranging from 1 to 13 years in three

Table 2. — *Fetal outcome in 109 pregnancies (112 infants) complicated by hyperthyroidism.*

Fetal outcome (n = 112)	Number	Percent
Abortion at 0-12 weeks	9	8.03
Abortion at 13-28 weeks	2	1.78
Stillbirth	3	2.67
Neonatal death	1	0.89
Congenital malformation (*)	4	3.57
Neonatal goitre	4	3.57

(*) Down's Syndrome (trisony 21), transposition of the great arteries, cleft lip, penile hypospadias.

series ([88-90]). This small experience suggests that antithyroid drugs given during pregnancy do not have detrimental long-term effects on the offspring. All babies born to mothers with present or previous hyperthyroidism should be examined for the presence of goitre and clinical or biochemical evidence of thyroid dysfunction. Satisfactory results in terms of foetal and perinatal loss have been reported for mothers treated by antithyroid drugs alone ([72, 73, 91-96]) or in combination with l-thyroxine ([43, 65, 74,86, 94, 97]). A comparison of the results of these two forms of treatment based on a review of the literature over thirty years was made by Chahal *et al.* ([75]). Two hundred and fifty eight patients were treated by antithyroid drugs alone with 14 (5.4%) perinatal deaths while 162 were treated by a combination of antithyroid drugs and thyroid supplements with 7 (4.3%) perinatal deaths. It must be emphasized that our approach to treatment is empirical; regrettably the minimum effective dose of carbimazole is not known with certainty and varies among patients ([98]). Meticulous antenatal care with frequent clinical and biochemical assessment of maternal thyroid status and foetal growth by experienced observers is of vital importance irrespective of treatment regime. Preliminary reports suggesting that estimates of amniotic fluid T4 ([24]) and rT3 ([23, 99]) might be useful in the evaluation of foetal hypothyroidism have not been substantiated ([26, 100, 101]).

Thyroid storm may be precipitated by labour or caesarean section ([102]) although this is now a rare complication of pregnancy. There has not been a death from thyroid crisis at these hospitals since 1948 (Annual Report of the National Maternity Hospital, Dublin, 1948), during which period there have been approximately half a million deliveries. Treatment of thyroid storm includes general measures such as the correction of precipitating factors, eg, infection; rehydration, antipyretic and anticonvulsant therapy. Specific measures include iodine, antithyroid drugs, betablockers and corticosteroids.

PRIMARY HYPOTHYROIDISM

A decreased conception rate ([103]), increased foetal wastage, premature delivery, foetal malformation and abnormal mental development have been reported in the offspring of untreated hypothyroid mothers ([104-107]). Winikoff and Malinek ([108]) suggested that spontaneous abortion could be predicted on the basis of biochemical indices of hypothyroidism, but the low protein bound iodine reported in women who abort may be secondary to abortion related placental insufficiency ([109]). Successful pregnancies in untreated mothers with unequivocal biochemical evidence of hypothyroidism have been reported ([110-112]) of hypothyroid women have been reported by one of us ([113]), and clearly the foetal prognosis is not as poor as had been believed.

A high index of suspicion is fundamental in the diagnosis of hypothyroidism. Laboratory confirmation is based on low serum T4 and T3 levels in association with an elevated TSH. The resin T3 uptake is not helpful in the diagnosis of hypothyroidism.

Treatment of hypothyroidism is with l-thyroxine in full replacement doses of 0.1 to 0.2 mg ([114]). It has been suggested that T3 should be given in addition because of its relatively greater potential for transplacental passage ([115]). It has also been proposed that 0.3 mg of l-thyroxine might be required initially to saturate the increased number of TBG binding sites which are present in pregnancy ([116]). Pregnant patients in whom the diagnosis was not adequately established before commencing treatment may present on replacement doses of thyroxine. It is better to continue with therapy until delivery at which time treatment can be stopped and thyroid status can be fully defined.

THYROID CANCER

A combined total of 130 patients with previous treated (n = 108) or concurrent (n = 22) thyroid carcinoma have been reviewed by Hill *et al.* ([117, 118]). These authors found no evidence that pregnancy influenced the course of thyroid carcinoma. Thus the diagnosis of thyroid cancer during pregnancy is not an indication for termination of the pregnancy; neither is pregnancy a contraindication to thyroid surgery. Painful goitre, cervical lymphadenopathy or hoarseness should alert the clinician to the possibility of malignancy.

Since 1975, five pregnant patients with previously treated thyroid carcinoma have been seen bv one of us (MID). Four had a follicular carcinoma and one had a papillary carcinoma. All were on full replacement doses of l-thyroxine following thyroidectomy and one patient conceived two years following an ablative (79 mCi) dose of ^{128}I. All five patients had full term normal deliveries; one patient with follicular carcinoma developed skull secondaries in the third trimester. These remitted after delivery and she remains well eighteen months later.

