Antithyroid drug treatment of Graves' disease in pregnancy: Long-term effects on somatic growth, intellectual development and thyroid function of the offspring

Peter M. Messer¹, Berthold P. Hauffa², Thomas Olbricht¹, Georg Benker¹, Peter Kotulla³ and Dankwart Reinwein³

Abstract. With regard to their thyroid function, somatic and intellectual development, we compared 17 children of 13 hyperthyroid mothers (group I) receiving antithyroid drug treatment during their pregnancies with 25 children of 15 mothers who were euthyroid without any antithyroid treatment during their pregnancy (group II). Mean duration of maternal treatment was 3.5 months in group I, using carbimazole or thiamazole (N=12) and propylthiouracil (N=1). Age at examination in group I was 7.2±6.2 years, in group II 8.7±7.1 years (mean±sd). Both groups showed no significant differences in the results of the clinical examination and in the degree of their mental and psychomotoric development at the time of study. We found the mean birth weight of the infants in group I significantly lower than in group II (3165±339 vs 3666±670 g, p<0.03). The individual birth weights, however, were normal for gestational age. The body weight difference between groups disappeared during the further somatic development of the children. The serum concentration of free thyroxine in group I was significantly higher than in group II (17.2±2.4 vs 14.9±1.9 pmol/l, p<0.003), but fell in both groups within the normal range. The evaluation of the psychomotoric and intellectual capacity of the children at different developmental stages showed no abnormalities detectable by our tests. Thus, in the children of the two groups we found no adverse effects of a maternal antithyroid drug treatment during pregnancy or of inactive maternal Graves' disease alone, neither on thyroid gland size and function nor on the physical or intellectual development, after the neonatal period.

A pregnancy complicated by hyperthyroidism is not a rare event. Its prevalence has been estimated from 0.02-3.0% of all pregnancies (1,2). Severe hyperthyroidism in a pregnant woman is an absolute indication for therapy. Today, the treatment with antithyroid drugs during pregnancy is widely accepted and regarded as the treatment of choice (1,3). Only in the presence of a massive goitre causing mechanical obstructions, when medical treatment is complicated by allergic-toxic reactions, or in the case of lack of patient compliance, surgical treatment may become necessary (4).

There is a known risk for fetal malformation attributed to antithyroid drug treatment during pregnancy. Malformations of the earlobe, omphalocele, and aplasia cutis congenita have been described after maternal antithyroid treatment (5-9). Nevertheless it has been shown that untreated hyperthyroidism in pregnancy is associated with an even higher rate of congenital malformations (8).

Most studies of children born to mothers with Graves' disease, either receiving antithyroid drug therapy during pregnancy or being euthyroid with-
out specific therapy, are limited to the neonatal period or have only compared serum concentrations of thyroid hormones (8,10). We have studied thyroid size and function, somatic and intellectual development of children who were exposed to antithyroid drug treatment in utero (group I), and of children whose mothers did not receive any antithyroid treatment during pregnancy (group II).

Patients and Methods

Patient population
From the patient registry of the Department of Endocrinology of the University Hospital of Essen, the following women were included in the study: patients with a history of Graves' disease, one or more pregnancies after the onset of Graves' disease, and documented metabolic state during pregnancy.

Fifty-eight women fulfilled these criteria, and 28 of them consented to participate in our study together with their children. Thirteen women with 17 pregnancies had to be treated with antithyroid drugs (carbamazepine or propylthiouracil N=12, propylthiouracil N=1) to achieve an euthyroid metabolic state (group I). Carbimazole or thiouracil were used during 16 pregnancies. In 9 patients antithyroid treatment was required only in the first trimester. In 5 patients therapy extended through the second trimester, and in two treatment was interrupted from the 5th to the 7th month, and from the 7th to the 9th month, respectively. Propylthiouracil was used throughout pregnancy in one patient. In all cases an antithyroid monotherapy without additional L-thyroxine substitution was administered. Fifteen women with 24 pregnancies (one twin pregnancy) were clinically and metabolically euthyroid during the complete pregnancy without any specific therapy (group II). Out of these mothers 13 had been treated surgically (nearly total thyroidectomy) before pregnancy. Seven of these women were taking L-thyroxine at different doses throughout pregnancy.

Testing
Parents and, as far as possible, the children gave informed consent to participate in the study; 6 patients did not agree to participate in the psychological testing. The age of the children ranged from 3 months to 26.5 years (group I: 7.2±6.2, group II: 8.7±7.1 (mean±SD)). Children of both groups were examined physically after history taking. Supine length or standing height and weight of the children were recorded and converted into standard deviation scores to make the individual values comparable independent of age and sex. The calculation was performed using reference values of the First Zurich Longitudinal Growth Study (11). Birth length and birth weight were compared with the 10th-90th percentile values of the Bayerische Neugeborenenschule studie (12).

