Thyroid size and thyroid function during pregnancy: an analysis

Arie Berghout and Wilmar Wiersinga 1
Department of Medicine, Zuiderziekenhuis, Rotterdam, The Netherlands and 1Department of Endocrinology, Academic Medical Center, Amsterdam, The Netherlands
(Correspondence should be addressed to A Berghout, Department of Medicine, Zuiderziekenhuis, Groene Hilledijk 315, 3075 EA Rotterdam, The Netherlands)

Abstract
An analysis of all available studies of thyroid size and function in pregnancy reveals that thyroid size, estimated by inspection and palpation or measured more accurately by ultrasonography, increases in pregnancy in areas of iodine deficiency but not in those with sufficient iodine. The increase in average thyroid size is within the normal range, and can partly be prevented by treatment with extra iodine or thyroxine.

There is a slight transient increase in free thyroxine in the first trimester, probably as a result of physiological stimulation of thyroid function by human chorionic gonadotrophin. These levels then decrease by about 30% to low normal values in the second and third trimesters of pregnancy in both iodine-depleted and -replete areas. These changes resemble those of non-thyroidal illness and may well play a role in reducing energy expenditure during pregnancy.

The increase in thyroid size in iodine-deficient areas is probably due to autoregulatory mechanisms of iodine on thyroid growth. The hypothesis is supported by the fact that, during pregnancy, thyroid volume and thyroid function adapt in a physiological way to meet the increased demands for iodine and energy.

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Introduction
Historically, there has been a widely held belief that the thyroid increases in size during pregnancy, as depicted in hieroglyphics in Ancient Egypt and in paintings, such as Saint Luke Painting The Virgin by Roger van der Weyden (Alte Pinakothek, Munich, Germany). According to the older literature, the thyroid gland shows some degree of enlargement during gestation, notably in areas of low environmental iodine (1–3). Marine & Kimball, in 1921, considered the goitre of pregnancy to be a form of work hypertrophy due to iodine deficiency, and concluded that the enlargement could be prevented by iodide therapy (1). However, there is still confusion among clinicians about the entity ‘goitre of pregnancy’. Moreover, the question of whether a goitre of pregnancy is solely prevalent in areas of iodine deficiency is not settled (4). The aim of our study was to review studies on thyroid size and growth as well as thyroid function during pregnancy in order to clarify these matters.

Study design and methodology
We have analysed all available studies that have looked systematically into thyroid size in relation to pregnancy. The data are analysed with regard to year of publication, country of origin, iodine supplementation, method of thyroid investigation, study design, number of females studied, time points of observation before, during or after pregnancy, and outcome. Data of parity or thyroid autoantibody status were either not available or the sample size was too small to draw firm conclusions. No systematic studies were published before 1957. Iodine supplementation has been divided into sufficient (i.e. mean 24 h urinary iodine excretion at or above 100 μg), moderate (75–100 μg) or low (50–75 μg) (5). From 1987 onwards, the inaccurate estimation of thyroid size by inspection and palpation (6, 7) has been largely replaced by determination of thyroid volume by ultrasonography (8–10). The major limitation of ultrasonography that it cannot measure a retrosternal extension of the thyroid does not apply to our study population because the thyroid in child-bearing females is usually small or moderately enlarged.

The oldest study is of thyroid weight at autopsy in a large cohort of pregnant and non-pregnant women of similar age (11). All studies before 1987 are cross-sectional (12–16) during the second or third trimester of pregnancy (not clearly stated in most studies) and compare data with those for non-pregnant (12–14, 16) or historical (15) controls. One study provides a prevalence of goitre during pregnancy (16). Most
studies from 1987 onwards have a longitudinal design, i.e. thyroid volume is measured in the first trimester and the measurement is repeated in the second and/or third trimester (17–21). Two studies are cross-sectional (22, 23). Some studies measure thyroid volume during pregnancy and again during the first week after delivery (22, 24) or later in the postpartum period (18, 20). One study limits the observations to the postpartum period (25). Only one study has a prospective design, i.e. with measurement of thyroid volume before pregnancy followed by repeat measurements in the same subjects during pregnancy (21). Lastly, supplementation with iodine or thyroid hormones in pregnancy was studied in three reports (19, 20, 24).

