PREGNANCY PLUS

Unresolved questions in managing hypothyroidism during pregnancy

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Diagnosing and managing hypothyroidism during pregnancy can be problematic. The scenario box on this page illustrates some typical problems encountered and raises pertinent questions concerning good medical practice. In this article, we define autoimmune thyroiditis as the presence of measurable circulating antithyroid autoantibodies (to thyroglobulin or thyroperoxidase), irrespective of abnormalities of thyroid function. Subclinical hypothyroidism is defined as an increase in serum thyroid stimulating hormone (TSH; usually 4-10 mU/l) associated with normal concentrations of serum thyroxine and triiodothyronine. Overt hypothyroidism is defined as an increase in serum TSH (usually >10 mU/l) associated with a decreased concentration of thyroxine, as a result of negative feedback; at that stage, most patients have symptoms and benefit from treatment.

How common is hypothyroidism in pregnant women?

The prevalence of autoimmune thyroiditis in women of childbearing age in the developed world is 5-15%; that of overt hypothyroidism is estimated at

Table 1 | Dose of serum thyroid stimulating hormone (TSH) and thyroxine in the patient during pregnancy (see Scenario box)

Hormone	Weeks of gestation				
	14	19	24	31	40
TSH (mU/l)	150	1.08	2.11	0.94	0.53
Thyroxine (µg/day)	150	150	150	150	150

0.3-0.5% and subclinical hypothyroidism at 2-3%.^{w1 w2} Prevalence rates are similar during pregnancy.^{w3 w4} In a prospective population study of 9471 pregnant women, autoimmune thyroiditis was present in 55% of the women with subclinical hypothyroidism (serum TSH 6-10 mU/l) and in more than 80% of women with overt hypothyroidism (serum TSH 11-200 m U/l).¹ Thus, the main cause of hypothyroidism during pregnancy is chronic autoimmune thyroiditis, at least when iodine intake is adequate. On a worldwide basis, however, the most common cause of thyroid insufficiency is iodine deficiency, which affects more than 1.2 billion people.

How does pregnancy affect hypothyroidism?

Pregnancy can trigger progression to hypothyroidism in women with autoimmune thyroiditis. This is because the maternal thyroid gland needs to produce more thyroid hormone during pregnancy and women with thyroid autoimmune disease or hypothyroidism are less able to sustain this necessary increase. Women with subclinical hypothyroidism have a reduced functional reserve in the thyroid, so hypothyroidism often develops or worsens as gestation progresses.²

How does hypothyroidism affect pregnancy and pregnancy outcome?

Women with hypothyroidism can still conceive, although infertility rates are higher and failure of in vitro fertilisation is more likely.³ Pregnant women with hypothyroidism have a greater risk of early and late obstetric complications such as miscarriage, anaemia, gestational hypertension, placental abruption, premature delivery, postpartum haemorrhage, and admission of their baby to neonatal intensive care (particularly for respiratory distress syndromes) ^{w5 w6} Obstetric complications are associated with both

SCENARIO

Mrs SC, aged 29 years, has a family history of goitre. Nine months after a first delivery in 1999, she had positive antithyroid peroxidase antibodies and a serum thyroid stimulating hormone (TSH) concentration of 3.1 mU/l. No treatment was given, but she was told that she should have her thyroid function monitored, advice that she did not follow. Two years later, when she was six weeks pregnant, she was diagnosed with hypothyroidism of autoimmune origin: serum TSH 150 mU/l, free thyroxine 2.6 pmol/l (normal 10-26), antithyroid peroxidase antibodies 990 U/ml (normal <60). She presented with severe hypothyroidism during the first weeks of pregnancy, although we cannot tell whether it was present before conception (though this is likely) or developed after the onset of pregnancy. Treatment with thyroxine was started immediately, and thyroid function returned to normal and remained so throughout the remainder of her pregnancy (table 1). Delivery was full term and obstetrically uneventful. After parturition, the mother's thyroid function was equilibrated with 75 µg thyroxine/day. Six months postpartum, TSH rose transiently to 10.4 mU/l, as a result of postpartum thyroiditis, and thyroxine was increased to 100 µg/day.

