Original article

A Study on maturation of thyroid gland in human fetuses

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Abstract

The thyroid gland is the first endocrine gland to appear on the embryonic period. Its organogenesis begins when the medium endoderm cells start getting thick, forming a diverticulum, in the primitive pharynx floor. In this report, we describe the histological maturation of thyroid gland in human fetuses, correlating the tissue aspects with pregnancy stage. Twenty human fetuses were used in this study in different developmental stages. The fetuses from 20 to 36 weeks (gestational age) were dissected and the thyroid gland removed. The gland was then embedded in paraffin, cut in frontal plans portions and stained with Hematoxylin and Eosin (H&E). We observed that the maturation process of the thyroid follicles was directly correlated with the gestational age, where human fetus with 23 weeks of age did not show any sign of follicles or colloid and the one with 35 weeks of age presented follicles with colloid. The conclusion of this study was that maturation process of the thyroid follicles tissue is a linear process with the fetal development.

Keywords: thyroid gland, human fetuses, pregnancy stage.

1 Introduction

The thyroid gland is the first endocrine gland to appear on the embryonic period. Its organogenesis begins when the medium endoderm cells start getting thick, forming a diverticulum, in the primitive pharynx floor. This diverticulum descends, and at the seventh week of pregnancy it stops at cervical spine height. The follicles cells, responsible for hormonal biosynthesis, derive almost completely of the primary thyroid. The differentiations begin when the migration finishes (PERONE, TEIXEIRA, CLARA et al., 2004).

The Thyroid Stimulating Hormone Receptor (TSHR) is the receptor responsible for intermediation of TSH actions in growth, metabolism and cells functions. TSHR intracellular mechanisms can damage the usual reaction towards the TSH, even though being biologically active (MACHIA, 2000). This condition is called the TSH resistance. TSH total insensibility results in hypoplastic thyroid gland characterized by the reduction in thyroid hormones synthesis (LIM, HERRING, LEEF et al., 2005). Furthermore, alterations in thyroid formation, such as the thyroid dysgenesis, on account of mutation, are responsible for most of the permanent cases of primary congenital hypothyroidism (SCHOEN, CLAPP and FIREMAN, 2004).

In the human being, the transient hypothyroxinemia on those extreme preterm infants who are hypothyroxinemic should allow its entrance on clinical trials of thyroxin substitution. Indeed, that transient hypothyroxinemia is defined by postnatal serum T_4 levels, which are cord levels corrected to an equivalent gestational age of the fetuses that remained in the uterus. Those levels are significantly adjusted during prenatal and intrapartum. Nevertheless, serum T_3 and thyroid-stimulating hormone levels do not contribute to a diagnosis of transient hypothyroxinemia according to Williams, Visser and Hume (2006), Williams and Hume (2008) and Williams, Mires, Barnett et al. (2005). Nevertheless, there are no evidences that correlate very low birth weight (VLBW) neonates with thyroid development.

Nowadays, VLBW neonates represent approximately 4-7% of all live births and their mortality is very high. The survival rate seemed to increase with the rise of birth weight and gestational age like described by Patel, Piotrowski, Nelson et al. (2001) and Tsou and Tsao (2003). More recently confirmed by Sritipsukho, S., Suarod and Sritipsukho, P. (2007), Basu, Rathore and Bhatia (2008) and Vimercati, Scioscia, Panella et al., (2008). Thus, the extreme preterm birth, <28 weeks of gestation, represents a public health concern with major economic implications, being the leading cause of neonatal mortality and morbidity. In different studies, only extreme prematurity (< or = 25 weeks) and birth weight <500 g were significantly associated with mortality. The prehospital survival rates in extreme prematures (from 500 to 1,000 g), both in Brazil (LEONE, SADECK, VAZ et al., 2001) and in United States and Canada (HORBAR, BADGER, CARPENTER et al., 2002) vary from 25 a 64%. The management of preterm labour at the limit of viability is always challenging and we agree with Hakansson, Farooqui, Holmgren et al. (2004) and Rovet and Simic (2008). The parameters such as gestational age and weight do not appeared to be good predictors of positive outcomes and it is well established that neonates bellow 500 g are impractical and cardiopulmonary resuscitation is not recommended in these cases reported in service in middle ninnies by Goldsmith, Ginsberg and McGettigan (1996) and still confirmed by Hussain and Rosenkrantz (2003) at the beginning of new century.