In summary, there are major differences in study design; nevertheless, some general conclusions can be made.

Results

Thyroid size during pregnancy

Seven studies were performed in areas with sufficient iodine intake (11, 13–15, 17, 21, 25), three in areas with moderate iodine intake (12, 18, 23), and five in areas with low iodine intake (16, 19, 20, 22, 24) (Table 1).

The cross-sectional studies in which thyroid size was assessed by inspection and palpation were all performed in areas with sufficient iodine and consistently failed to find a difference between cases and controls (including the only blinded matched study by Levy et al. (14)). Crooks et al. observed a difference between cases and controls in a study in iodine-deficient Scotland (12), but not in a similar study performed in Iceland (13), an iodine-abundant area (26). Long et al. recorded a prevalence of 6% of goitre in a large cohort of pregnant teenagers, which was not different from historical controls (15).

The studies performed by ultrasonography are generally designed with repeated measurements. Nelson et al. (25), in the USA, observed, in 16 subjects in the period shortly after delivery compared with 6 months postpartum, a significant (13%) decrease in the mean thyroid volume, from 7.5 ml (5.0–11.4 ml) to 6.5 ml, and infer that thyroid size had been enlarged during pregnancy (25). In iodine-sufficient Finland, thyroid volume does not increase during pregnancy nor is it different from controls (17). The two studies from iodine-deficient Denmark are comparable in design (18, 20). Rasmussen et al. (18) found an increase in thyroid volume from 20.2 ± 2.0 ml in the second trimester to 24.1 ± 2.2 ml near term, decreasing to 18.4 ± 2.0 ml 12 months postpartum. Pedersen et al. (20) observed an increase of 31% during pregnancy; in pregnant subjects treated with KI solution (200 µg iodine daily) the increase was 15%. Thyroid volume postpartum returned to values very close to the initial value in the first trimester. Glinoer et al. (22), in iodine-deficient Belgium, observed an increase in thyroid volume from 12.1 ± 4.5 to 13.9 ± 4.8 ml during pregnancy (cross-sectional data), further increasing shortly after delivery to 15.0 ± 6.8 ml (longitudinal observations). In a randomized double-blind study of the treatment of 180 pregnant females with placebo, 100 µg iodide (KI) or 100 µg iodide together with 100 µg l-thyroxine daily, thyroid volume increased by 30, 15 and 8% respectively (24). Smyth et al. (23), from Ireland, also an iodine-deficient area, observed increasing thyroid volumes during pregnancy, from 13.9 ± 4.2 ml to 16.0 ± 4.9 ml; whereas lower values of 14.8 ± 4.0 ml were observed 3 months postpartum. In Italy, an iodine-deficient region as well, an increase in thyroid volume, from 10.1 ± 2.3 ml in the first to 11.7 ± 2.3 ml in the third trimester (16%), was observed in 18 subjects, but not in 17 controls who were treated with iodide salt (120–180 µg iodine daily) (19). We, in the iodine-replete country of The Netherlands, did not observe any increase in thyroid volume during pregnancy in a prospective follow-up study, i.e. all subjects were studied at a median of 3.5 months before conception and again at each trimester during pregnancy (21). Thyroid volume was 10.3 ± 5.1 ml before pregnancy and 10.6 ± 4.4 ml, 9.6 ± 3.8 ml and 9.4 ± 3.0 ml in the first, second and third trimester respectively.

Taken together, the findings of the studies performed with either the assessment of thyroid size by inspection and palpation or by thyroid volume by ultrasonography are remarkably consistent: no increase in thyroid size in iodine-replete areas and an increase in thyroid size in iodine-deficient areas during pregnancy. The only exception to this generalization is the study by Nelson et al. (25), but their observations were made in the postpartum period only.

The question remains whether the observed increase in thyroid size during pregnancy reflects a physiological adaptation in areas of moderate and low iodine or may be regarded as a pathological condition indicating iodine deficiency. It should be mentioned in this respect that the normal values of thyroid volume are a function of the ambient iodine intake (10).

The outcome of the three intervention studies (19, 20, 24) supports the hypothesis that the observed increase in thyroid size in areas with below acceptable iodine supplementation is indeed related to a further increase in iodine deficiency during pregnancy. This increase can partly be prevented by supplying extra iodine (at least 100 µg a day).

