Thyroxine treatment modified in infertile women according to thyroxine-releasing hormone testing: 5 year follow-up of 283 women referred after exclusion of absolute causes of infertility

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BACKGROUND: Mild hypothyroidism may contribute to disturbed reproductive function. We hypothesized that frequent thyroxine-releasing hormone (TRH) testing to fine-tune thyroxine (T4) therapy instituted upon every TRH-induced thyroid-stimulating hormone (TSH) rise above the mean of a healthy population (i.e. 15 mIU/l) would improve fecundity compared with historical data. METHODS: In a cohort of 283 infertile women followed over 5 years, we assessed (i) pregnancy, abortion and delivery rates, (ii) thyroid function over time in women who conceived compared with those who did not, and (iii) various thyroid parameters with respect to fertility. RESULTS: Overall conception rate of 37% was higher ($P < 0.05$) than previously reported and independent of thyroid function prior to T4 therapy, thyroxine dose or elevated thyroid autoantibodies. Never achieving basal TSH <2.5 IU/l or TRH-stimulated TSH <20 mIU/l with T4 therapy resulted in lower conception rates ($P < 0.05$). Median time to conception was 6 months, but 18 months in women who declined TRH testing ($P < 0.02$). Overall abortion rate was 9%. Only first trimester miscarriages occurred. CONCLUSIONS: Based on the presented protocol, high pregnancy and parturition rates were observed. Whether this is due to early T4 therapy remains to be determined. Abortions appeared to be associated with higher TSH but not with elevated thyroid antibodies.

**Key words:** cohort study/infertility/mild hypothyroidism/thyroxine therapy/TRH test

**Introduction**

Approximately 10–15% of all married couples in the USA are childless (Davajan and Israel, 1998). Examination of parish registries between 1550 and 1850 in Cambridge, UK, from an era that predated contemporary methods of sterilization and contraception, revealed that 8% of married women were sterile throughout their reproductive life (Trussel and Wilson, 1985). Population-based infertility data of women with subclinical hypothyroidism are not available. Hyperprolactinaemia due to increased hypothalamic thyroxine-releasing hormone (TRH) secretion was suggested 17 years ago as a cause of infertility in hypothyroidism (Thomas and Reid, 1986). However, pulsatile secretion of LH, FSH and prolactin is not altered in infertile women with overt hypothyroidism (Tomasi et al., 1997) or with a TRH-stimulated thyroid-stimulating hormone (TSH) >20 mIU/l in the presence of a normal basal TSH (Bals-Pratsch et al., 1997). In addition, basal and TRH-stimulated serum prolactin concentrations in mild and severe hypothyroidism are not different from euthyroid subjects (Bigos et al., 1978). This corresponds to recent epidemiological and clinical observations of a large number of patients demonstrating that hypothyroidism is associated with only minor menstrual disturbances and minimal changes in the serum prolactin concentrations (Vanderpump et al., 1998; Krassas et al., 1999; Raber et al., 2003).

Thyroid hormones, on the other hand, play a role in the modulation of the LH- and FSH-mediated control of granulosa cell function. There are experimental data of both stimulatory (Maruo et al., 1987; Wakim et al., 1995) and inhibitory effects (Channing et al., 1976; Wakim et al., 1993; Cecconi et al., 1999) of thyroid hormones on mammalian granulosa cell gonadotropin-induced steroidogenesis. These controversial (stimulatory or inhibitory) effects of thyroid hormones may be due to the different responsiveness to tri-iodothyronine (T3) of granulosa cells isolated from follicles at different stages of antral development, with small and medium follicles displaying a higher number of T3 binding sites than large antral follicles (Maruo et al., 1993). They may, on the other hand, also be due to the different species studied, and/or due to different culture conditions used (Cecconi et al., 1999). In fact,
stimulatory effects of T3 on mammalian granulosa cell steroidogenesis have been suggested to depend upon the presence of insulin in the culture medium (Channing et al., 1976; Wakim et al., 1993; Cecconi et al., 1999). As obtained from patients undergoing therapeutic abortions at 7–8 weeks gestation, thyroxine (T4) and T3 in first trimester placentas were amplifiers of differentiated trophoblast function (Maruo et al., 1991). In addition, data from clinical studies have demonstrated that thyroid hormone replacement therapy increased the success rate of ovulation induction by clomiphene citrate in women with subclinical hypothyroidism (Maruo et al., 1993). Taken together, hypothyroidism may, even at an early stage, have an important impact on conception.