Laboratory methods
To assess thyroid function, serum concentrations of T₄, free T₄ (FT₄), T₃, free T₃ (FT₃), TSH, basal secretion before and after stimulation with thyroliberin (TRH), thyroglobulin, thyroxine-binding globulin (TBG), microsomal (Mi-ab) and thyroglobulin (Tg-ab) antibodies and TSH binding inhibiting antibodies (TBI-ab) were measured.

The following commercially available radioimmunoassay kits were used: free thyroxine: Amerlex M Free T₄ RIAKit (Amersham, Braunschweig, FRG); L-thyroxine: T₄ RIA; triiodothyronine: T₃ RIAid; free triiodothyronine: FT₃ RIAid, TSH: TSH IRMAclon (monoclonal ¹²⁴I-labelled TSH antibodies); thyroglobulin: TgRIA; TBG: TgB RIA (all Henning Berlin GmbH, FRG). Thyroid autoantibodies were determined by hemagglutination inhibition: microsomal antibodies: Thymune M; thyroglobulin antibodies: Thymune T (both Wellcome GmbH, Burgwedel, FRG). The thyrotrin stimulation was performed with 200 μg TRH iv (Antepan® Henning Berlin GmbH, FRG). TBI-ab was determined with a radioligand receptor assay (13).

Ultrasound
Volume and echogenicity of the thyroid gland were determined by ultrasound with a Toshiba SAL 38 B ultrasonic diagnostic system using a 7.5 MHz transducer with a water bath. Thyroid volume was calculated using the following formula: length × thickness × 0.459 (ml) (14).

Psychological tests
Since there is no single test suitable for children of all ages, the following tests were chosen according to the individual age of each child: Denver Test (0-6 years) (15), Marburger Verhaltensliste/MVL (6-12 years) (16), Culture Fair Intelligence Test/CFT 20 (8½-18 years) (17), Hamburger Neurotizismus- und Extraversions-Skala für Kinder und Jugendliche/HANES KJ (8.0-17.1 years) (18), Eysenck-Persönlichkeits-Inventar/EPI (18 years and older) (19,20), and the Standard Progressive Matrices/SPM (18 years and older) (21,22).

Statistical methods
Groups were compared using the Mann-Whitney U-test (23). All values are given as mean ± standard deviation.

Results
The two groups of children did not differ significantly as to the results of the clinical and psychomotoric examination at the time of study. The birth weight of the children in group I was significantly lower (p<0.03) than in group II, although gestational ages were not different. In the children of
Table 1.
Comparison of somatic and laboratory values of the children of both groups.

<table>
<thead>
<tr>
<th></th>
<th>Group I (N=17) mean ± 1SD</th>
<th>Group II (N=25) mean ± 1SD</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight (g)</td>
<td>3164±339</td>
<td>3666±670</td>
<td>2800-4150</td>
</tr>
<tr>
<td>Birth length (cm)</td>
<td>51.7±2.2</td>
<td>52.5±2.5</td>
<td>48.5-53.5</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>39.6±0.9</td>
<td>39.8±2.1</td>
<td>38.0-42.0</td>
</tr>
<tr>
<td>At follow up:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>7.2±6.2</td>
<td>8.7±7.1</td>
<td></td>
</tr>
<tr>
<td>T₄ (nmol/l)</td>
<td>118.4±17.2</td>
<td>111.1±19.1</td>
<td>58.0-154.0</td>
</tr>
<tr>
<td>FT₄ (pmol/l)</td>
<td>17.2±2.4</td>
<td>14.9±1.9</td>
<td>11.0-28.0</td>
</tr>
<tr>
<td>T₃ (nmol/l)</td>
<td>2.78±0.48</td>
<td>2.77±0.50</td>
<td>1.2-2.8</td>
</tr>
<tr>
<td>FT₃ (pmol/l)</td>
<td>7.53±1.29</td>
<td>7.20±1.44</td>
<td>3.4-8.5</td>
</tr>
<tr>
<td>TSH basal (mU/l)</td>
<td>1.71±0.93</td>
<td>1.35±0.45</td>
<td>0.5-4.0</td>
</tr>
<tr>
<td>TSH after TRH (mU/l)</td>
<td>12.8±4.7</td>
<td>10.8±4.2</td>
<td>6.8-29.6</td>
</tr>
<tr>
<td>Thyroglobulin (nmol/l)</td>
<td>293.4±258.7</td>
<td>299.6±47.7</td>
<td>200.0-340.0</td>
</tr>
<tr>
<td>TBG (nmol/l)</td>
<td>311.4±59.2</td>
<td>299.6±47.7</td>
<td></td>
</tr>
<tr>
<td>Mi-ab</td>
<td>2 × positive</td>
<td>2 × positive</td>
<td>negative</td>
</tr>
<tr>
<td>Tg-ab</td>
<td>1 × positive</td>
<td>1 × positive</td>
<td>negative</td>
</tr>
<tr>
<td>TBI-ab</td>
<td>1 × positive</td>
<td></td>
<td>negative</td>
</tr>
</tbody>
</table>

Group I serum concentrations of FT₄ were significantly higher than in group II (p<0.003), but were in both groups within the age-dependent normal range. The serum concentrations of T₃, T₄, FT₃, TSH basal, TSH after stimulation (ΔTSH), thyroglobulin and TBG did not show any significant differences between the two groups (Table 1). Microsomal antibodies were detected in two children of each group, thyroglobulin antibodies in one child of each group. TBI-ab was found to be positive in
one child of group I. This child (age 8.25 years) was healthy and did not differ in any aspect from the other children.