The importance of this work was to show the tissue maturation of thyroid gland in human fetuses, with the objective of correlating the morphological aspects and the

stage of human developmental. The basic science studies on the maturation process of the thyroid gland should imply morphological and functional aspects that can provide information to propose new therapeutic techniques and even prevention. All these approaches can reduce the costs for the Healthy System on newborn thyroid dysfunction.

2 Material and methods

Twenty human fetuses (Tables 1, 2) were collected at Hildete Falcão Batista Maternity in the city of Aracaju. This project was approved by the Universtiy Hospital Ethics and Research Committee of the Sergipe Federal University and it was also legally authorized by the donors' parents, which was obtained by the Maternity Social Department, before the fetuses were incorporated into the research. The fetuses in natura were frozen at low temperature (4 °C) during 30-45 days in the maternity ward. They were transported packed in iceboxes from the maternity ward to the Molecular Anatomy Laboratory Room 20 of the Morphology Department at the Federal University of Sergipe (UFS).

At the university, the human fetuses were kept frozen at low temperature (4 °C), and later thawed individually in running water. Then, they were submitted to thyroidectomy. Notes were taken about location, topographic relations, size and morphology of the glands using magnifying glasses. The thyroids were submerged in a 10% formaldehyde solution, and then embedded in paraffin. Then several frontal plane cuts, seven microns, were done and these cuts were then stained with Hematoxylin and Eosin (H&E). Subsequently, each slide was examined on an optical microscope and submitted to histomorphometric analysis, and then registered in photographs.

3 Results

The anthropometrics parameters studied were: gender (twelve males and eight females), weight in grams (varied from 300 to 1,400 g, with an average of 649.5 g) and an estimation of the stage of pregnancy, which presented an average of 6 months and 12 days (Table 2). Two out of the twenty fetuses studied revealed morphological anomalies. One of them did not display an isthmus region, and the other one presented a pyramidal lobe. In order to calculate gestacinal age, the vertex buttock measurement, based on classic table by Lagman in apud Sadler (2010) was used.

All of the histological analysis was observed and documented with an Olympus light microscope (Figure 1). In this analysis, all of the thyroids from five to six month-old fetuses showed immaturity in the tissues and the follicles' organization. The cells did not yet display a cubic shape, but instead showed an oval shape, and the mass of cells were organized in such a way that they were intermingled with the estrum conjunctive tissue. Neither follicles nor colloid were formed (Figure 1a). Two of the samples showed probable traces of thymus tissue.

Analyzing three to seven month-old fetuses, it was found that one had a thyroid cellular organization similar to the one found in five to six month-old fetuses. No follicle formation or colloid was found, and the number of cells in the lumen was much reduced. In another sample, a great number of mature follicles were detected, but most of them were diminished in size, and with no signs of colloid (Figure 1b). The last sample showed mature follicle tissues and colloid (despite the fact that only a small amount of them were found), and the rest of the parenchyma was formed by cellular mass.

The eight month-old fetuses showed a histological aspect almost identical to a normal adult's gland. The follicles were spherical (but most of them were still reduced in size when compared to the adult size), with low-density colloid inside of them and the majority of the cells were in low cubic form (Figure 1c).

Table 1. Distribution of human fetal gender in the weeks of pregnancy.

Gender (n)	Weeks of pregnancy		
	20-27	28-31	32-36
Male (12)	7 (58.3%)	4 (33.3%)	1 (8.4%)
Female (8)	5 (62.5%)	1 (12.5%)	2 (25%)

4 Discussion

Although, many forms of the thyroid gland can be found in human fetuses during early development, (COLZANI, ALEX, FANG et al., 1999) a similar type of growth to the one found in this research. Pregnancy age is directly related to the growth of the thyroid, as illustrated on Figures 1a, b and c as well as its locations on the neck during development. Since they have an intimate relationship with the embryological approach, this anatomical study is useful for groups that work in early intra-uterine diagnoses of thyroid problems.

Previous study using microscopic anatomic descriptions revealed differences in tissue development (Volumenie, Polak Guibourdench et al. (2000). However, we showed herein a linear histological maturation (Figures 1a, b, c). This might be related to the thyroid tissue maturation at the end of gestacional age. The changes in the morphological description have an importance because when properly analyzed they can prevent hyperthyroidism and hypothyroidism. Both these disorders produce malformation and a variety of neurological problems that can bring serious consequences

Table 2. Weight (mean ± standard deviation) in human fetal distributed in the weeks of pregnancy.

