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# MORPHOGENESIS OF BRANCHIOGENIC GLANDS OF THE NECK IN THE FETAL PERIOD OF ONTOGENESIS

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***Summary***

*Branchiogenic glands play an important role in the control of calcium and iodine levels and thus have a direct impact on muscle contraction and neurotransmission. Variations in the structure and ectopic location of parathyroid and thyroid glands increase the complexity of thyroid and parathyroid surgery.*

***Aim.*** *To study the variants of structure and anatomical features of the parathyroid and thyroid glands at different stages of fetal development.*

***Materials and methods.*** *To study the anatomical variability of the branchiogenic glands of the neck in the fetal period of ontogenesis, we chose a set of classical methods of morphological research: morphometry, thin dissection under the control of a microscope, and photographic documentation. The material for the study were 48 preparations of human fetal cadavers from the 4th to the 10th month of intrauterine development. Digital parameters of organs and their correlation with neighboring organs and structures were grouped into appropriate age groups and processed by non-parametric methods of variation statistics with calculation of their arithmetic mean, its error and determination of probability of differences by Student's t-test using MS Excel and Biostatistics programs. The study was conducted in accordance with the main provisions of the Law of Ukraine ¹ 1801-XII «Fundamentals of the Legislation of Ukraine on Health Care», GCP (1996-2016), the Declaration of Helsinki of the World Medical Association for the Ethical Principles of Scientific Medical Research Involving Human Subjects (1964-2013), the Convention of the Council of Europe on Human Rights and Biomedicine (04.04.1997), Order of the Ministry of Health of Ukraine No. 690 dated 23.09.2009, and therefore concluded that the proposed study should be recommended for publication.*

*The article is a fragment of the research work of the Department of Surgery № 1 of Bukovinian State Medical University: 'Development, substantiation and implementation of new approaches to the diagnosis and treatment of some acute surgical diseases, prediction of their course and prevention of complications', state registration number – 0121U110501: 01.2021-12.2025.*

***Results.*** *At the beginning of the fetal period of human ontogenesis there is an intensive development of the parathyroid glands. Variability of morphology of upper and lower parathyroid glands was found in 15 fetuses of 4-5 months of age. During this period, the following forms were observed: elongated, oval, bean-shaped, crescent-shaped. In the study of 15 fetuses at the age of 6-7 months, the following variations in the shape of the upper and lower parathyroid glands were found: oval, elongated, round, crescent, lenticular, bean-shaped. Topographically, we found the following variations in the location of the upper parathyroid glands: 1) between the upper and middle thirds of the thyroid lobes; 2) at the level of the upper third of the thyroid gland; 3) at the level of the middle third of the thyroid gland; 4) in the parenchyma of the thyroid gland; 5) above the thyroid lobes – 40 % (20 cases), 36 % (18 cases), 10 % (5 cases), 8 % (4 cases), 6 % (3 cases), respectively.*

***Conclusions.*** *1. The variants of the structure and topography of the thyroid gland, the upper parathyroid gland and the lower parathyroid gland, which we have identified, can be anatomical conditions for the development of both congenital pathology and variants of normal structure, which can nevertheless cause iatrogenic disorders during surgery. 2. In fetuses of 4-10 months of age, numerous variants of the structure and topography of the upper parathyroid gland and lower parathyroid gland are observed, which differ significantly from their typical structure. 3. The aplasia of the upper pineal gland detected in two human fetuses of 7 months of age is due to the peculiarities of their organogenesis and the formation of syntopia in the embryonic and prenatal periods of prenatal morphogenesis. 4. The obtained data on individual anatomical variability of the pineal glands should be taken into account by endocrinologists and ultrasonographers when performing diagnostic and surgical procedures.*

***Key words:*** *Thyroid Gland; Parathyroid Glands; Neck; Anatomy; Fetus.*

## Introduction

Specific diseases in thyroid surgery are a very acute problem both in Ukraine and in the world due to the large number of thyroid (TG) surgeries (in Ukraine – 11-12 thousand surgeries per year) and the steady trend of increasing incidence of diseases [1, 2]. The most frequent specific iatrogenic pathologies of thyroid surgery are laryngeal nerve damage with subsequent laryngeal paresis and hypoparathyroidism with hypocalcemic syndrome. Postoperative decrease in parathyroid hormone secretion, which occurs in 20-60 % of cases, is the most common type of adverse effects of surgery and causes a significant deterioration in the quality and duration of life [3-5]. Therefore, in order to avoid postoperative hypoparathyroidism, it is important to know the topographic anatomy of the parathyroid glands (PTGs) and possible variations in their structure [6-9].