Once pregnancy has occurred, thyroid hormones contribute to the stability of the feto-placental unit, protecting from early loss of the conceptus (Maruo et al., 1992; La Marca et al., 1998). In that context it is worth mentioning that until recently it was believed that fetal human tissues during early phases of development are exposed to only trace amounts of thyroid hormones (Burrow et al., 1994). However, it was lately demonstrated that amniotic fluid, coelomic fluid and fetal blood T4 concentrations of first trimester human pregnancies (as early as the 5th week of gestation) are in the same range as those available to adult tissues and depend ultimately on the circulating maternal T4 serum concentrations (Calvo et al., 2002).

In the present study, a cohort of 283 infertile women was followed over 5 years under routine daily outpatient care. After exclusion of absolute causes of sterility (such as bilateral tubal obstruction and azoospermia of the male partner) all women with primary or secondary infertility were included. Due to the lack of prospective data on the influence of thyroid hormone replacement on fertility in women with mild thyroid impairment and on the optimal TSH threshold for therapy, patients with a TRH-stimulated TSH response to >15 mIU/l [the mean of healthy euthyroid subjects (Keller, 1986; Vierhapper, 1997)] were treated with T4. This allowed us to compare our results with those of previously reported cohorts who were treated according to similar thresholds (Bohnet et al., 1981; Merzough et al., 1990; Gerhard et al., 1991; Moltz et al., 1991; Bals-Pratsch et al., 1993). Women were invited every 3 months until conception, and, if pregnancy occurred, every 4 weeks until the 12th week, then every 3 months until delivery. Except for the time during gestation, TRH tests were performed at every visit to allow the fine adjustment of T4 therapy (Carr et al., 1988).

At first visit either ultrasonographic thyroid echographic pattern (by Ultrasound System Sonoline Prima LC; Siemens, Erlangen, Germany, with a Siemens 7.5L75G Ultrasound Transducer, 7.5 MHz linear array probe) as described previously (Raber et al., 2002), or thyroid peroxidase (TPO) and thyroglobulin (TG) antibody serum concentrations (normal: <100 IU/ml; ORGenTec, Mainz, Germany; calculated functional sensitivity 10 IU/ml, coefficients of variation <5, <7 and <12% at plasma concentrations of 70, 250 and 1000 IU/ml respectively) were obtained as a surrogate to the diagnosis of chronic autoimmune thyroiditis.

Pregnancy, abortion and delivery rates were compared between women with different thyroid function at first presentation as outlined in Table I [group 1 = mild (subclinical) hypothyroidism I: elevated basal TSH in the presence of normal T4; group 2 = mild hypothyroidism II: normal basal TSH but exaggerated TRH-stimulated TSH (the latter according to 2 definitions; see Table I) in the presence of normal T4; group 3 = euthyroidism: normal basal and TRH-stimulated TSH in the presence of normal T4; group 4 = no TRH test: normal basal TSH in the presence of normal T4 but without TRH test at first visit]. Only healthy babies had been delivered. Thyroid function over the observation period was compared between women who conceived with those who did not. Parameters such as thyroid function at first visit, thyroid function achieved during the observation period, T4 substitution dose, duration of sterility prior to first presentation, length of follow-up, number of ambulatory visits, the total number of TRH tests, the presence/absence of autoimmune thyroiditis, and age were analysed to identify ‘fertility’ factors.

