Guidelines for TSH-receptor antibody measurements in pregnancy: results of an evidence-based symposium organized by the European Thyroid Association

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Hyperthyroidism due to Graves' disease is induced by autoantibodies stimulating the thyroid-stimulating hormone (TSH) receptor. In most patients these antibodies can be measured in serum. Graves' disease is common in women of reproductive age, with a prevalence rate of past or present disease of 0.5–1% (1). Classically, three therapeutic approaches are used: (i) Antithyroid drugs given for a long period, which is commonly 1–2 years. During therapy most patients enter remission, but relapses are frequent (around 50%) after withdrawal of medication; (ii) Radioiodine therapy. This may initially aggravate the autoimmune reaction, but most patients become euthyroid or hypothyroid, due to the reduction in thyroid follicular cell mass; (iii) Subtotal or near total thyroidectomy.

Pregnancy is commonly accompanied by a fall in thyroid autoimmune activity, and women with Graves' disease may spontaneously enter remission during pregnancy. However, disease activity persists in some pregnant patients, and occasionally onset of Graves' disease is seen. The recommended therapy for Graves' disease during pregnancy is monotherapy with antithyroid drugs (propylthiouracil, methimazol or carbimazol).

While thyroid hormones produced by or given to the mother cross the placenta in only limited amounts, both TSH-receptor stimulating antibodies and antithyroid drugs readily cross the placenta and affect fetal thyroid function. Ideally, a balance between stimulating antibodies and drugs which keeps the mother euthyroid will also maintain euthyroidism in the fetus. Fortunately this is close to reality; during therapy with antithyroid drugs the thyroid state of the fetus parallels that of the mother, but with a tendency to be slightly lower (2). Hence, a pregnant woman with Graves' disease and an intact thyroid should receive the minimal dose of antithyroid drugs which keeps her thyroid function near the upper end of normality.

After delivery, antithyroid drugs are cleared from the neonatal circulation within the first days, whereas TSH-receptor antibodies disappear much more slowly and may stimulate the thyroid during the first weeks or even months of life. Delayed neonatal hyperthyroidism may therefore develop, constituting a potentially life-threatening medical condition.

The situation is different when a pregnant woman has previously been treated for Graves' hyperthyroidism with radioiodine or surgery, and especially when she is receiving thyroxine substitution therapy. In this situation, the thyroid function of the mother does not reflect thyroid function in the fetus. If the mother still produces large amounts of TSH-receptor stimulating antibodies, fetal hyperthyroidism may develop. Also, neonatal hyperthyroidism may be present at birth and last for months if left untreated.

Occasionally antibodies against the TSH receptor will bind to the receptor without stimulation, but rather will block the normal effect of TSH. This may cause hypothyroidism in the mother and the fetus, and transiently in the newborn. This rare variant, which has been detected in 1 in 180 000 newborns in North America (3), is not discussed in detail.

Methods

The clinical value of measuring TSH-receptor antibodies in pregnant women to predict neonatal hyperthyroidism has been examined in several studies. To evaluate the evidence for recommending such measurements, the European Thyroid Association initiated a symposium in September 1997 at its meeting in Munich. All reports on the subject containing original data were identified by a systematic reference search (29 articles). They were thoroughly read by the present authors. Among them 11 articles fulfilled the following criteria: a systematic investigation of more than 12 pregnant women with Graves' disease including evaluation of neonatal thyroid function and measurements of TSH-receptor antibodies. They also included data on more than one case of neonatal hyperthyroidism. Two of the articles more or less described patients also published in another article. Hence, nine reports were finally selected for detailed evaluation and discussion during the symposium. A total of 454 pregnant women (462 pregnancies) with Graves' disease (range 14–107 women in individual papers) and their 466 newborns were described. There were three reports from Europe (4–6), three from Japan (7–9), two from the USA (10, 11) and one from Australia (12).

Results

The main features were as follows.

(i) Similar findings have been reported from different parts of the world, including areas with different iodine intake levels.