Thyroid function during pregnancy

Rasmussen et al. (18) found no change in thyrotrophin (TSH) levels during pregnancy, as compared with 12 months postpartum. Romano et al. (19) reported TSH levels within the normal range with no difference between the iodine-treated and control groups. Pedersen et al. (20) observed a fall in free thyroxine (FT4) levels in...
**Table 1** Review of studies on thyroid in pregnancy.

<table>
<thead>
<tr>
<th>First author</th>
<th>Ref.</th>
<th>Year</th>
<th>Country</th>
<th>Iodine intake</th>
<th>Method</th>
<th>Design</th>
<th>Number</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stoffer</td>
<td>11</td>
<td>1957</td>
<td>USA</td>
<td>Sufficient</td>
<td>Thyroid weight at autopsy</td>
<td>Cross-sectional/ vs 47 controls</td>
<td>65*</td>
<td>No difference</td>
</tr>
<tr>
<td>Crooks</td>
<td>12</td>
<td>1964</td>
<td>Scotland</td>
<td>Moderate</td>
<td>Inspection/ palpation</td>
<td>Cross-sectional/ vs 116 controls</td>
<td>184*</td>
<td>70% goitre vs 38% controls</td>
</tr>
<tr>
<td>Crooks</td>
<td>13</td>
<td>1967</td>
<td>Iceland</td>
<td>Sufficient</td>
<td>Inspection/ palpation</td>
<td>Cross-sectional/ vs 108 controls</td>
<td>227*</td>
<td>23% goitre vs 19% controls</td>
</tr>
<tr>
<td>Levy</td>
<td>14</td>
<td>1980</td>
<td>USA</td>
<td>Sufficient</td>
<td>Inspection/ palpation</td>
<td>Cross-sectional/ vs 49 controls</td>
<td>49</td>
<td>No difference</td>
</tr>
<tr>
<td>Long</td>
<td>15</td>
<td>1985</td>
<td>USA</td>
<td>Sufficient</td>
<td>Inspection/ palpation</td>
<td>Cross-sectional/ vs 600 historic controls</td>
<td>309</td>
<td>No difference</td>
</tr>
<tr>
<td>Bauch</td>
<td>16</td>
<td>1986</td>
<td>East Germany</td>
<td>Low</td>
<td>Inspection/ palpitation</td>
<td>Cross-sectional</td>
<td>489*</td>
<td>60% goitre</td>
</tr>
<tr>
<td>Nelson</td>
<td>25</td>
<td>1987</td>
<td>USA</td>
<td>Sufficient</td>
<td>Ultrasound† after pregnancy</td>
<td>Longitudinal</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Brander</td>
<td>17</td>
<td>1989</td>
<td>Finland</td>
<td>Sufficient</td>
<td>Ultrasound† vs 22 controls</td>
<td>Longitudinal</td>
<td>7</td>
<td>21</td>
</tr>
<tr>
<td>Rasmussen</td>
<td>18</td>
<td>1989</td>
<td>Denmark</td>
<td>Moderate</td>
<td>Ultrasound‡</td>
<td>Longitudinal</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Glinoer</td>
<td>22</td>
<td>1990</td>
<td>Belgium</td>
<td>Low</td>
<td>Ultrasound†</td>
<td>Cross-sectional/ longitudinal</td>
<td>168</td>
<td>172</td>
</tr>
<tr>
<td>Smyth</td>
<td>23</td>
<td>1991</td>
<td>Ireland</td>
<td>Moderate</td>
<td>Ultrasound†</td>
<td>Cross-sectional/ vs 95 controls</td>
<td>95</td>
<td>73</td>
</tr>
<tr>
<td>Romano</td>
<td>19</td>
<td>1991</td>
<td>Italy</td>
<td>Low</td>
<td>Ultrasound†</td>
<td>Longitudinal</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Pedersen</td>
<td>20</td>
<td>1993</td>
<td>Denmark</td>
<td>Low</td>
<td>Ultrasound‡</td>
<td>Longitudinal</td>
<td>26 (2×)</td>
<td>26</td>
</tr>
<tr>
<td>Berghout</td>
<td>21</td>
<td>1994</td>
<td>Netherlands</td>
<td>Sufficient</td>
<td>Ultrasound‡</td>
<td>Longitudinal and prospective</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Glinoer</td>
<td>24</td>
<td>1995</td>
<td>Belgium</td>
<td>Low</td>
<td>Ultrasound†</td>
<td>Longitudinal</td>
<td>60</td>
<td>60</td>
</tr>
</tbody>
</table>