Gender (n)	Weeks of pregnancy			Statistical significance	
	20-27	28-31	32-36	p value	remark
Male (g)	521 ± 73.6	762.5 ± 148.6	1400	p = 0,0051*	Highly Significant
Female (g)	452 ± 152.2	700	965 ± 120.21	p = 0,0086**	Highly Significant
Male+female(g)	492.5 ± 112.5	750 ± 131.7	1110 ± 265.4	p < 0,01	Highly Significant

*Anova comparison of male between 20-27 and 28-31 weeks of pregnancy. **Anova comparison of female between 20-27 and 32-36 weeks of pregnancy.

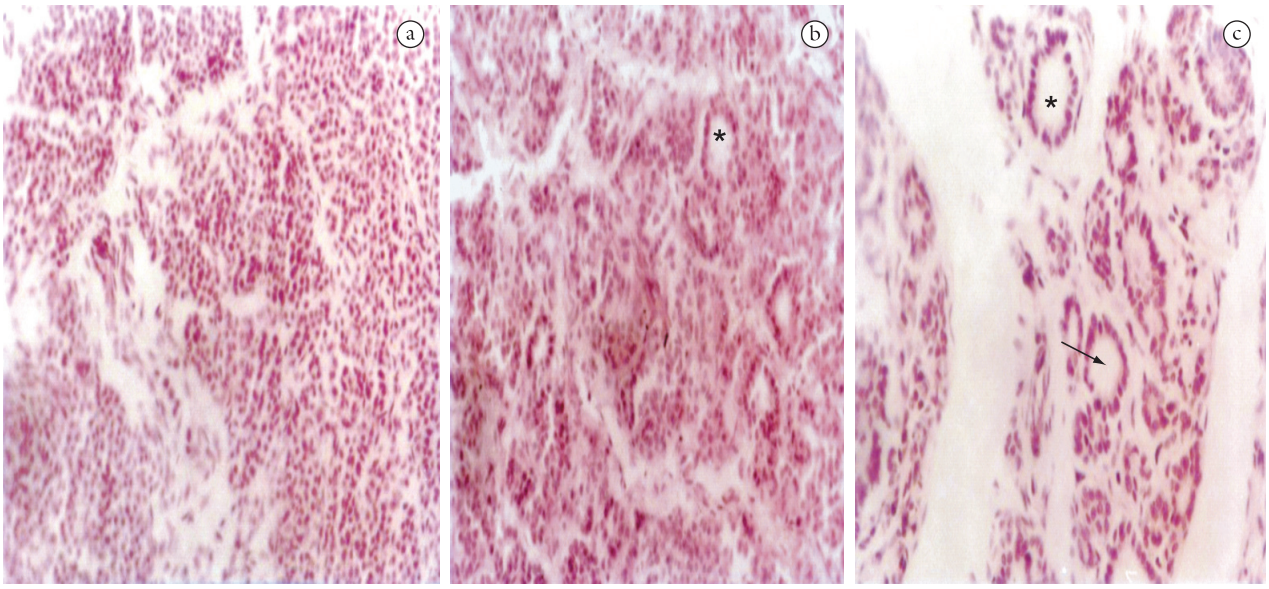

Figure 1. a) Photomicrograph of a 5 µm section of human fetus with 23 weeks of age showing immature tissue, no organization follicular and colloid observed. This section was stained with H&E stain and observed with 400× magnification. b) Photomicrograph of a 5 µm section of human fetus with 30 weeks of age showing cellular differentiation most incomplete, with partial mature follicular organization, we observed few complete follicles composed by small number of cells and, and no colloid observed (asterisk). This section was stained with H&E stain and observed with 400× magnification. c) Photomicrograph of a 5 µm section of human fetus with 35 weeks of age showing cellular differentiation and follicular organization complete, we observed that the follicles were spherical (arrow), reduced size when compared with the adult size, inside of them with low-density colloid and the majority of the cells were cubic low form (asterisk). This section was stained with H&E stain and observed with 400× magnification.

to the Health Care System since the costs of treating these diseases in newborns are elevated.

Overall, the tissue maturation is a gradual process and it is complete by the end of the pregnancy. This research is a preliminary study. It considered only the fetus information, lacking better data when it came to the mother. The legal wait time of the fetuses in the maternity ward was a bit much, thirty to forty days, and it will have to be improved for future papers.

5 Conclusion

In general, the tissue maturation is a process that is all done close to the pregnancy terminal. Actually, it`s around to the delivery time. The conclusion of this study was that maturation process of the thyroid follicles tissue is linear correlated with the gestational age.

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