Persistent high TRAb values during pregnancy predict increased risk of neonatal hyperthyroidism following radioiodine therapy for refractory hyperthyroidism

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Abstract. Serum levels of TSH receptor antibody (TRAb) often increase after radioiodine treatment for Graves’ disease, and high-serum levels of maternal TRAb in late pregnancy indicate a risk of neonatal hyperthyroidism. The aim of this retrospective study is to investigate the characteristics of Graves’ women who had a history of radioiodine treatment for intractable Graves’ disease, and whose neonates suffered from hyperthyroidism. The subjects of this study were 45 patients with Graves’ disease who underwent radioiodine treatment at Ito Hospital. 25 of the 45 subjects had a history of hyperthyroidism following radioiodine treatment. 19 pregnancies were excluded because of artificial or spontaneous abortion. In the remaining 44 pregnancies of 35 patients, neonatal hyperthyroidism developed in 5 (11.3%) pregnancies of 4 patients. Serum levels of TRAb at delivery were higher in patients whose neonates suffered from hyperthyroidism (NH mother) than those of patients who delivered normal infants (N mother). Furthermore, serum levels of TRAb in NH mother did not change during pregnancy, although those of 4 patients of N mother, in which serum levels of TRAb before radioiodine treatment were as high as in NH mother, decreased significantly during pregnancy. In conclusion, women who delivered neonates with hyperthyroidism following radioiodine treatment seem to have very severe and intractable Graves’ disease. Persistent high TRAb values during pregnancy observed in those patients may be a cause of neonatal hyperthyroidism.

Key words: TSH receptor antibody, Graves’ disease, Neonatal hyperthyroidism, Radioiodine treatment, Pregnancy

SERUM concentrations of TSH receptor antibodies (TRAb) often increase after radioiodine therapy for Graves’ disease [1, 2]. On the other hand, high-serum levels of maternal TRAb in late pregnancy indicate a risk of neonatal hyperthyroidism [3, 4]. Therefore, there seems to be concern about neonatal hyperthyroidism during pregnancy following radioiodine therapy for Graves’ disease. However, only a few cases have been reported of neonatal hyperthyroidism and previous maternal radioiodine therapy [5, 6]. Kaplan et al. wrote in their review on treating hyperthyroidism with radioactive iodine that women who are planning to conceive more than a few months in the future are good candidates for radioactive iodine therapy because, during future pregnancies, such women will need no thyroid medication [7].

We summarized the results of pregnancy in patients with Graves’ disease who received radioiodine therapy at our institute, and reported a high incidence of neonatal hyperthyroidism in infants at the 73rd Annual Congress of the Japan Endocrine Society in 2000 [8]. The aim of this retrospective study is to investigate the characteristics of Graves’ women whose neonates suffered from hyperthyroidism during pregnancy after radioiodine treatment.

Patients and Methods

The subjects of this study were 45 patients with Graves’ disease who became pregnant during the
period from 1988 to 1998 after receiving radioiodine treatment at Ito hospital. Their ages were 28.8 ± 7.3: mean ± SD y/o when treated with radioiodine, and 34.7 ± 4.1 when pregnant. No patients had a history of pregnancy before radioiodine treatment. Out of 45 patients, 25 had had a relapse of hyperthyroidism after surgical treatment.

TRAb was measured by radioreceptor assay (PEG method) using a commercially available kit (TSH Receptor Antibody Assay kit, Cosmic Co., Tokyo, Japan). The reference range for TRAb was -10% to +10%.

**Statistical analysis**

Non-parametric Mann-Whitney’s U test was used for comparing two groups, and paired t-test was used to compare means of the same subject over time. A probability of less than 0.05 was considered significant.

**Results**

**Outcome of pregnancy**

63 pregnancies were observed in 45 patients. Of those 63 pregnancies, artificial abortion was performed on 11 pregnancies, and spontaneous abortion was observed in 8 pregnancies. 44 pregnancies of 35 patients gave birth. Premature birth and malformation were not observed. Neonatal hyperthyroidism was observed in 5 (11.3%) pregnancies of 4 patients.

**Comparison of patients who delivered infants with neonatal hyperthyroidism and normal infants**

Table 1 shows a comparison of patients who delivered infants with neonatal hyperthyroidism (NH mother) and patients who delivered normal infants (N mother). The dose of $^{131}$I was larger, thyroid weight before treatment was greater, and the serum level of TRAb before radioiodine treatment was higher in NH mother than in N mother, but the differences were not significant. There was no significant difference in days from radioiodine treatment to pregnancy between the 2 groups. The serum level of TRAb at delivery was significantly higher in NH mother than in N mother. Thyroid function at delivery was normal in all patients, while 3 of NH mother and 10 of N mother were being treated with an antithyroid drug. 1 of NH mother and 3 of N mother were being treated with iodine, and 6 of N mother were being treated with levothyroxine.

Changes of serum levels of TRAb in NH mother after radioiodine treatment were compared to those in 4 patients of N mother in which serum levels of TRAb before radioiodine treatment were as high as in the NH group (severe N mother; Fig 1). Serum levels of TRAb in NH mother did not change after radioiodine treatment, even during pregnancy, but that in severe N mother decreased significantly following radioiodine treatment and during pregnancy. There were no significant differences in serum levels of TRAb before radioiodine treatment were as high as in the NH group (severe N mother; Fig 1). Serum levels of TRAb in NH mother did not change after radioiodine treatment, even during pregnancy, but that in severe N mother decreased significantly following radioiodine treatment and during pregnancy. There were no significant differences in serum levels of TRAb before radioiodine treatment and at the first trimester between NH mother (before treatment 75.7 ± 7.4%, mean ± SD, at the first trimester 63.3 ± 18.9) and severe N mother (77.8 ± 7.5, 47.2 ± 17.7). However, serum levels of TRAb in NH mother at delivery (65.8 ± 22.5) were significantly higher than in severe N mother (26.7 ± 7.0, P < 0.05). There was a significant difference in the ratio of TRAb at delivery to TRAb at first trimester between NH mother and severe N mother (Fig 2). Dose of $^{131}$I, thyroid weight before radioiodine treatment, and days from radioiodine treatment to pregnancy in NH mother were not different from those in severe N mother.