Identification of PTGs during surgery can be difficult due to their small size, number, anatomical variations, proximity to important structures, and unreliable visualization [10-13].

PTGs play an important role in controlling calcium levels and thus have a direct impact on muscle contraction and neurotransmission. Variations in the structure and ectopic location of PTGs increase the complexity of thyroid and parathyroid surgical procedures [11-14].

Heterotopy of PTGs due to aberrant migration in the early stages of development and the inability to identify it can lead to intraoperative errors on the thyroid and parathyroid glands, in the neck, and in the mediastinum.

According to anatomical studies, the prevalence of ectopic PTGs ranges from 2 to 43 % in patients with primary hyperparathyroidism and from 14 to 16 % in patients with secondary hyperparathyroidism. Most commonly, ectopic lower parathyroid glands (LPTG) are found in the anterior mediastinum. Abnormal locations of the upper parathyroid glands (UPTG) include their location in the tracheoesophageal groove or behind the esophagus [15-18].

Determination of patterns of structure formation and syntopic relations of organs and structures during the fetal period is important for interpretation of mechanisms of normal organ formation, occurrence of anatomical variants and congenital malformations [19-22]. The complex task of fetal anatomy is to study the forms of variant anatomy of organs and structures, especially glands of internal secretion, at each stage of fetal development. Scientific reports in periodicals sometimes contain data on the results of studies of anatomical variability of the thyroid and parathyroid glands, but they are rare and fragmentary [23-25]. As for comprehensive studies of fetal variant anatomy of branchiogenic glands of the neck, there is no information about them.

### Relation to scientific programs, plans, themes

The article is a fragment of the research work of the Department of Surgery No. 1 of the Bukovinian State Medical University: «Development, substantiation and implementation of new approaches to diagnosis and treatment of certain acute surgical diseases, prediction of their course and prevention of complications», state registration number 0121U110501.

**Aim.** To study the variants of structure and anatomical features of the parathyroid and thyroid glands at different stages of fetal development.

**Materials and methods** of the study. To achieve this goal, we studied 50 preparations of human fetal cadavers of 4-10 months of prenatal development using a set of classical methods of anatomical research: morphometry, photographic documentation, and conventional and thin dissection under the control of a microscope. The experimental material (fetal cadaver preparations) was divided into 3 groups: Group I – fetuses of 4-5 months of intrauterine development; Group II – fetuses of 6-7 months of intrauterine development; Group III – 8-10 months of intrauterine development. To ensure adequate access to the neck organs, incisions were made along the upper and lower borders of the anterior neck: from the chin, along the lower edge of the mandible, to the mastoid process and down the outer edge of the trapezius muscle to the acromial end of the clavicle. The incision was then continued along the upper surface of the clavicle, medially to the jugular notch of the sternum. The skin with subcutaneous fat and subcutaneous muscle was removed.

The digital parameters of organs and their correlation with adjacent organs and structures were grouped into appropriate age groups and processed by nonparametric methods of variation statistics with the calculation of their arithmetic mean, its error and determination of the significance of differences by Student's t test using MS Excel and Biostatistics software.

The study was performed in compliance with the main provisions of the Law of Ukraine No. 1801-XII 'Fundamentals of the Legislation of Ukraine on Health Care', GCP (1996-2016), the Declaration of Helsinki of the World Medical Association for the Ethical Principles of Scientific Medical Research Involving Human Subjects (1964-2013), the Council of Europe Convention on Human Rights and Biomedicine (04.04.1997), Order of the Ministry of Health of Ukraine № 690 of 23.09.2009, and therefore concluded that the proposed study should be recommended for publication.

The theme of the complex research work «Development, justifi cation and implementation of new approaches to the diagnosis and treatment of some acute surgical diseases, prediction of their course and prevention of complications (state registration number: 0121U110501, terms of execution: 01.2021-12. 2025).

### Results and discussion

In a fetus with a PCL of 170.0 mm, an H-shaped thyroid was observed with an LPTG located below the inferior pole of the left lobe, which was 3.7 mm high and 4.6 mm wide, adjacent to the inferior end of the left thyroid lobe and located between the trachea and the right common carotid artery (Fig. 1). The remainder of the UPTG and LPTG had a classic topography. The isthmus of the thyroid was located at the level of the 3rd intercostal space. The left lobe of the thyroid was in contact with the lateral surface of the trachea, esophagus and cricoid cartilage.