Two children of group I had a goitre at birth. The children were diagnosed as euthyroid by clinical examination. The goitre disappeared with L-thyroxine therapy after one and six months, respectively. One of these children had had slightly increased levels for $T_4$ and $T_3$ in vitro uptake. Nothing is known about the thyroid antibody status of the two mothers and their children at the time of delivery. In another child of this group Type I diabetes mellitus was diagnosed at age 3.5 years. The standard deviation scores for weight and height did not differ significantly (Fig. 1a and 1b). Compared with published reference ranges (24-28) the children had a thyroid gland of normal size for sex and age. None of the children had any of the malformations reported previously (8).

**Discussion**

The aim of our study was to investigate whether Graves' disease in a pregnant woman affects thyroid function, somatic and intellectual development of the offspring, and whether this adverse effect extends beyond the neonatal period. We compared children of mothers being spontaneously euthyroid or euthyroid by antithyroid drug treatment.

Two children, both belonging to group I, had a euthyroid neonatal goitre and were treated with L-thyroxine in the postpartum period. Their mothers had been treated with thiamazole and carbimazole, respectively. Neonatal goitre has been reported previously after maternal thionamide therapy, in most instances associated with hypothyroidism of the newborn (29,30). A goitre combined with a neonatal hyperthyroid metabolic state is frequently seen in association with placental transfer of maternal antibodies stimulating fetal thyroid growth and function (31,32). A hyperthyroid goitre was not seen in any of our patients. Since thyroid hormone and TSH concentrations were not measured routinely in clinically euthyroid neonates, we cannot exclude the presence of transient, compensated hypothyroidism in children of treated mothers during the neonatal period.

Although 9 of 17 fetuses were exposed to antithyroid drugs in utero during the first trimester, none of the children of group I nor of group II showed any of the reported malformations. The rate of malformations has been found to be 1.7% in newborns after maternal methimazole therapy and up to 6% in newborns after untreated maternal hyperthyroidism during pregnancy (8).

Birth weight was significantly lower in the children of group I, although the mean gestational age in both groups did not differ. All the children had a normal birth weight for their gestational age. A lower birth weight has been reported in children of mothers with untreated hyperthyroidism compared with those born to healthy mothers (33). In another study a lower birth weight has also been found in children from carbimazole-treated women when compared with those of normal healthy pregnant women (2). This is not necessarily due to antithyroid drug treatment, but might result from insufficient control of hyperthyroidism. However, this appears not to be the case in our patients, whose metabolism and therapy had been closely monitored during pregnancy. The lower birth weight found in our children more likely depends on other, extrathyroidal factors affecting mother and fetus. Our results clearly show that the weight difference disappears during the later somatic development of the children. Standard deviation scores, particularly those for body weight, are not significantly different between the two groups or from other healthy children.

There were no significant differences between the groups with regard to the other parameters, except for the serum concentration for free thyroxine, which we found significantly higher in the children of the treated mothers. Each individual value in both groups fell within the normal range. Since the basal TSH concentration and the TSH increase after TRH stimulation were normal, a dysfunction of the hypothalamic-pituitary-thyroidal axis that might explain this difference, is highly unlikely.

The results of our psychological tests did not show any differences between the group of children born to the treated mothers and the group of children born to untreated mothers. The individual results of the children of both groups did not differ from the normal range for the test population. Two previous studies (34,35) used similar psychological tests on comparable groups of patients. In the first study, the children were aged between 3-15 years when examined and their mothers had received carbimazole and L-thyroxine during pregnancy. These children did not differ in growth.
and development from children of normal pregnancies. The second study describes the effect of a maternal propylthiouracil therapy during pregnancy on the later intellectual and somatic development of the children. Here 28 children aged between 2 and 28 years were examined, 23 of whom had been exposed to propylthiouracil in utero during the third trimester and only four during the first and second trimester. As in our study, there were no differences in the results of the intellectual tests. In contrast to this study most of our mothers had been treated during the first trimester.

All these studies, including ours, cover a wide age range and are cross-sectional. Thus, transient changes in psychomotor achievement or minor changes over time in a single child may have gone undetected. Such subtle or transient changes, however, are unlikely to affect overall intellectual and psychomotor outcome to a major extent.

Our data indicate that maternal antithyroid drug therapy during pregnancy with substances as carbimazole, thiamazole and propylthiouracil is unlikely to cause long-term impairments of the somatic and psychomotor development in children. This confirms the safety of antithyroid drug treatment during pregnancy, even in the first trimester, with regard to child development.

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References


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