Morphometric studies on the development of human thyroid gland in early fetal life

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Summary. Histological and morphometric studies were performed on 30 thyroid glands obtained from normal human fetuses. Their crown-rump length (CRL) ranged from 57 to 190 mm, corresponding to the gestational age of 10 - 20 weeks.

The weight of the thyroid gland increased proportionally in relation to CRL, foot length and fetus weight. The first follicles containing PAS-positive colloid were observed in the peripheral part of the thyroid gland of 57 mm CRL fetus. The number of follicles per 1 mm² of thyroid surface section increased up to 85 mm CRL and thereafter gradually declined for the end of studied period of fetal life. The volumes (in mm³) of thyroid epithelium, colloid and stroma, beginning from 85 mm increased proportionally to the CRL while the height of epithelial cells did not change. The epithelium/colloid ratio decreased notably to 165 mm CRL and thereafter remained constant.

Results of the present study suggest that the thyroid gland of human fetus approaches structural maturity in 17.5 week of gestation.

Key words: Human fetus, Thyroid gland, Development, Morphometry, Stereology

Introduction

The human thyroid gland develops from an epithelial outgrowth in the floor of the foregut, between the first and second branchial arches, at the end of the third week of intra-uterine life (Politzer, 1952; Dussault, 1981; O'Rahilly, 1983). This endodermal anlage evaginates as a diverticulum and descends caudally to the definitive site on the thyroid cartilage.

Thyroid function in the fetus develops autonomously from maternal hypothalamo-pituitary-thyroid gland axis function. The human fetal thyroid gland is capable of organically binding iodine and forming iodothyronines by the 10th week of gestation and thyroxine is identified in fetal serum between weeks 10 - 11 of development (Andreoli and Robbins, 1962; Shepard, 1967; Greenberg et al., 1970). This corresponds to the differentiation period of the gland in which colloid formation is first noted (Shepard, 1967, 1968).

Cytological differentiation of the human pituitary gland begins at the 9th week of gestation while TSH is found in the fetal serum at the 78th day of the development (Pearse, 1982; Greenberg et al., 1970). The fetal hypothalamo-pituitary complex is capable of synthesizing TRH and TSH at 9 - 10 weeks of development (Fisher, 1986).

The present study was designed to characterize, by means of morphometry, the development of the human fetal thyroid gland between weeks 10 - 20 of intrauterine life.

Materials and methods

Studies were performed on 30 thyroid glands obtained from normal human fetuses, from the collection of the Department of Anatomy, University School of Medical Sciences, Poznań, Poland. The collection consisted of fetuses obtained from spontaneous abortions or from artificial abortions due to social-legal causes.

The developmental stage was estimated according to the Carnegie staging data of O'Rahilly (1973, 1975). All fetuses were weighed and their crown-rump length (CRL) and foot length were measured. Detailed data of studied fetuses are shown in Table 1. Fetuses were fixed by infusion of 10% formaldehyde via umbilical vein and subsequently they were also preserved in 10% formaldehyde. Thyroid gland was carefully excised under a dissecting microscope, weighed to the nearest 0.1 mg, embedded in paraffin and serially sectioned at 6 - 7 μm. Sections were stained with haematoxylin-eosin or the
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**Fig. 1.** Thyroid gland weight (mg) as a function of the body weight (g) of fetuses between 10 - 20 weeks of intra-uterine life. Each point presents one fetus.

\[ y = 0.76x + 26.60 \]
\[ r = 0.985 \]

**Fig. 2.** The relation between thyroid gland weight (mg) and the foot length (mm) of fetuses between 10 - 20 weeks of intra-uterine life. Each point presents one fetus.

\[ y = 14.17x - 143.13 \]
\[ r = 0.980 \]

**Fig. 3.** The relation between thyroid gland weight (mg) and the crown-rump length (mm) of fetuses between 10 - 20 weeks of intra-uterine life. Each point presents one fetus.