This is one of a series of occasional articles about how to manage a pre-existing medical condition during pregnancy. If you would like to suggest a topic for this series please email [Kirsten Patrick](mailto:Kirsten.Patrick@bmj.com) ([kpatrick@bmj.com](mailto:Kirsten.Patrick@bmj.com))

overt and subclinical hypothyroidism. Adequate treatment with thyroxine, with subsequent restoration of normal thyroid function, greatly reduces the frequency of such complications.⁴ In a recent prospective randomised intervention trial, miscarriage and preterm delivery rates were much lower in women with autoimmune thyroiditis given thyroxine (started at five to 10 weeks) throughout gestation to keep them euthyroid than in controls. The miscarriage rate was reduced by 75% and preterm delivery by 69% in women given thyroxine.^{5 w7}

The detrimental effects of maternal thyroid deficiency on fetal development are thought to depend on the severity and early onset of a reduced availability of maternal thyroid hormone. Severe impairment of fetal neurodevelopment is also thought to require prolonged hypothyroxinaemia.^{w8} Recent studies indicate that undiagnosed (and hence untreated) hypothyroidism during the first half of pregnancy is associated with a risk of a poorer neurodevelopmental outcome in the progeny.^{w8} In iodine deficiency, maternal and fetal thyroid glands are affected early on, and maternal hypothyroidism is present during early gestation. Severe iodine deficiency leads to endemic cretinism, as a result of irreversible damage to the fetal brain. Even in less severe iodine deficiency, a meta-analysis showed an overall reduction in cognitive functions of 13.5 IQ points.^{w9} A recent study showed that when maternal hypothyroidism is due to chronic autoimmune thyroiditis, the offspring of untreated (or suboptimally treated) women are at risk for clinically relevant cognitive deficits.⁶ Even isolated hypothyroxinaemia during early gestation (defined as serum free thyroxine near the lower limit of normality, normal TSH, and no detectable thyroid antibodies) may be associated with a lower psychodevelopmental index in the offspring. None the less, free thyroxine values spontaneously returned to normal during later gestation in most of these women and their fetuses developed normally.⁷ It is unclear whether women with isolated hypothyroxinaemia need treatment, as no evidence based information is available to prove that such patients benefit from thyroxine administration. The results of a large scale randomised trial presently under way will be important for developing screening and management guidelines.^{w10}

What are the unresolved questions?

We do not know how low maternal serum free thyroxine values need to be before normal fetal development is affected. The relative roles of early versus late gestational hypothyroidism are also unclear. Moreover, maternal hypothyroidism may not be diagnosed (and therefore not treated) during pregnancy and may even remain undiagnosed for several months after delivery. It is unclear how detrimental this may be for the development of the neonate. The consequences of maternal hypothyroidism on the fetus or neonate are probably the result of several factors acting in combination, such as decreased availability of maternal thyroid hormones at crucial times in fetal brain development, obstetric events

associated with maternal hypothyroidism, and possibly prolonged undisclosed maternal hypothyroidism during pregnancy.

Answers to these questions are needed to help us improve guidance for clinical management, such as how and when screening programmes should be established during pregnancy. In the meantime, we have to rely on individual clinical judgment to decide how and when to diagnose and treat women at risk of hypothyroidism during pregnancy.

Another ethically important—but debatable—question is whether clinicians should recommend terminating pregnancy when severe hypothyroidism is diagnosed late in gestation. Present consensus among obstetric care providers and endocrinologists is against recommending abortion, but despite the administration of thyroxine future parents cannot be fully reassured about potential brain damage as a result of longstanding and severe intrauterine undiagnosed hypothyroidism.

How should we manage hypothyroidism during pregnancy?

An international ad hoc committee under the auspices of the American Endocrine Society has recently produced consensus guidelines for managing thyroid disease during pregnancy. The guidelines have not officially been published, but they recommend adjusting the dosage of thyroxine to reach a serum TSH value not higher than 2.5 mU/l in women with hypothyroidism who intend to conceive and are taking thyroxine.^{w11} This recommendation could be extended to euthyroid women with autoimmune thyroiditis, although the proof of a clear benefit in such women is lacking. It is regrettable that thyroid function was not closely monitored in the case presented here (because of the patient's non-compliance; see scenario box). Whether the patient should have received thyroxine at the time of initial investigation is debatable. Some authors have recommended that the reference range for serum TSH should be narrowed from 0.40-4.0 mU/l to 0.40-2.5 mU/l to make it more representative of the normal physiological range.^{w12-w16}