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**Table 1** Comparison of Graves’ mothers treated with radioiodine (RI) who delivered infants with neonatal hyperthyroidism (NH mother) and normal infants (N mother)

<table>
<thead>
<tr>
<th></th>
<th>NH mother</th>
<th>N mother</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>4</td>
<td>31</td>
</tr>
<tr>
<td>Number of pregnancies</td>
<td>5</td>
<td>39</td>
</tr>
<tr>
<td>Dose of $^{131}$I (mCi)</td>
<td>40.2 ± 33.0 (4)</td>
<td>8.7 ± 11.9 (27)</td>
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<tr>
<td>Thyroid weight before RI treatment</td>
<td>87.5 ± 38.6 (4)</td>
<td>54.0 ± 21.1 (16)</td>
</tr>
<tr>
<td>Days from RI treatment to pregnancy before RI treatment</td>
<td>1127 ± 809 (5)</td>
<td>1844 ± 1916 (38)</td>
</tr>
<tr>
<td>TRAb (%) at delivery</td>
<td>65.8 ± 22.5 (5)</td>
<td>23.3 ± 16.0 (14)</td>
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( ):n ns: not significant
**Radioiodine treatment and pregnancy**

Graves’ disease during the period from 1988-1989 at Ito hospital, but the number of patients who became pregnant after radioiodine treatment during the same period was 45 as shown in this study; that is, about 1% of those patients. Most were intractable Graves’ disease, including recurrent cases after surgical treatment, and this may be a reason why a high incidence of neonatal hyperthyroidism was observed in this study. Patients who delivered neonatal hyperthyroidism seemed to have had very severe and intractable Graves’ disease because dose of $^{131}$I and thyroid weight before treatment were both large, and serum levels of TRAb were very high before radioiodine treatment in those patients although the differences were not significant. This is supported by a report of Tajiri that the incidence of neonatal hyperthyroidism was not high in infants born to ordinary Graves’ mothers after radioiodine treatment with serum levels of TRAb of more than 50% before therapy [10].

There is no doubt that the occurrence of neonatal hyperthyroidism results from the transplacental passage of maternal TRAb. On the other hand, serum levels of TRAb often increase after radioiodine treatment and begin to decrease long after treatment [11, 12, and 13]. Therefore, the occurrence of neonatal hyperthyroidism seems to be a matter of concern in pregnancies of severe Graves’ patients after radioiodine treatment. However, in most cases, as reported by Tajiri, neonatal hyperthyroidisms do not occur because serum TRAb usually decreases during pregnancy even if the serum level of TRAb is high at the first trimester [10, 14]. In this study, among patients with high serum TRAb at the first trimester, serum levels of TRAb of mothers

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**Fig. 1** Comparison of changes of serum TRAb levels after radioiodine (RI) treatment in mothers who gave birth to neonates with hyperthyroidism (a, ● ; NH mother) with those in mothers in whom serum TRAb before RI treatment was as high as that of mothers of neonates with hyperthyroidism, but who gave birth to normal infants (b, ○ ; severe N mother). ns: not significant

**Fig. 2** The ratio of TRAb at delivery to TRAb at first trimester in mothers who gave birth to neonates with hyperthyroidism (NH mother) and in mothers in whom serum TRAb before radioiodine treatment was as high as that of mothers of neonates with hyperthyroidism, but who gave birth to normal infants (severe N mother).

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**Discussion**

Neonatal Graves’ thyrotoxicosis occurred in fewer than 2% of infants born to mothers who had Graves’ thyrotoxicosis during or before pregnancy [9]. In this report, the incidence of neonatal hyperthyroidism in infants born to mothers with Graves’ disease who received radioiodine therapy was 11.3%. Before 1998, when these patients were treated with radioiodine, it had been thought in Japan that radioiodine treatment was contraindicated for Graves’ patients who wanted to get pregnant in the future. As a matter of fact, there were nearly 5000 pregnant cases complicated with Graves’ disease during the period from 1988-1989 at Ito hospital, but the number of patients who became pregnant after radioiodine treatment during the same period was 45 as shown in this study; that is, about 1% of those patients. Most were intractable Graves’ disease, including recurrent cases after surgical treatment, and this may be a reason why a high incidence of neonatal hyperthyroidism was observed in this study. Patients who delivered neonatal hyperthyroidism seemed to have had very severe and intractable Graves’ disease because dose of $^{131}$I and thyroid weight before treatment were both large, and serum levels of TRAb were very high before radioiodine treatment in those patients although the differences were not significant. This is supported by a report of Tajiri that the incidence of neonatal hyperthyroidism was not high in infants born to ordinary Graves’ mothers after radioiodine treatment with serum levels of TRAb of more than 50% before therapy [10].

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Although the increase of serum TRAb after radioiodine treatment may not relate to the occurrence of neonatal hyperthyroidism, it is difficult to treat fetal hyperthyroidism occurring in pregnancy following radioiodine treatment. Because there is no way to predict the change of serum TRAb during pregnancy in individual patients at the present time, patients with intractable Graves’ disease who want to get pregnant in the near future and who have extremely high TRAb levels should be informed of the risks of developing fetal and/or neonatal hyperthyroidism during pregnancy after radioiodine treatment.

References