Intra-Individual Variation of Serum Thyroxin and Triiodothyronine in Pregnancy

Wieland G. E. Hötzel¹ and Waldemar Deschner²

The mean concentrations of triiodothyronine (T₃) and thyroxin (T₄) in serum were increased in pregnancy, the increases for individuals remaining stable from week 16 to week 40 of gestation. For this period biological intra-individual variations of T₃ and T₄ in serum were estimated and compared with those of non-pregnant women. The average biological intra-individual CVs for T₃ and T₄ were of the same order for pregnant and non-pregnant women (6.9–8.4%). The ratios of the biological intra-individual CVs to the biological group CVs were 0.5 to 0.6. Individual values were normally distributed. There was no increase of the intra-individual variation with the lapse of time between two consecutively observed values. The estimated average biological intra-individual CVs were used to derive decision-making criteria in monitoring thyroid function during the 2nd and 3rd trimester of gestation.

There are conflicting reports on values for the free hormones T₃ and T₄ in pregnancy (1–4), so determination of the total hormones is still important for monitoring thyroid function. It is well known that the concentration of total T₃ and T₄ increases in parallel with the estrogen-induced increase in plasma thyroxin-binding globulin, but Weeke et al. (2) have shown that the increase occurs during the 1st trimester of gestation and the levels remained high and nearly stable during the 2nd and 3rd trimester. For this period of gestation, decision-making criteria derived from the intra-individual variation of the analytes can be used to judge changes of values observed in monitoring thyroid function. In the past, some authors studied the intra-individual variation of T₃ and T₄ in normal subjects (5–9), but there are no data for pregnant women. Therefore, we studied the intra-individual variation of T₃ and T₄ in the 2nd and 3rd trimester of pregnancy to develop information that is important for establishing decision-making criteria based on subject-specific reference values (10):

- the stability of the individual T₃ and T₄ concentrations in serum
- the average biological intra-individual variation and its homogeneity
- the time dependence of the intra-individual variation
- the statistical distribution of the individual values

Materials and Methods

Subjects

All subjects were volunteers. During the course of the study, none had any illness or injury.

Nonpregnant women. Thirteen apparently healthy pregnant women, ages 19 to 40 years (average 25.9 years), week 16–40 of gestation, and taking no drugs. None had previous disease of the thyroid. There were no complications during the course of pregnancy and a normal delivery. All the infants were healthy. The weeks of gestation were calculated from the last menstrual period.

Specimen Collection

Blood was drawn by an experienced phlebotomist between 0630 and 0800 hours. The serum was stored at −196 °C until analysis. Blood was taken from the normal women once a week for eight weeks, and from the pregnant women at weeks 16, 20, 24, 28, 32, 35, 37, and 39 of gestation.

Analytical Procedure

All samples from one individual were analyzed within a single run. Comparability between runs was ensured by stringent quality-control measures. T₃ and T₄ were assayed by radioimmunoassay ("T₃-RIA" and "T₄-RIA"); Isocommerz GmbH, Berlin), as published (11). The within-run CVs were 4.5% for T₃ and 4.6% for T₄. The analytical CVs were calculated from results of triplicate analyses of each sample.

Statistical Analysis

The total variances, s², were considered to be the sum of the biological variances, s²b, and the analytical variances, s²a. The biological variances were calculated by subtracting the analytical variances from the total variances. For estimating the average biological intra-individual CV, the analyte values for each individual were transformed into a percentage of the arithmetic mean for that analyte and individual. Differences of the variances were checked by the F-test. Homogeneity of the intra-individual variances was checked by an approach suggested by Harris (12, 13). The type of distribution was investigated by the chi-square goodness-of-fit test. Linear regression analysis was used to investigate whether the concentration of the analytes changed from week 16 to week 40 of gestation and whether the intra-individual variations increased with the lapse of time between consecutive measurements.