* No specific time of observation in the 2nd or 3rd trimester indicated by the authors.
† By ellipsoid method.
‡ By transversal section method.
both control and iodine-treated groups but a rise in plasma TSH in the control group only. In the study of Glinoer et al. (22) plasma FT4 as well as FT3 decreased during pregnancy (cross-sectional data), whereas TSH levels increased, in negative correlation with plasma human chorionic gonadotrophin (hCG) levels. In the second study by Glinoer et al. (24), on subjects selected by the criteria of low FT4 levels, a high T3/T4 ratio and a high thyroglobulin concentration comprising less than 10% of a large cohort, a decrease in FT4 was observed in the untreated control group and again a rise in TSH in the third trimester.

An analysis of papers with a longitudinal study design, the exclusion of subjects with thyroid disease, medication interfering with thyroid hormone regulation or metabolism and complicated pregnancy, and the measurement of FT4 by a valid assay; as judged by a minimal decrease in FT4 on dilution of the serum sample (28, 29), reveals that FT4 significantly decreases by about 30% to low normal values in the second and third trimester of pregnancy (21, 30–33) in both iodine-depleted and -replete areas. The vast majority of the transversal studies published after 1980 employing free hormone immunoassays also indicate a fall in serum FT4. FT4 values in the second and third trimester are generally lower than outside pregnancy. However, a small transient increase in FT4 in the first trimester (34–36) was observed in three studies that subdivided the first trimester into weeks. The two prospective studies, i.e. with FT4 values from the same females measured before pregnancy (21, 31), did not find a difference between pre-pregnancy and first-trimester values, but the sampling time during the first trimester was not indicated in these studies.

The decrease in serum FT4 in pregnancy cannot be explained by changes in plasma volume or concentrations of albumin, thyroid-binding globulin and free fatty acids in the serum. There are at present no data indicating that thyroid hormone production is increased during pregnancy in order to meet increased maternal and fetal demands. Although renal iodine clearance is increased during pregnancy, probably by increased glomerular filtration rate, absolute thyroidal iodine uptake remains unchanged (37). Moreover, relative iodine deficiency cannot fully explain the decrease in FT4, because it is observed in iodine-deficient as well as iodine-replete areas. The decrease in FT4 is associated with a similar decrease in FT3, which also argues against an iodine-related phenomenon, since, in iodine deficiency, T3 values are normal or even increased. Lastly, net T4 turnover and presumably also thyroid hormone requirements are unaltered in human pregnancy (38), i.e. 90 µg per day in non-pregnant women vs 97 µg per day in pregnant women.

In a prospective study we observed a gradual decline in FT4 and FT3 concentrations during pregnancy, whereas free reverse T3 levels rose (21). FT3/FT4 ratios and free reverse T3/FT3 ratios remained unchanged (in contrast with the rise observed in patients with hypothyroidism), whereas free reverse T3/FT3 ratios increased. Similar changes are found in patients with non-thyroidal illness (39), and, interestingly, also in a study of pregnant rats near term (40). Further, in a study on energy requirements of pregnancy in The Netherlands (41), it was found that the energy intake during the second and third trimester of pregnancy is lower than the calculated need for energy. The additional energy cost of pregnancy comprises the energy required for the synthesis of new tissues together with the associated increase in basal metabolism, calculated at 1020 kJ/day. However, the increase in energy intake was found to be very small, approximately 80 kJ/day, resulting in an estimated energy gap of approximately 940 kJ/day. This is only partially bridged by reduction in physical activity accounting for a saving of 355 kJ/day. A shortfall of 585 kJ/day has still to be met, and it is in this respect that down-regulation of thyroid hormone action as evident from the decrease in FT4 and FT3 (as in non-thyroidal illness) may contribute to the saving of energy.