(ii) Precise information allowing an estimate of the incidence of neonatal hyperthyroidism is scarce, since nearly all groups of pregnant women investigated were biased by selection. From the available data it seems that 2–10% of pregnant women with active Graves' disease will have newborns with hyperthyroidism.

(iii) This is the 2–10% of pregnant women with the highest levels of TSH-receptor antibodies in serum.

(iv) If a pregnant woman is euthyroid after a previous medical therapy for Graves' disease, the risk for neonatal hyperthyroidism is negligible.

(v) If a pregnant woman is euthyroid but has previously been treated for Graves' disease by radioiodine or thyroid surgery, the risk for neonatal hyperthyroidism is not negligible, and depends primarily on the level of TSH-receptor antibodies in her serum.

(vi) The best predictor of neonatal hyperthyroidism is a high level of TSH-receptor antibodies in the pregnant woman measured late in pregnancy.

(vii) Assays specifically measuring antibodies stimulating the thyroid have clear theoretical advantages and are useful. In the studies reported it has, however, repeatedly been demonstrated that the generally available and technically relatively simple assays measuring TSH-receptor antibodies by competitive inhibition (not indicating whether the antibodies are stimulating the thyroid) will predict nearly all cases of neonatal hyperthyroidism.

From these features the following recommendations emerged:

Guidelines for measurements of TSH-receptor antibodies in pregnancy

(i) **A euthyroid pregnant woman, without medication, but who has previously received antithyroid drugs for Graves' disease:** the risk for fetal and neonatal hyperthyroidism is negligible. Measurements of TSH-receptor antibodies are *not necessary*. Thyroid function should be evaluated as part of normal pregnancy care.

(ii) **A euthyroid pregnant woman (with or without thyroid hormone substitution therapy) who has previously received radioiodine therapy or undergone thyroid surgery for Graves' disease:** the risk for fetal and neonatal hyperthyroidism depends on the level of TSH-receptor antibodies in the mother. Antibodies should be measured *early in pregnancy* to evaluate the risk for fetal hyperthyroidism.¹

If antibodies are absent, or the level low, no further special evaluation is recommended. If the level is high the fetus should be followed carefully for signs of hyperthyroidism (high pulse rate, impaired growth rate, goitre).

Also TSH-receptor antibodies should be measured again in the last trimester to evaluate the risk for neonatal hyperthyroidism.²

(iii) **A pregnant woman who takes antithyroid drugs for Graves' disease to keep thyroid function normal (therapy has been started before or during pregnancy):** TSH-receptor antibodies should be measured in the *last trimester*. If antibodies are absent, or the levels low, neonatal hyperthyroidism is unlikely. If antibody levels are high, evaluation for neonatal hyperthyroidism is needed (clinical evaluation and thyroid function tests on cord blood and again after 4–7 days to detect early and delayed hyperthyroidism).

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¹ Even though systematic studies of fetal hyperthyroidism are scarce, it was decided to advocate a clinical practice which also includes evaluation of the risk for fetal hyperthyroidism. If a pregnant woman has an intact thyroid, and if no therapy or only antithyroid drugs crossing the placenta are given, then the thyroid function of the mother yields a reliable operational estimate of the thyroid function of the fetus. Hence, measurements of TSH-receptor antibodies early in pregnancy to evaluate the risk for fetal hyperthyroidism is only appropriate in pregnant women with a history of Graves' disease treated by surgery or radioiodine.

Very rare cases of neonatal (and probably also fetal) hyperthyroidism have been described in the offspring of women with a history of autoimmune thyroiditis without clinical signs of hyperthyroid Graves' disease (10). They will not be detected by the present protocol. Neither will the very rare cases of fetal and neonatal hyperthyroidism due to TSH-receptor activating mutations (13).

² Various methods are available for measuring TSH-receptor antibodies. In Europe a widely used method is TRAK (Brahms, Berlin, Germany). With this method levels above approximately 40 U/l are considered high enough to indicate risk of neonatal hyperthyroidism.

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Received 15 September 1998

Accepted 29 September 1998