In the other case, a horseshoe-shaped thyroid was observed in a 195.0 mm PCL fetus. The right LPTG was located 5 mm inferior to the left thyroid lobe and slightly lateral. It was characterized by an oval shape with dimensions of 7.2 mm in height and 3.3 mm in width. Its posterior surface was in contact with the trachea (Fig. 2).

At the beginning of the fetal period of human ontogenesis there is an intensive development of the thyroid gland. Variability in the morphology of the UPTG and LPTG was found in 15 fetuses of 4-5 months of age. During this period, the following forms of UPTG and LPTG were observed: elongated, oval, bean-shaped, crescent-shaped (Table 1).

In fetuses of 4-5 months the UPTG were located mainly at the level of the middle third of the posterior surface of the thyroid gland (6 cases, 40 %) or at the border of the upper and middle thirds of the thyroid gland (4 observations, 26. 7 %), less frequently – at the level of the upper third of the thyroid lobe – 20 % (3 cases), between the middle and lower third of the thyroid – 6.6 % (1 case), in the thyroid parenchyma – 6.6 % (1 case). Topographically, both LPTG were located as follows: on the posterior surface of the lower third of the thyroid lobes – 33.3 % (5 cases), near the lower poles of the thyroid lobes – 26.7 % (4 cases), at the border of the middle and lower thirds of the thyroid lobes – 20 % (3 cases), between the components of the neurovascular bundles of the neck – 13.3 % (2 cases), in the thyroid parenchyma – 6.7 % (1 case).

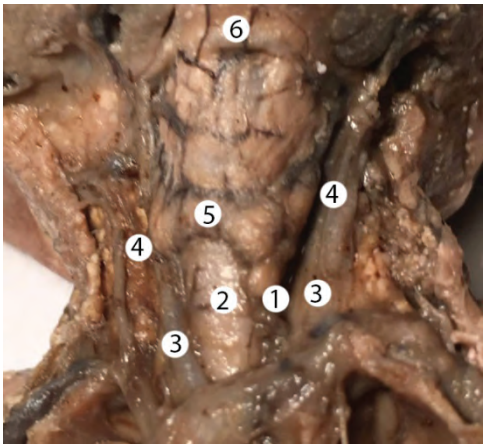


**Figure 1. Fetal neck organs of a 170.0 mm PCL. Macroscopic view. Magnification ×2.6:**

*1 – Left inferior parathiroid gland;*
*2 – Trachea;*
*3 – Common carotid arteries;*
*4 – Vagus nerve;*
*5 – Isthmus of thyroid gland;*
*6 – Cricoid cartilage arch;*

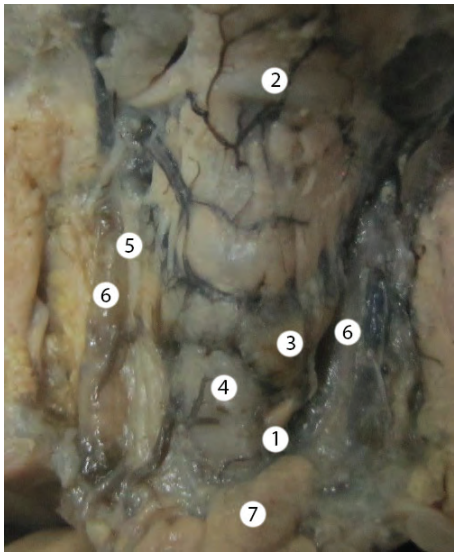


**Figure 2. Fetal cervical organs of 190.0 mm PCL. Macroscopic view. Magnification ×2.7:**

*1 – Left lower parathyroid gland;*
*2 – Isthmus of thyroid;*
*3 – Left lobe of thyroid;*
*4 – Trachea;*
*5 – Right vagus nerve;*
*6 – Common carotid arteries;*
*7 – Thymus.*

**Table 1**

**Anatomical variability inf the shape of the upper and lower parathyroid glands in the early fetal period of intrauterine development**

| UPTG form variants | Case number (%) |
|---|---|
| Oval | 5 (33,3) |
| Bean-shaped | 3 (20) |
| Elongated | 7 (46,6) |
| LPTG form variants | |
| Rounded | 7 (46,7) |
| Crescent-shaped | 1 (6,7) |
| Elongated | 3 (20) |
| Oval | 4 (26,7) |

In the study of 15 fetuses aged 6-7 months, aplasia of the parathyroid gland was detected in 2 observations (fetuses of 255.0 and 260.0 mm PCL). The following variations in the shape of the UPTG and LPTG were observed: oval, elongated, rounded, crescent, lenticular, and bean-shaped (Table 2).