Materials and methods

Patients
From January 1998 until January 2002, 283 women with primary (when conception has not occurred after 1 year of unprotected intercourse) or secondary (when at least one previous conception has been either hormonally or histologically documented) infertility (Davajan and Israel, 1998) were referred to our thyroid outpatient unit to exclude hyper- and hypothyroidism as part of a routine infertility work-up. Pregnancy rates of regularly menstruating women (72% of our cohort) were not different from those with irregular menstrual cycles or oligomenorrhea (when the interval between two cycles was >35 days). In addition, women with abnormalities in one of the commonly used infertility tests often also had a borderline and even pathological result in another, although this did not preclude successful conception. There are few data on the predictive values of commonly employed infertility tests (Guzick, 2001). Short of absolute infertility factors (bilateral tubal obstruction or azoospermia of the male partner) which would necessitate assisted reproductive technology, an abnormal result of one of these infertility tests cannot be suggested as being the cause of sterility in a particular couple (Guzick et al., 1994). Therefore no effort was made to exclude patients other than those with absolute causes of infertility.

Methods

Thyroid function tests at first visit included total T4, total T3, T4-binding globulin (TBG), basal and TRH (400 μg i.v. bolus, Relefact®; Aventis, Frankfurt, Germany)-stimulated serum TSH (assessed 20 min after the TRH bolus) by conventional radioimmunooassay (Rodent et al., 1993). All patients had normal TBG serum concentrations. Due to the lack of prospective data on the influence of thyroid hormone replacement on fertility in women with mild thyroid impairment and the optimal threshold for therapy, all patients with a TRH-stimulated TSH response to >15 mIU/l [the mean of healthy euthyroid subjects (Keller, 1986; Vierhapper, 1997)] were treated with T4. This allowed us to compare our results with those of previously reported cohorts who were treated according to similar thresholds (Bohnet et al., 1981; Merzough et al., 1990; Gerhard et al., 1991; Moltz et al., 1991; Bals-Pratsch et al., 1993). Women were invited every 3 months until conception, and, if pregnancy occurred, every 4 weeks until the 12th week, then every 3 months until delivery. Except for the time during gestation, TRH tests were performed at every visit to allow the fine adjustment of T4 therapy (Carr et al., 1988).
Thyroxine therapy in infertile women according to TRH testing

Table I. Criteria used for the grouping of patients according to thyroid function at first visit

<table>
<thead>
<tr>
<th>Group</th>
<th>Diagnosis</th>
<th>Criteria</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (n = 76)</td>
<td>Subclinical hypothyroidism</td>
<td>Basal TSH &gt;4.0 mIU/l, plus normal total T4 (5.0–11.2 μg/dl), T3 (0.9–1.8 ng/ml), and TBG (12–32 μg/ml)</td>
<td>Cooper (1994)</td>
</tr>
<tr>
<td>2a (n = 60)</td>
<td>Exaggerated TRH-stimulated TSH rise (population-based)</td>
<td>TRH-stimulated TSH &gt;25 μIU/l (absolute) or to &gt;20 μIU/l above baseline plus normal basal TSH, total T4, total T3, and TBG</td>
<td>Keller (1986)</td>
</tr>
<tr>
<td>2b (n = 95)</td>
<td>Exaggerated TRH-stimulated TSH rise (one ‘gynaecological’ criterion)</td>
<td>TRH-stimulated TSH &gt;15 μIU/l (absolute) plus normal basal TSH, total T4, total T3, and TBG</td>
<td>Bohnet et al. (1981) and Merzough et al. (1990)</td>
</tr>
<tr>
<td>3 (n = 52, or n = 17)</td>
<td>Euthyroidism</td>
<td>Normal basal and TRH-stimulated TSH plus normal total T4, total T3, and TBG</td>
<td></td>
</tr>
<tr>
<td>4 (n = 35)</td>
<td>No TRH testing at first visit</td>
<td>Normal basal TSH, total T4, total T3, and TBG, but no TRH testing</td>
<td></td>
</tr>
</tbody>
</table>

TSH = thyroid-stimulating hormone; T4 = thyroxine; T3 = tri-iodothyronine; TBG = T4-binding globulin; TRH = thyroid-releasing hormone.