Results and Discussion

Stability of T₃ and T₄ Concentrations

The mean T₃ and T₄ concentrations for the pregnant women are significantly higher than those of the non-pregnant women (Table 1). The relative increase in T₃ is higher than that in T₄. This may be an iodine-saving mechanism to maintain the euthyroid state. Our subjects were located in a territory where there is iodine deficiency. As is shown in Figures 1 and 2, there is no statistically significant trend in the individuals' values for either analyte from week 16 to week 40 of gestation. This stability enables the estimation of the intra-individual variation.
Biological Group and Intra-Individual Variation

The average biological intra-individual CV (CVb), the biological group CV (CVbg), the ratio (Q) of CVb to pregnant women to that of normal women, and the ratio (R) of CVb to CVbg are presented in Table 1. Although there are great differences in the mean concentrations, all CVb's are similar. The CVb of T3 for pregnant women is slightly but significantly higher than that for normal women. The ratios of CVb to CVbg range from 0.5 to 0.8 for all groups. Because the biological intra-individual variations are significantly smaller than the group variations, decision-making criteria derived from intra-individual variations are more sensitive in detecting alterations of thyroid function than are conventional population-based reference groups.

Time Dependence of the Intra-Individual Variation

The intra-individual variation of T3 and T4 showed no significant increase during the interval between two observations for normal and pregnant women, so that the same decision-making criteria can be taken independently of different spans of time between consecutively observed values.

Homogeneity of Intra-Individual Variation

In the group of normal women there were no significant differences between the intra-individual variances of the subjects for T3 and T4. The average CVb is a good estimate for those of the single subjects. In the group of pregnant women we also found no significant inhomogeneity of the intra-individual variances of T3, but T4 showed a significant inhomogeneity, so that the average CVb of this analyte is only a rough estimate of those of the single subjects.

Statistical Distribution of the Individual Values

The chi-square test showed good conformity to a gaussian distribution for the distribution of the individual values for normal and pregnant women for both analytes. Therefore, no transformation of the observed values is necessary, and decision-making criteria can be calculated on the basis of the gaussian distribution.

Decision-Making Criteria

For calculating decision-making criteria, the estimated average biological intra-individual variation must be combined with estimate of the analytical precision as follows:

\[ CV_I = \sqrt{CV_{bi}^2 + CV_a^2} \]

Table 1. Average Biological Intra-Individual Variations

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Group</th>
<th>X, nmol/L</th>
<th>CVbg, %</th>
<th>CVb, %</th>
<th>Q</th>
<th>R</th>
</tr>
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<tbody>
<tr>
<td>T3</td>
<td>N</td>
<td>1.68</td>
<td>11.6</td>
<td>6.9</td>
<td>0.60</td>
<td></td>
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<tr>
<td></td>
<td>P</td>
<td>2.96**</td>
<td>16.4</td>
<td>8.4</td>
<td>1.21*</td>
<td>0.50</td>
</tr>
<tr>
<td>T4</td>
<td>N</td>
<td>85.7</td>
<td>11.0</td>
<td>6.9</td>
<td>0.53</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>108.0**</td>
<td>12.5</td>
<td>7.3</td>
<td>1.06</td>
<td>0.58</td>
</tr>
</tbody>
</table>

X = mean concentration of analyte for all individuals of a group. Statistically significant difference from the mean value for normal women at **P < 0.01.

CVbg = biological CV of the group.

CVb = average biological intra-individual CV.

Q = ratio of CVb for pregnant women to that for normal women. Statistically significant at *P < 0.05.

R = ratio of CVb to CVbg.

Fig. 1. Individual values for triiodothyronine (T3) in serum during weeks 16 to 40 of gestation

Arithmetic mean + SEM of the transformed individual values x%.

Fig. 2. Individual values for thyroxin (T4) in serum during weeks 16 to 40 of gestation

Arithmetic mean + SEM of the transformed individual values x%.

where CVa is the analytical CV of the laboratory, and CVb is the total CV for intra-individual variation. A difference between two consecutively observed values is significant if it exceeds 2.8 CVa (P < 0.05). This is exactly valid for analytes without significant differences in the magnitude of intra-individual variations between subjects (10) as is the case for T3. For T4 we get only a rough estimate by this approach. Nevertheless, the average CVb should also be considered with this fact in mind. The derivation of criteria on the basis of the subject-specific intra-individual variation is more complicated (13), and in practice lacks a sufficient number of individual values. Assuming a long-term analytical CV of 5% for both tests (state of the art), changes more than 27% for T3 and more than 25% for T4 between two consecutively observed values are a sign of a significant change in thyroid function during the 2nd and 3rd trimester of gestation.

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References


