CASE REPORT

ACUTE HYPERTHYROIDISM DURING PREGNANCY: A CASE REPORT AND CRITICAL ANALYSIS

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INTRODUCTION

The occurrence of hyperthyroidism during pregnancy is exceptional. Usually, the disease precedes pregnancy which exerts a favorable influence on its clinical course; remission occurs mainly between the twelfth and sixteenth gestational week, as shown by Jonckheer et al. (1976).

Many authors (Emslander et al., 1974; Goluboff et al., 1974; Worley and Crosby, 1974; Burrow, 1975, 1978; Prout, 1975; Innerfield and Hollander, 1977; Serup and Petersen, 1977; Solomon, 1981) state that preference should be given to antithyroid drugs to treat maternal hyperthyroidism during pregnancy. However, the lowest possible dose should be used to achieve normal thyroid function, since neonatal hypothyroidism, albeit transient, may be the result (Low et al., 1978; Caplan and Wickes, 1979; Hollingsworth et al., 1980; Momotami et al., 1980; Cheron et al., 1981; Solomon, 1981). Even when very low doses have been used (Low et al., 1978; Hollingsworth et al., 1980; Cheron et al., 1981), a significant reduction of serum thyroxin levels in neonates has been demonstrated. These cases of neonatal hypothyroidism are usually transient. The impact of this transitory condi-
tion on the future development of the neonate remains uncertain, and though the condition is far from synonymous with genuine neonatal hypothyroidism, it should be prevented as long as one is not certain that its effects on further development are unimportant. Substitution with thyroid hormone preparations has proven unsatisfactory in that respect since, in contrast to antithyroid drugs, thyroid hormone preparations cross the placental barrier to a minimal extent.

Neonates born of mothers who suffered acute and rapidly evolving hyperthyroidism during pregnancy are particularly at risk. In this paper a case of acute hyperthyroidism during pregnancy is reported and discussed.

CASE HISTORY

Mrs. B.E., an otherwise healthy 24-yr-old caucasian primigravida, stopped oral contraception in November 1979 (withdrawal date unknown). Her family and personal histories were uneventful. In early April, 1980, an ophthalmologist was consulted because of eye irritation, but no treatment was offered. Though she had been examined on April 14th and 25th, 1980, by a private gynecologist, she sought advice at our antenatal clinic on July 15th, where she presented with exophthalmos, an obvious goiter, and many signs which were typical for hyperthyroidism, such as excessive lacrimation and perspiration, photophobia, prethyroid thrill, vascular murmur, palpitations, tachycardia, tremor, and hyperkinetic behavior.

Gynecological examination revealed a normal status. Echography showed a gestational age of 21 wk. Fetal heart rate exceeded 180 beats/min. The consulted ophthalmologist confirmed the presence of a serious infiltrative endocrine exophthalmos. Blood was drawn for assessment of thyroid function: values reached upper limits of determination (Table I).

Subsequent therapeutic attitudes were dictated by the rapidly evolving eye symptomatology. For this reason it was decided to perform a subtotal thyroidectomy. As a preparatory treatment, lugol (3 X 10 drops daily) and propranolol (Inderal®, 3 X 30 mg daily) were given orally. As a result of this preparation, thyroxin (T₄) and triiodothyronine (T₃) serum levels showed a sharp decline (Fig. 1). On July 28th, subtotal thyroidectomy was performed. Transient hypocalcemia (7.6 mg%) ensued, manifested by short-lasting paresthesias. Normalization was obtained through administration of calcium gluconolactate and calcium carbonate during 1 mth. Postoperative substitution therapy consisted of l-thyroxine (Elthyron®, 0.1 mg twice daily) and, initially, propranolol (20 mg 3 times daily), taken orally. However, propranolol was soon discontinued. The patient remained euthyroid after thyroidectomy. During the subsequent twice-weekly follow-up, only a short-lasting exacerbation of exophthalmia was noticed. Since T₃ serum levels remained within normal ranges (Fig. 1) and since the patient remained clinically euthyroid, therapy was not altered. After the operation was performed, fetal tachycardia was no longer detected by external cardiotocographic monitoring, which was performed eighteen times after the operation. Conse-
TABLE I
THYROID FUNCTION ASSESSMENT IN MATERNAL SERUM AT VARIOUS INSTANCES OF PREGNANCY (T₄, T₃, TBG AND TSH)