Table II. Characteristics of the study cohort divided into the groups outlined in Table I (patients lost to follow-up excluded)

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (years)</th>
<th>Duration of infertility prior to first visit (months)</th>
<th>Follow-up (months)</th>
<th>No. of visits</th>
<th>Untreated T4 (μg/dl)</th>
<th>Untreated basal TSH (mIU/l)</th>
<th>Untreated stimulated TSH (mIU/l)</th>
<th>Percentage visits with basal TSH &lt;2.5 μIU/l</th>
<th>Percentage visits with stimulated TSH &lt;20 μIU/l</th>
<th>T4 dose (μg/day)</th>
<th>Autoimmune thyroiditis (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>29±5</td>
<td>2±10</td>
<td>25±14</td>
<td>5±3</td>
<td>8.4±1.6</td>
<td>8.2±9.0</td>
<td>40.9±10.3</td>
<td>43±23</td>
<td>22±29</td>
<td>84±30</td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td>31±6</td>
<td>37±22</td>
<td>14±11</td>
<td>4±2</td>
<td>7.9±2.2</td>
<td>9.0±10.0</td>
<td>36.6±8.2</td>
<td>36±25</td>
<td>35±37</td>
<td>68±30</td>
<td>71</td>
</tr>
<tr>
<td>3</td>
<td>36±6</td>
<td>30±20</td>
<td>21±13</td>
<td>6±3</td>
<td>8.6±1.8</td>
<td>2.8±0.7</td>
<td>28.7±6.1</td>
<td>55±23</td>
<td>20±33</td>
<td>40±55</td>
<td>19</td>
</tr>
<tr>
<td>4</td>
<td>33±6</td>
<td>30±20</td>
<td>17±18</td>
<td>4±2</td>
<td>8.3±1.5</td>
<td>2.7±0.7</td>
<td>29.7±6.3</td>
<td>51±28</td>
<td>32±31</td>
<td>52±40</td>
<td>19</td>
</tr>
<tr>
<td>P-value</td>
<td>NS (0.09)</td>
<td>NS</td>
<td>0.004</td>
<td>0.006</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>0.05</td>
<td>NS</td>
</tr>
</tbody>
</table>

*According to a population-based definition of an exaggerated TRH-stimulated TSH rise (Keller, 1986).

Only patients with TRH testing at first visit (groups 1–3) are considered. Groups are separated into patients who became pregnant and those who did not. Data are mean±SD.

TSH = thyroid-stimulating hormone; T4 = thyroxine; NS = not significant.