\[ y = 3.93x - 296.80 \]
\[ r = 0.978 \]

**Fig. 4.** The relation between the relative thyroid gland weight (mg/mg) and crown-rump length (mm) of fetuses between 10 - 20 weeks of intra-uterine life. Each point presents one fetus.

\[ y = -0.04x + 14.48 \]
\[ r = -0.603 \]

**Fig. 5.** The number of thyroid follicles per unit of surface of thyroid section (n/mm²) in relation to the crown-rump length (mm) of fetuses between 10 - 20 weeks of intra-uterine life. The means ±SD are shown. Each point presents one fetus.

\[ y = -0.13x + 330.00 \]
\[ r = -0.952 \]

PAS reaction was performed.

Stereologic studies were performed by the method of Weibel (1979). Under magnification of x 400, using the M49 test point system, the volume fractions of epithelium, colloid and stroma (connective tissue and blood vessels), and the number of thyroid follicles per test area, were estimated directly on the screen. Haematoxylin-eosin staining did not permit the recognition of thyroid cells, therefore these cells were included with the follicular cells. The area of a single analyzed field was 8.1 x 10⁻²mm². In the earliest stages of development (up to 93 mm CRL) all sections of the gland were analyzed. In the older fetuses 5 sections of the thyroid gland were randomly chosen and in each section 10 fields were counted along the lines passing through the central part of the thyroid lobe. The specific gravity of the thyroid gland was assumed to be 1.060 mg/mm³ (Malendowicz and Bednarek, 1986). Knowing
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The weight of the gland and its specific gravity, the volume (in mm³) of epithelium, colloid and stroma was calculated.

The height of the thyroid follicular cells was measured by means of a micrometer eye-piece (K-15 PZO), under magnification of x 450. In each thyroid gland 10 follicles were analyzed along the line passing through the central part of the gland. In each case 4 cells located at the angle 0°, 90°, 180° and 270° from the centre of the follicle were measured.

The results were processed statistically and graphically by Statgraf programme for IBM PC AT.

Results

As shown in Figs. 1 - 3 the thyroid gland weight of human fetuses increased proportionally with respect to the body weight, foot length and CRL. Only the three
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Table 1. Crown-rump (CRL) and foot length [mm], body [g] and thyroid [mg] weight, sex and age (in postovulatory weeks) of studied fetuses.

<table>
<thead>
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<th>No.</th>
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<th>Thyroid weight</th>
<th>Age</th>
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Youngest fetuses did not show the interrelationship as far as foot length and CRL were concerned. In the studied period of the development the relative thyroid gland weight insignificantly decreased (Fig. 4) and there was no difference between the thyroid gland weight of male and female fetuses.

The first follicles containing PAS-positive colloid were observed in the peripheral part of thyroid gland of 57 mm CRL fetus. In older fetuses follicles of the central part of the thyroid lobe were always smaller than the peripheral ones. The number of follicles per 1 mm² of the thyroid surface section increased up to 85 mm
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CRL and thereafter gradually declined up to the end of the studied period of fetal life (Fig. 5).

The volume (in mm³) of thyroid epithelium, colloid and stroma, starting from 85 mm, increased proportionally according to the fetus CRL (Figs. 6, 7, 9). The epithelium/colloid ratio decreased notably to 165 mm CRL and thereafter remained while the height of epithelial cells did not change during the studied period of development (Figs. 8, 10).

Discussion

Numerous morphologic papers dealing with the development of the human thyroid gland in intra-uterine life contain mainly qualitative descriptions of this processes and report changes in the weight of the gland. Results of the present study confirm the earlier findings of Shepard et al. (1964a) which relation to the weight of the fetal thyroid gland to the body weight, foot length and CRL, and on lack of sex differences in the weight of the gland. However, in their studies the relative thyroid gland weight increased up to 80 mm CRL of development and thereafter remained rather constant with the mean 0.0458% of body weight, the value very close to that of the newborns. In the present study a small decrease in the relative thyroid gland weight between weeks 10 - 20 of gestation was found and the mean was higher than in the studies of Shepard et al. (1964a) and comparable to the values calculated from Jackson’s (1909) data.