<table>
<thead>
<tr>
<th>Date</th>
<th>T₄ (µg/100 ml)</th>
<th>TSH (µIU/ml)</th>
<th>T₃ (ng/100 ml)</th>
<th>TBG (mg/100 ml)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>16.07.80</td>
<td>32.5</td>
<td>&lt;1</td>
<td>406</td>
<td>3.4</td>
<td>First consultation (21st wk)</td>
</tr>
<tr>
<td>24.07.80</td>
<td>10.3</td>
<td>&lt;1</td>
<td>190</td>
<td>—</td>
<td>Preoperative lugol treatment</td>
</tr>
<tr>
<td>29.08.80</td>
<td>25.1</td>
<td>&lt;1</td>
<td>310</td>
<td>4.6</td>
<td>Postoperative day 1; 23rd wk</td>
</tr>
<tr>
<td>18.09.80</td>
<td>27.9</td>
<td>&lt;1</td>
<td>230</td>
<td>3.9</td>
<td>29th wk</td>
</tr>
<tr>
<td>03.10.80</td>
<td>25.7</td>
<td>&lt;1</td>
<td>244</td>
<td>4.5</td>
<td>31st wk</td>
</tr>
<tr>
<td>17.10.80</td>
<td>19.7</td>
<td>&lt;1</td>
<td>168</td>
<td>4.8</td>
<td>33rd wk</td>
</tr>
<tr>
<td>22.10.80</td>
<td>21.7</td>
<td>&lt;1</td>
<td>174</td>
<td>—</td>
<td>34th wk</td>
</tr>
<tr>
<td>31.10.80</td>
<td>21.1</td>
<td>&lt;1</td>
<td>206</td>
<td>—</td>
<td>1 wk postpartum</td>
</tr>
<tr>
<td>03.02.81</td>
<td>16.4</td>
<td>&lt;1</td>
<td>192</td>
<td>2.7</td>
<td>14 wk postpartum</td>
</tr>
</tbody>
</table>

Normal values: 5—11 µg/100 ml
T₄ serum values (mg/100 ml)

Fig. 1. Graphical representation of maternal thyroid function during pregnancy, assessed by T₄ (µg/100 ml), T₃ (ng/100 ml), TBG (mg/100 ml) and TSH (µIU/ml) measurements.
quently, propylthiouracil (Strumanzol®), a widely used antithyroid drug, was not added to the therapeutic regimen.

Biparietal diameters, as a measure for intrauterine growth, evolved normally.

Although no obvious contractions were registered by ECTG, and although bed-rest was observed prophylactically, routine pelvic examination in the antenatal clinic revealed that the cervix had shortened and dilated, necessitating hospitalization at 34 wk gestation.

Beta-mimetic drugs, being contra-indicated in case of maternal hyperthyroidism because of their cardiovascular side-effects, were not given. Naproxene (Naprosyne®, 4 × 250 mg daily), a prostaglandin synthesis inhibitor, was started. However, on October 24th, 1980, labor could no longer be inhibited. After an explosive first stage of labor, delivery was accomplished by means of vacuum extraction, indicated by persistent fetal bradycardia. The infant, at birth, weighed 2090 g and had Apgar-scores of 8 and 9 after 1 and 5 min, respectively.

The neonate was hyperthyroid, showing bilateral exophthalmos and signs of hemodynamic disturbances. Therapy was immediately instituted, consisting of lugol (3 × 1 drop daily), propanolol (3 mg daily). Both T₃ and T₄ serum levels declined rapidly (Fig. 2). When thyroid suppression appeared

![Graph](image-url)

Fig. 2. Graphical representation of neonatal thyroid function, assessed by T₄ (μg/100 ml), T₃ (ng/100 ml) and TSH (μIU/ml) measurements.
too pronounced, causing danger for hypothyroidism, l-thyroxine (10 μg daily at first and 25 μg daily subsequently), was added. The clinical features of both mother and neonate are illustrated in Fig. 3. Length, weight and head circumferences of the baby are illustrated in Fig. 4, using curves according to Lubchenko (1966).