Table III. Pregnancy and abortion rates of infertile women in retrospective studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Cohort n</th>
<th>Subclinical HT n (%)</th>
<th>Subclinical HT Definition</th>
<th>Overall conceptions in the study n (%)</th>
<th>Pregnancies in treated subclinical HT n (%)</th>
<th>Overall abortions n (%)</th>
<th>Abortions in subclinical HT n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bohnet et al. (1981)</td>
<td>150</td>
<td>20 (13)</td>
<td>bTSH &gt;3 or sTSH &gt;15 μIU/l (400 μg TRH)</td>
<td>NG</td>
<td>2 (10)</td>
<td>NG</td>
<td>NG</td>
</tr>
<tr>
<td>Gerhard et al. (1991)</td>
<td>181</td>
<td>74 (41)</td>
<td>bTSH &gt;6 or sTSH &gt;20 μIU/l (200 μg TRH i.v.)</td>
<td>91 (50)</td>
<td>8 (11)</td>
<td>24 (15)</td>
<td>NG</td>
</tr>
<tr>
<td>Bals-Pratsch et al. (1993)</td>
<td>118</td>
<td>29 (25)</td>
<td>sTSH &gt;12.5 μIU/l (200 μg TRH i.v.)</td>
<td>13 (9)</td>
<td>0 (0)</td>
<td>NG</td>
<td>NG</td>
</tr>
<tr>
<td>Moltz et al. (1991)</td>
<td>307</td>
<td>65 (21)</td>
<td>bTSH &gt;3 or sTSH &gt;17.5 μIU/l (400 μg TRH i.v.)</td>
<td>52 (17)</td>
<td>NG</td>
<td>NG</td>
<td>NG</td>
</tr>
<tr>
<td>Merzough et al. (1990)</td>
<td>857</td>
<td>95 (27)</td>
<td>bTSH &gt;5 or sTSH &gt;20 μIU/l (200 μg TRH i.v.)</td>
<td>134 (15.6)</td>
<td>23 (24)</td>
<td>32 (23.5)</td>
<td>NG</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages.

HT = hypothyroidism; bTSH = basal TRH-stimulated TSH serum concentration; sTSH = TRH-stimulated TSH serum concentrations; TSH = thyroid-stimulating hormone; TRH = thyroid-releasing hormone; NG = not given.

(Keller, 1986). The latter had been obtained in 100 healthy subjects and revealed an increase to >25 μIU/l (absolute) or 20 μIU/l above baseline as the upper limit (defined by the mean + 2 SD) of normal (Keller, 1986). Subclinical hypothyroidism was defined by an elevated basal TSH (>4.0 μIU/l) in the presence of normal T4, T3 and TBG serum concentrations (Cooper, 1994). Conception times were compared with the Mann–Whitney U-test. Thyroid function at various time-points was compared by analysis of variance (ANOVA) and the Kruskal–Wallis test between women who conceived and those who did not.
ANOVA with the Scheffe post-hoc multiple comparison procedure were used to compare means of the different parameters outlined above between women who conceived with those who did not.

Results

Basic characteristics (Tables I and II)

Sixty women (21%) were lost to follow-up after their first visit. There was no difference with respect to age, duration of infertility, T4, and basal or stimulated TSH serum concentrations at referral compared with the other 223 patients.

A total of 223 women aged (mean ± SD) 32 ± 7 (range: 19–49) years were followed for 20 ± 14 (3–60) months. Patients had been sterile for a mean of 2.1 years (range: 1–13) prior to referral. This cohort included 160 (72%) women with primary and 63 (28%) with secondary infertility. Autoimmune thyroiditis was present in 41% (n = 66) and 48% (n = 30) of patients with primary and secondary infertility respectively (P = not significant). Thirty-three of the 63 women with secondary infertility were childless after one abortion (n = 20), two (n = 10), three (n = 2) or 13 (n = 1) miscarriages. The percentage of autoimmune thyroiditis in women with secondary infertility who had not given birth was similar to that in the 30 women with secondary infertility who already had children (39 versus 57% respectively).

There was no history of ablative (radioiodine or surgical) therapy of prior hyperthyroidism in any patient. Fifteen women (7%) were on T4 therapy for primary hypothyroidism (among them n = 10 with elevated basal TSH).

Pregnancy, abortion and delivery rates

Population-based definition of euthyroidism (Figure 1)

Pregnancy rates of the four groups were similar [group 1: 31% (95% CI: 21–41%), group 2: 46% (95% CI: 35–58%), group 3: 37% (95% CI: 33–50%), group 4: 33% (95% CI: 24–42%)]. Conception occurred later in group 4 than in all other groups (P < 0.02) with a median time to pregnancy of 18 months compared with 6 months (group 1 and 2), and 9 months (group 3) respectively (Figure 2).