The increase in FT4 in the first trimester is best explained by the coincident peak of hCG secretion in this trimester. Serum TSH, as measured by sensitive assays, is reciprocally decreased at the time of the hCG peak. These changes reflect thyroidal stimulation by hCG, which peaks in the first trimester and decreases to a plateau during the second and third trimesters (22, 34, 36, 42, 43). Stimulators of thyroid growth during pregnancy

Putative stimulators of thyroid growth in pregnancy are TSH, hCG and iodine. Serum TSH was found to be either unchanged during pregnancy (18) or within the normal range (19). Pedersen et al. (20) observed a rise in plasma TSH by about 21% in untreated pregnant females from week 17 to week 37 of pregnancy, compared with only 5% in those treated with iodine. In the study of Glinoer et al. (22), also performed in an iodine-deficient area, TSH values increased within the normal range towards the end of gestation and were negatively correlated with hCG levels. Interestingly, thyroid volume correlated negatively with TSH levels. We observed a decline in serum TSH in the first trimester returning to pre-pregnancy levels in the third trimester (21).

In conclusion, in an iodine-replete area, no increase in serum TSH during pregnancy is found, whereas in iodine-deficient areas both an increase and no change are observed in combination with an increase in thyroid volume. We feel therefore, taking also into consideration that the changes in TSH are within the normal range, that it is not very likely that thyroid size increases during pregnancy as a result of stimulation by TSH only.
hCG has an intrinsic thyrotrophic activity (43–46). This is well documented at high concentrations of hCG in cases of molar pregnancy (47, 48). It is not known whether hCG also stimulates thyroid growth, and this has not been investigated in the studies reviewed above. It should be mentioned in this respect that thyroid size increases, if at all, during the last trimester of pregnancy, whereas serum hCG levels peak during the first trimester. In a study on the role of hCG and its subunits in relation to maternal thyroid function, mean thyroid volume in the first trimester was increased in a subgroup of women with greatly elevated hCG levels and low serum TSH compared with pregnant women with 1-6-1-8 times lower hCG levels and normal TSH levels (thyroid volume was 14 ml vs 12 ml, P < 0.02) (49). However, the thyroid volumes of the two groups did not differ significantly in the third trimester (17.5 ml vs 14.2 ml), when hCG levels were still higher in the first group. From experimental studies, few data on thyroid growth stimulation by hCG are available. Growth is stimulated in FRTL-5 cells when incubated with hCG, and the effect is comparable with that of TSH (50–52). The data from clinical studies on the thyroid-stimulatory activity of hCG, although convincing, are conflicting when applied to human thyroid cells (53). We are not aware of any studies on hCG levels in pregnancy in areas of depleted and replete iodine.

The mechanism of thyroid growth stimulated by iodine deficiency in pregnancy has not been studied. In the non-pregnant state, however, autoregulatory mechanisms probably play a role in the stimulation of thyroid growth by iodine. In animal and in vitro studies, iodine has been shown to affect thyroid size both in the presence and absence of TSH (54, 55). Moreover, there is evidence that the thyroid growth response to TSH is higher in cases of more severe iodine depletion (56). Lastly, in humans, thyroid volume differs but plasma TSH values are similar in areas of sufficient and low iodine intake (57). Taken together, in iodine-sufficient areas thyroid size does not increase during pregnancy despite increased hCG levels in the first trimester. This could be explained by the concomitant decrease in TSH at times of peak hCG levels. On the other hand, in iodine-deficient areas, thyroid size increases and this is probably mediated by autoregulatory mechanisms of iodine on thyroid growth.

Conclusions

There is sufficient evidence that thyroid size increases during pregnancy in areas of moderate or low iodine, whereas it does not increase in areas of sufficient iodine. The increase in thyroid volume can be completely or partially prevented by iodine supplementation at a dose of at least 100 μg a day. FT₄ decreases by about 30% to low normal values in the second and third trimester of pregnancy in both iodine-depleted and -replete areas. These changes resemble those of non-thyroidal illness and may well play a role in reducing energy expenditure during pregnancy.

There is a slight transient increase in FT₄ in the first trimester, probably as a result of physiological stimulation of thyroid function by hCG.

In summary, we find evidence to support the hypothesis that, during pregnancy, thyroid volume and thyroid function adapt in a physiological way to meet the increased demands for iodine and energy.

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