Neonatal serum antithyroglobulin levels remained negative. However, antimicrosomal antibodies initially showed high serum levels, but declined progressively, showing constantly low serum levels after 4 wk. At that moment, the neonate was not yet euthyroid and treatment had to be con-
Fig. 4. Evolution of neonatal length, weight and head circumference, plotted on evolution curves according to Lubchenko (1966).

continued for another 4 wk. After 8 wk, he became euthyroid and treatment was discontinued.

DISCUSSION

The decision to administer antithyroid drugs to a pregnant hyperthyroid woman is dependent mainly on serum thyroid function tests (Chan et al., 1975; Finucane et al., 1976; Wallace and Gandhi, 1978; Soler and Nicholson, 1979). As a rule, the lowest possible dose must be given. However, it has been demonstrated that even very low doses (e.g., 100--200 mg propyl-
thiouracil daily) may result in a hypothyroid neonate (Cheron et al., 1981), even when thyroid hormone is added.

If, during pregnancy, a diagnosis is made of acute hyperthyroidism with severe eye symptoms evolving very rapidly and a sizeable goiter, it may be an indication to diverge from the classical therapeutic attitudes as mentioned above. In the case discussed, oral administration of antithyroid drugs for a period of 4–6 wk until the patient would have been euthyroid might have been too long and with an uncertain result. Therefore, a surgical approach was preferred after preparatory treatment with lugol for an 8-day period. Since the patient became euthyroid after thyroidectomy, which was the mainstay of therapy in this case, and remained so during the entire time afterwards, it seemed unnecessary to add antithyroid drugs, at least from the maternal point of view.

Another reason why antithyroid drugs might have been added would have been if the fetus was suspected of being hyperthyroid. Practically speaking, this condition should be suspected when persistent fetal tachycardia (180 beats/min) is demonstrated (Serup and Petersen, 1977). Measurement of fetal movements (Solomon, 1981), or measurements of rT₃ concentrations in amniotic fluid (Solomon, 1981) are less reliable, or carry their own intrinsic risks. Maternal antibody concentrations have been used but data are based on anecdotal information or limited personal experience. Prior to thyroidectomy, fetal tachycardia was noted on only one occasion, namely at the patient's first antenatal visit. Between thyroidectomy and delivery, eighteen ECTG monitorings were performed. Not one showed fetal tachycardia, and it did not seem necessary, therefore, to add antithyroid drugs from the fetal point of view either. It should not be concluded, however, that the absence of fetal tachycardia excludes fetal hyperthyroidism completely, as this case clearly demonstrated.

Propranolol and other beta-sympathomimetic drugs may affect the fetal outcome (Burrow, 1978). Moreover, the oocytic activity of these compounds, acting as antagonists to endogenous catecholamines for uterine beta-receptor binding sites, is a further argument not to use these drugs for a prolonged period of time during pregnancy.

The neonate in the case studied, was not euthyroid. This suggests that, even when the mother was euthyroid, intrauterine exposure to thyroid-stimulating antibodies may disturb fetal and neonatal thyroid function and regulation.

Hollingsworth et al. (1980) and others (Pharaoh et al., 1976; Harada et al., 1979; Hales et al., 1980) demonstrated that the fetal outcome did not correlate with maternal thyroid status during pregnancy. Congenital Graves—Basedow disease is now considered to be much more than a mere result of fetal exposure to maternal antibodies, exhibiting a clinical picture that is as wide and variable as in the adult. From their study material, these authors conclude that for children, born from mothers with hyperthyroidism, irrespective of whether the hyperthyroidism occurred before or during pregnancy, and irrespective of whether the mother was hyper- or hypothyroid
or euthyroid during pregnancy, congenital Graves—Basedow disease brings about a very high incidence of problems, such as preterm birth (38%), intrauterine growth retardation and dysmaturity (42%) and a number of congenital malformations including cardiac anomalies. A long-term follow-up of neonates from this study material showed that after 14 yr, 2 out of 26 children died, whereas of the remaining 24, 12 were euthyroid, but 8 were still hyperthyroid after 1 yr. Seven out of the 26 neonates were hypothyroid at birth. All were born of mothers treated with antithyroid drugs.