Because of the potentially serious adverse effects of maternal hypothyroidism on the fetus, targeted case finding is recommended at the first prenatal visit. For women taking thyroxine before conception, the dosage should normally be incremented as early as four to eight weeks' gestation, usually by 30-50%.^{w17} It has been suggested that women who are already taking thyroxine should increase the dosage by about 30% as soon as they know they are

Table 2 | Guide to managing hypothyroidism during pregnancy

Serum TSH (mU/l)	Increase in thyroxine (µg/day)
5-10	25-50
10-20	50-75
>20	100

TSH, thyroid stimulating hormone.

Table 3 | Thyroxine treatment during pregnancy in women with hypothyroidism and resulting TSH values^{w18}

Thyroxine dose and TSH	Trimester		
	First	Second	Third
Average dose of thyroxine (µg/day)	100	125	150
Range of thyroxine doses (µg/day)	25-275	25-300	25-325
Median serum TSH value (mU/l)	2.6	1.8	1.1
Upper TSH value (mU/l)	34.4	68.7	95.7

TSH, thyroid stimulating hormone.

pregnant (before seeking evaluation) to avoid early maternal hypothyroidism.⁸ The size of this increase depends on the cause of hypothyroidism—women with no residual thyroid tissue need a greater and more rapid increment than those with Hashimoto's thyroiditis.⁹ A simple rule of thumb has been established to guide the clinician (table 2).^{w5}

When overt hypothyroidism is diagnosed during pregnancy, thyroid function tests should be normalised as rapidly as possible. To achieve this aim, and to rapidly normalise the extrathyroidal thyroxine pool, some authors recommend using two to three times the estimated final daily dose. However, presently we have no proof of a real advantage in doing this. Thyroid function tests should be performed again four to five weeks after the onset of treatment and every six weeks thereafter, until after mid gestation at least. The dose of thyroxine should be titrated to reach and maintain serum TSH concentrations no more than 2.5 mU/l in the first trimester (<3 mU/l in the second and third trimester).

In principle, the administration of thyroxine should be straightforward. However, this is not the case in clinical practice (table 3).^{w18} A retrospective study of 167 pregnant women with hypothyroidism showed that despite increasing the mean dosage of thyroxine (from 100 to 150 µg/day between the first and third trimester) and adequate median serum TSH values, thyroxine dosage varied greatly (25-325 µg/day). Also, some women had raised serum TSH (almost 100 mU/l), indicating that increases in thyroxine dose were insufficient or came too late.

Postpartum period

After parturition, the dosage of thyroxine should be decreased in most women, over a period of two to four weeks.^{w19} Women with features of thyroid autoimmunity are at risk of developing postpartum thyroiditis, which may justify differences in thyroxine requirements before and after pregnancy.^{10 w20}

METHODS

This review was based on personal reference archives, including references used to write the chapter on pregnancy in *Thyroid Disease Manager* (www.thyroidmanager.org). We also used references that were reviewed by the ad hoc international guidelines committee of the American Endocrine Society, of which we are active participants

Thyroid function tests should therefore be monitored in the mother for at least six months after delivery.

Conclusions

Because hypothyroidism has potentially serious adverse effects on the mother and the fetus, targeted case finding is recommended at the first prenatal visit. If hypothyroidism is diagnosed before pregnancy, the dose of thyroxine should be adjusted to reach a serum TSH **not higher than 2.5 mU/l and the dosage** should be increased further by four to eight weeks' gestation. When overt hypothyroidism is diagnosed during pregnancy, thyroid function tests should be normalised as soon as possible. Because euthyroid women with features of thyroid autoimmunity are at risk of developing hypothyroidism during pregnancy, they should be monitored for an increase in serum TSH. Subclinical hypothyroidism is associated with an adverse outcome in pregnancy. Although the efficacy of treating women with subclinical disease has not been proved, thyroxine administration is recommended, as the potential benefits greatly outweigh the potential risks. In addition, undiagnosed (or untreated) hypothyroidism and hypothyroxinaemia in the first half of pregnancy (when availability of maternal thyroxine is particularly important for the fetus) are associated with a risk of cognitive impairment in the progeny.

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