Abortion rates were not different between groups 1 and 2 [20% (95% CI: 2–37%) versus 18% (95% CI: 0–43%)]. There was only one miscarriage in group 3 and none in group 4, so comparisons could not be made with these two groups. Only first trimester miscarriages were observed. No correlation was observed between abortion and the presence of autoimmune thyroiditis.
Partsurition rates were based on data that were 92, 88, 94 and 92% complete, of groups 1, 2, 3 and 4 respectively, as some patients were still pregnant at the time of this report. No differences were observed between groups [group 1: 22% (95% CI: 13–31%), group 2: 30% (95% CI: 17–42%), group 3: 28% (95% CI: 17–44%), and group 4: 24% (95% CI: 14–35%)].

Figure 3. Kaplan–Meier plots for groups divided by a ‘gynaecological’ definition of an exaggerated thyroid-releasing hormone-stimulated thyroid-stimulating hormone serum concentration at referral (as outlined in Table I). Parturition rates are based on data that were 92, 93, 94 and 89% complete for groups 1, 2, 3 and 4 respectively. At the start, groups 1, 2, 3 and 4 comprised n = 76, n = 95, n = 17 and n = 35 patients respectively. n.s. = not significant.

‘Gynaecological’ definition of euthyroidism (Figure 3)
Again, pregnancy rates were not different between any of the groups [group 1: 31% (95% CI: 20–40%), group 2: 46% (95% CI: 31–52%), group 3: 31% (95% CI: 15–47%), and group 4: 24% (95% CI: 14–35%)]. Abortion rates were not different between groups 1 and 2 [18% (95% CI: 3–47%) versus 29% (95% CI: 8–50%)]. No abortions were observed in groups 3 and 4. Delivery rates were based on data that were 92, 93, 94 and 89% complete, for groups 1, 2, 3 and 4 respectively. There was no difference between patient groups [group 1: 22% (95% CI: 12–31%), group 2: 30% (20–38%), group 3: 19% (95% CI: 4–32%), group 4: 24% (8–39%)].
Thyroid function upon T4 therapy (Figure 4, Table II)

Thyroid function normalized in most patients during follow-up. With our treatment protocol, all but n = 17 patients were treated with T4, so thyroid function was not expected to be different between groups over time. However, irrespective of thyroid function at baseline, women who never achieved a basal TSH <2.5 mIU/l or a TRH-stimulated TSH <20 mIU/l were encountered more frequently (P < 0.05) among persistently infertile women than in those who successfully conceived (Table II).

Thyroid function at the time of (including 3 months prior to) conception did not differ between groups nor was it different in women who conceived compared with those who did not at a comparable time after referral. Women at the time of abortion displayed higher (P < 0.03) basal and TRH-stimulated TSH but not T4 serum concentrations than at the time of conception and also than compared with those who delivered a healthy baby at the time of their conception (Figure 4).

Parameters associated with an increased pregnancy rate (Table II)

Younger age and a higher number of outpatient visits were independently associated with an increased pregnancy rate. Neither a short duration of sterility, a long follow-up, a higher T4 and lower basal or TRH-stimulated TSH at first visit, a higher T4 dose, nor the absence of autoimmune thyroiditis was associated with a better outcome.

Discussion

Out of a cohort of 283 infertile women referred for thyroid evaluation and treatment, we followed 223 patients (79%) for up to 5 years. With the diagnostic work-up and treatment protocol presented we observed a higher pregnancy rate (37%) than previously described (Bohnet et al., 1981; Merzough et al., 1990; Gerhard et al., 1991; Moltz et al., 1991; Bals-Pratsch et al., 1993). Higher number of visits and younger age were independently associated with a higher pregnancy rate. However, the degree of thyroid dysfunction at referral, the presence of autoimmune thyroiditis, longer duration of sterility prior to referral, or the T4 substitution dose did not influence conception and abortion rates. On the other hand, women who never achieved basal TSH <2.5 mIU/l or TRH-stimulated TSH <20 mIU/l had lower conception rates.