These data serve as evidence that children born of mothers with Graves—Basedow disease are at high risk for neonatal hyper- or hypothyroidism, preterm birth, dysmaturity and congenital malformations. When hyperthyroidism is recorded in a pregnant woman’s history, she should be closely watched antenatally and have endocrinologic, echographic and ophthalmologic evaluations.

Transplacental transport of thyroid-stimulating immunoglobulins is not the only factor determining neonatal outcome, as observations with monozygous twins of hyperthyroid mothers have shown. Hales et al. (1980) have shown that placental transmission of thyroid stimulating immunoglobulins may occur without neonatal hyperthyroidism. This suggests that genetic factors may play a significant role in the etiology of congenital hyperthyroidism.

In cases of acute hyperthyroidism, it is difficult to decide when to use antithyroid drugs. It should be remembered that a neonate born of a hyperthyroid mother always belongs to one of the following groups: the fetus or neonate (1) may be euthyroid; (2) may show transient hyperthyroidism because of a sudden lack of exposure to antithyroid drug therapy given to the mother; (3) may exhibit an existing hyperthyroidism as a result of exposure to maternal thyroid-stimulating antibodies, which do not disappear immediately; (4) may suffer a genuine congenital hyperthyroidism through combined immunogenetic defects; or (5) may be hypothyroid as a result of maternal antithyroid drug treatment. Neonatal hyperthyroidism which is dependent upon maternal thyroid-stimulating immunoglobulins will resolve itself spontaneously when these antibodies disappear from the serum of the neonate.

Initially, it was thought that these antibodies, mainly antithyroid microsomal antibodies, antithyroglobulin antibodies and the long-acting thyroid stimulator, disappeared from neonatal serum after 6—8 wk. Antithyroid drug therapy of the neonate was therefore discontinued at that age. However, neonates have been noted to remain hyperthyroid much longer than might be expected from declining levels of the antibodies mentioned, as was observed in the present case. This could be due to a fourth group of thyroid stimulating antibodies, thyroid stimulator immunoglobulins (TSI’s), which may have a longer half-life in the neonate. Serum levels of TSI’s might show a better correlation with the clinical severity of hyperthyroidism in neonates than serum levels of other immunoglobulins, mentioned above. Unfortunately, quantitative assessment of TSI’s is still difficult and largely unreli-
able. The suggestion is put forward that treatment of hyperthyroidism should be continued until all demonstrable antibodies have disappeared from the serum. This could consist of the administration of sedatives, propanolol (Inderal®, 2 mg/kg daily) and antithyroid drugs (e.g., propylthiouracil, Strumazo®, 5–10 mg/kg daily). In severe cases, lugol and cardiotonic drugs should be added.

Other forms of treatment of hyperthyroidism during pregnancy, such as the use of radioactive iodine, or treatment with bed-rest and sedatives only, are not considered serious alternatives to either antithyroid or surgical treatment, the former being totally contraindicated during pregnancy, the latter being largely symptomatic and of little use in severe, acute cases with rapidly evolving clinical symptomatology.

CONCLUSION

The obstetrician must be aware of the possible coincidence of hyperthyroidism and pregnancy (0.2–0.5%). Symptoms of hyperthyroidism may be masked by normal signs of pregnancy and this may be responsible for late diagnosis. The occurrence of acute hyperthyroidism in pregnancy remains rare, but early diagnosis is imperative since treatment may differ from classical antithyroid drug treatment. To secure good fetal outcome, intensive antenatal care must be given once the diagnosis is made.

REFERENCES