HYDATIDIFORM MOLE AND CHORIOCARCINOMA

Hyperthyroidism associated with malignant trophoblastic disease has been recognised since 1940 ([119]). Myers ([120]) reported a patient with metastatic trophoblastic disease and hyperthyroidism while Tisne *et al.* ([121]) described the more common clinical association of hyperthyroidism and benign trophoblastic disease. The frequency of the association of biochemical abnormalities of thyroid function and trophoblastic disease has varied from 40% ([122]) to 100% ([123]). The frequency of clinical hyperthyroidism has also varied. Thus none of 15 patients with hydatidiform mole and biochemical hyperthyroidism reported by Nagataki ([122]) were clinically toxic, while 9 of the 14 reported by Higgins and Hersman ([124]) were toxic. Review of the literature on hyperthyroidism secondary of trophoblastic disease shows that goitre is an uncommon feature and that exophthalmos does not occur. Severe symptoms of hyperthyroidism including thyroid storm ([125, 126]) have been reported.

During the decade 1971-80 there were 53 molar pregnancies among 83,733 mothers (0.06%) delivered at the National Maternity Hospital, Dublin. None were clinically hyperthyroid but biochemical evidence of hyperthyroidism was not looked for routinely.

Bioassayable thyroid stimulator has been demonstrated both in patients sera and in molar tissue ([123,127, 128]). Present evidence suggests that human chorionic gonadotropin (HCG) has intrinsic thyrotropic activity and is synonymous with molar thyrotropin ([125, 129, 130]). The biological potency of HCG from different tumors may vary, thus accounting for the varying frequency of abnormalities of thyroid function in patients with trophoblastic disease. The hyperthyroidism associated with trophoblastic disease is cured by evacuation of molar tissue.

NEONATAL THYROTOXICOSIS

Neonatal hyperthyroidism has been recognised for over seventy years ([131]). It is said that 1-2% of babies born to mothers with Graves disease develop neonatal thyrotoxicosis ([65]). One has been seen by us (0.9%) ([87]); an elevated titre of long acting thyroid stimulator protector (LATS-p) was present in the serum of both mother and infant. The observations of Rosenberg *et al.* ([132]) that LATS was present in the serum of five mothers and four of their five offspring with neonatal hyperthyroidism suggested that neonatal thyrotoxicosis resulted from transplacental passage of thyroid antibody. Our understanding of the possible immunopathoge-

nesis of neonatal Graves is complicated by the bewildering nomenclature of thyroid stimulating antibodies (LATS, LATS-protector, thyroid stimulating immunoglobulin, thyroid binding inhibitor immunoglobulin) and by the variety of *in vivo* and *in vitro* assay systems for the detection of these antibodies. Following Rosenberg's observations, LATS negative, LATS-p positive cases of neonal thyrotoxicosis were reported [76, 88, 133-135], and it was suggested that neonatal thyrotoxicosis could be predicted on the basis of the LATS-p titre in maternal serum [76]. More recent data shows clearly that transplacental passage of immunoglobulins is not the only determinant of neonatal hypetrhyroidism. Holligsworth and Marbry [136] and Hollingsworth *et al.* [137] have reviewed 75 published cases of neonatal thyrotoxicosis with 26 cases of their own and noted a prolonged course (>six months) in 20% of cases. This cannot be explained on the basis of transplacental passage of thyroid stimulating immunolgobulins (tl/2=6 days). In three sets of twins, thyroid function in the neonatal period and early childhood were discordant despite identical exposure to maternal stimulating immunoglobulins. A case has been reported in which transplacental passage of the thyrotropin binding inhibitor immunoglobulins occurred without neonatal thyrotoxicosis [138]; a similar phenomenon has been noted by us (unpublished) and not all mothers or infants with neonatal thyrotoxicosis are LATS-p positive. It has been suggested that neonatal hyperthyroidism is an inherited phenomenon [137]. Children may be at risk of neonatal hyperthyroidism even when maternal thyroid function is normal or hypothyroid [139].

Persistent foetal tachycardia >160 [140] or 180 beats/minute [68], increased foetal movements [141] or increased amniotic fluid rT3 [141] may suggest foetal hyperthyroidism. Neonatal hyperthyroidism may not become manifest clinically for several days after delivery [76] and the clinical picture may be masked by the residual effects of antithyroid drugs which have crossed the placenta. Affected infants may be hyperkinetic with loose stools, tachycardia, thyroid enlargement and exophthalmos. Treatment of neonatal hyperthyroidism includes beta blockade [142], sedation, digitalisation, antithyroid drugs and corticosteroids [130, 131, 143].

The longterm course of neonatal hyperthyroidism may not be benign. Of 24 children in the series of Hollingsworth *et al.* [136], nine (35%) had hyperthyroidism beyond the first year of life, seven (27%) had psychomotor abnormalities and eleven (42%) had retarded skeletal growth.

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