The prevalence of subclinical hypothyroidism (as defined by an elevated basal TSH >4.5 and >4.1 mIU/l respectively) has been reported to be 0.7–2.3% in large series of unselected infertile women (Shalev et al., 1994; Lincoln et al., 1999). In the present study, 34% of patients were subclinically hypothyroid which mirrors the specific referral pattern and is certainly not representative for another setting. There is no prospective study on the impact of T4 substitution therapy on the pregnancy rate in infertile women with mild thyroid failure. Data on the natural history of infertility in untreated subclinical hypothyroidism are limited to one retrospective study suggesting that infertile women with untreated subclinical hypothyroidism do not conceive at all (Merzough et al., 1990). Our cohort was not left untreated when mildly hypothyroid. At the time of pregnancy, however, >25% of these patients were still subclinically hypothyroid (Figure 4) suggesting that conception is possible in a state of mild thyroid failure.

Previous retrospective series of infertile women (Bohnet et al., 1981; Merzough et al., 1990; Gerhard et al., 1991; Moltz et al., 1991; Bals-Pratsch et al., 1993) have not included information on thyroid function over time, and have selected various criteria for subclinical hypothyroidism and/or an exaggerated TRH-stimulated TSH response (Table III). However, T4 substitution therapy had been instituted in cohorts of infertile women with similar inclusion criteria and based on TRH-stimulated TSH concentrations similar to those of our study (Bohnet et al., 1981; Merzough et al., 1990; Gerhard et al., 1991; Moltz et al., 1991; Bals-Pratsch et al., 1993). Lower conception rates (0–24%) of infertile women with treated mild hypothyroidism than that observed in our study (37%) have been reported. Abortion or parturition rates are not available for infertile women with treated or untreated mild hypothyroidism. It is of note that the authors of the largest study of infertile women (Merzough et al., 1990, n = 857) report a ‘spontaneous’ conception rate (as defined by pregnancy occurring during a phase of diagnostic evaluation only or during a period of ≈3 months without any therapy) of 15.6% in their entire cohort (not just of women with mild hypothyroidism). Taking into account the abortion rate of 25.5% in the ‘spontaneous’ conception group, the delivery rate of their entire cohort was 12% (Merzough et al., 1990). The observed 27% overall delivery rate of our entire cohort was higher, suggesting superior outcome by means of the presented diagnostic and therapeutic approach.

Thirty-four women in our study refused TRH testing and displayed abortion and abortion rates similar to those who did not. However, time to conception was longer than those who had TRH tests (18 versus 6–9 months). In addition, women who never achieved a basal TSH <2.5 mIU/l or a TRH-stimulated TSH <20 mIU/l were observed more frequently among patients who did not become pregnant than among those who did. Serum TSH displays a high within-individual variation (Andersen et al., 2002). Documentation over a prolonged period of time of basal and TRH-stimulated TSH concentrations <2.5 mIU/l and <20 mIU/l respectively—values that are close to the population-based means (Keller, 1986; Hollowell et al., 2002)—may be necessary in order to improve conception. It is of note, however, that decreased pregnancy rates were observed with higher age, a well known fact, but also with less frequent outpatient visits. The latter may confound the possible negative effects on pregnancy rates of an elevated TSH over time. Baseline TSH in women with normal basal but elevated TRH-stimulated TSH was higher than in those with a normal TRH-stimulated TSH, although still within the normal range (1.7 versus 3.1 mIU/l; data not given). This suggests that the upper limit of normal (as defined by the mean + 2 SD of a healthy population) of a TRH-stimulated TSH (25 mIU/l; Keller, 1986) discloses a narrower diagnostic window, leading to a more sensitive assessment of ‘normality’ than the determination of a basal TSH (upper normal limit: 4.1 mIU/l; Hollowell et al., 2002). As discussed
recently, basal TSH concentrations in the upper reference range are often already associated with abnormal pathology of the thyroid (Dajan et al., 2002). This should apply even more for subjects with an elevated TRH-stimulated TSH in the presence of a high normal basal TSH. However, this is not the same as saying that T4 treatment would be beneficial in these individuals unless more data from epidemiological and prospective studies are available. Fine-tuning of thyroid function has long been known to be done best by TRH testing (Carr et al., 1988). With the emergence of highly sensitive TSH assays, it is suggested that TRH testing can be considered obsolete in clinical practice (Nicoloff and Spencer, 1990). However, the special situation of thyroid disease and pregnancy was not considered. Given the lack of data in infertile women, such a recommendation may not hold for thyroid function testing in these patients. The high fecundity rate observed in our cohort indeed suggests that frequent monitoring of thyroid function by a highly sensitive diagnostic tool such as TRH testing is beneficial.