Like other authors (Taki, 1958; Shepard, 1967; Nivelon and Tenenbaum, 1980; Dussult, 1981) we observed the first follicles with PAS-positive colloid in thyroids of fetuses from the 10th week of gestation.

Only scanty data are available on quantitative morphological changes in the human thyroid gland in the course of intra-uterine development. Results of the present study clearly demonstrate that the number of follicles per mm² of thyroid gland section markedly raised up to 85 mm CRL (week 12 of gestation) and thereafter gradually declined up to the end of the studied period. Obviously this decline is connected with the enlargement of the thyroid follicles in the course of their maturation. On the contrary, Albu and Georocenau (1986) described an increase in the number of thyroid follicles per unit area of the thyroid gland in the late fetal period (6-9 months, 276-316 follicles per 1 mm²) if compared with early fetal period (3-5 months, 211-224/mm²). It is difficult to explain this discrepancy, however in the present study 4.05 mm² of the thyroid surface section was analyzed while in the cited paper only 0.379 mm² (the total area of 5 randomly chosen tested fields).

Present study clearly demonstrate the linear increase in the volume of thyroid epithelium, colloid and stroma beginning from 85 mm CRL fetuses. This type of growth resulted from the nearly linear increase in the weight of the thyroid gland at the same period of development. Analysis of our data revealed, however, that up to 165 mm CRL the rate of colloid formation in fetal thyroid gland is higher than the rate of growth of thyroid epithelium. These processes resulted in a notable decrease in the epithelium/colloid ratio up to 17.5 weeks of gestation, thereafter this ratio remained constant.

As revealed in the present study, the height of thyroid epithelial cells did not change during the studied period of intra-uterine development, a finding confirming the earlier report of Shepard et al. (1964b). Our data did not show sex differences in the structure of fetal thyroid gland and are in consent with the results of Shepard et al. (1964b). On the contrary, in the thyroid gland of the females from the late fetal period Albu and Georocenau (1986) found more thyroid follicles per unit area of the gland than in male fetuses.

As mentioned earlier, iodothyronines have been detected in the fetal thyroid gland at the 10th week of gestation and thyroxine in fetal serum between 10 - 11 (Greenberg et al., 1970; Roti, 1988). This time-period corresponds very closely to the time of appearance of the first colloid-containing follicles in the gland. Small amounts of TSH in fetal serum have been found at the 12th week of gestation and its concentration gradually increased up to 22 - 24 (Fisher, 1986). This increase in serum TSH concentration may be responsible for the formation and maturation of the thyroid follicles. As evidenced by the present findings, the maturation of the thyroid follicles is best reflected by the changes in epithelium/colloid ratio. This ratio gradually decreased up to the 20th week of gestation. Whether this process depends on TSH action remains to be elucidated, the more so, as in adult laboratory animals TSH administration resulted in a marked increase in epithelium/colloid ratio (Uotila and Kanas, 1962; Palkovits, 1963). Moreover, evidence is available that in the absence of pituitary the human fetal thyroid develops the ability to concentrate iodide and makes thyroxine (Yamazaki et al., 1959). Since this process depends on the presence of colloid in the gland, these findings suggest that the development and maturation of human fetal thyroid follicles does not require the presence of fetal thyrotropic hormone.

Thus, results of the present study suggest that the human fetal thyroid gland attains structural maturity at 17.5 week of gestation. Moreover, results of the present study demonstrate that the changes in the epithelium/colloid ratio and in the number of thyroid follicles per unit area are the best morphometric parameters depicting the process of thyroid follicle formation and maturation, while the height of epithelial cells remains constant throughout the studied period of intra-uterine life.

References

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