Hypothyroidism has been suggested to jeopardize the feto–placental unit of early pregnancy. In a group of 45 women with threatened abortion—as defined by first trimester (mean gestational age 8.5 weeks) vaginal bleeding with or without contractions, a living fetus by ultrasound and a closed cervix—lower hCG and free T4, but higher TSH serum concentrations were observed in the 14 women who miscarried compared with the 31 who did not, and also compared with a control group of 30 healthy pregnant women in their first trimester (La Marca et al., 1998). These findings support the assumption that thyroid hormone could play a role in the evolution of threatened abortions, as a previous study found lower free T3 and free T4 levels in women who miscarried compared with those who did not (Maruo et al., 1993). We observed only first trimester miscarriages which occurred at higher basal and TRH-stimulated TSH serum concentrations compared with the time of conception, reinforcing the above presumption. Although an overall abortion rate of 15–23.5% has been reported in infertile women who became pregnant (Merzough et al., 1990; Molz et al., 1991), data are lacking for those who were hypothyroid. Fifty years ago, in an era that predated routine TSH testing, a 45% miscarriage rate of women with untreated overt hypothyroidism was reported (Hodes et al., 1952). More recently, in a follow-up study of patients with post-partum thyroiditis, women with persistent hypothyroidism had a higher rate of spontaneous abortions than those who returned to the euthyroid state (Othman et al., 2001). We observed an overall abortion rate of 13% that was not correlated with the degree of thyroid dysfunction prior to substitution therapy and was not associated with the presence of autoimmune thyroiditis. This is in contrast with previous observational data suggesting a strong association between abortions and the presence of elevated thyroid antibodies (Stagnaro-Green et al., 1990; Glinoer et al., 1991; Abramson and Stagnaro-Green, 2001). It is of note, however, that women who miscarried had a higher basal TSH at the time of abortion than at the time of conception, which was also higher than in those who delivered a healthy baby at a comparable time. This may support the supposition that the risk of pregnancy loss may be augmented with subtle deficiencies in thyroid hormone levels (Vaquero et al., 2000).

One limitation of the present study is the lack of data in women with untreated mild hypothyroidism. The overall high pregnancy and parturition rates of our cohort can therefore not be ascribed to the effects of T4 therapy alone. Moreover, the comparison of our data to historical cohorts may be inaccurate given the unmatched cohorts.

In summary, pregnancy rates higher than those reported previously were observed based on a rigorous diagnostic work-up with frequent TRH testing. This was used to fine-tune a therapeutic regimen of T4 therapy instituted upon every TRH-induced TSH rise above the mean of a healthy population. Patients with infrequent outpatient visits or those who never achieved basal TSH <2.5 mIU/l or TRH-stimulated TSH <20 mIU/l with T4 therapy had lower conception rates. Abortions appeared to have occurred with increased frequency with higher basal TSH but not with the presence of elevated thyroid antibodies.

References


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