**Table 2**

**Anatomical variability in the shape of the upper and lower parathyroid glands in fetuses at 6-7 months of fetal development**

| UPTG form variants | Case number (%) |
|---|---|
| Oval | 5 (33,3) |
| Rounded | 3 (20) |
| Elongated | 4 (26,7) |
| Lenticular | 1 (6,7) |
| Crescent-shaped | 2 (13,3) |
| LPTG form variants | |
| Rounded | 6 (40 %) |
| Lenticular | 3 (20 %) |
| Bean-shaped | 3 (20 %) |
| Elongated | 1 (6,7 %) |
| Oval | 2 (13,3 %) |

In fetuses aged 6-7 months, UPTG are usually localized at the border of the upper and middle thirds of the posterior surface of the thyroid lobes – 6 cases (40 %) and at the level of the middle third of the thyroid lobe – 4 cases (26.7 %), less often – at the level of the upper third of the thyroid lobe – 3 cases (20 %) or within the neurovascular bundles of the neck, lateral to the thyroid lobes – 2 cases (13.3 %).

In 46.6 % (6 cases) LPTG were localized on the posterior surface of the lower third of the thyroid lobes. In 26.6 % (4 cases) the LPTG was located under the thyroid lobes. In 20 % (3 cases), LPTG was located between the middle and lower thirds of the thyroid lobes. In 6.7 % (1 case) the LPTG was located between the components of the neurovascular bundles of the neck. In another 6.7 % (1 case) – behind the sternum.

We found a variant in the structure of the thyroid gland and, accordingly, in the topography of the LPTG. Thus, in a 225.0 mm fetus, the L-shaped thyroid gland had a vertically placed right lobe and pyramidal process, and a horizontally placed isthmus and left lobe. The left LPTG was located between the left common carotid artery and the trachea, ventrally adjacent to the inferior border of the left thyroid lobe, and dorsally adjacent to the left recurrent laryngeal nerve. The left lenticular LPTG was located below the left pole of the thyroid. Its dimensions: width – 6.0 mm, height – 3.0 mm.

In a fetus with a PCL of 240.0 mm, heterotopia of the left LPTG was noted, located within the left neurovascular bundle of the neck, between the left common carotid artery and the left internal jugular vein, and 4.0 mm below the left thyroid lobe. The left thyroid is oval in shape and its posterior surface is adjacent to the anterior surface of the left vagus nerve and the anterolateral surface of the left common carotid artery. The length of the left LPTG is 11.0 mm and the width is 5.5 mm. The thyroid gland is horseshoe-shaped, consisting of right and left lobes, which dorsally contact the cartilages I-III of the trachea.

In this case, the cricoid cartilage had a classic structure consisting of two symmetrical quadrangular lamellae joined at an obtuse angle. The cricoid cartilage is located above the isthmus of the TG and behind the right lobe with the pyramidal process. From the side, the right lobe of the thyroid was in contact with the right common carotid artery and the left lobe with the left vagus nerve and the left internal jugular vein.

We studied 20 fetuses of 8-10 months of intrauterine development. The anatomical variability of the LPTG and UPTG was demonstrated (Table 3).

**Table 3**

**Anatomical variability in the shape of the upper and lower parathyroid glands in fetuses at 8-10 months of fetal development**

| UPTG form variants | Case number (%) |
|---|---|
| Oval | 8 (40) |
| Rounded | 6 (30) |
| Elongated | 4 (20) |
| Flat | 1 (5) |
| Droplet-shaped | 1 (5) |
| LPTG form variants | |
| Rounded | 10 (50 %) |
| Lenticular | 6 (30 %) |
| Elongated | 3 (15 %) |
| Oval | 1 (5 %) |

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Topographically, we found the following variants of location of the UPTG: 1) between the upper and middle thirds of the thyroid lobes – 40 % (20 cases); 2) at the level of the upper third of the thyroid – 36 % (18 cases); 3) at the level of the middle third of the thyroid – 10 % (5 cases); 4) in the parenchyma of the thyroid – 8 % (4 cases); 5) above the thyroid lobes – 6 % (3 cases).

LPTG had the following topography behind the thyroid gland: 1) behind the lower third of the thyroid lobes – 40 % (20 cases); 2) under the poles of the thyroid lobes – 28 % (14 cases); 3) between the lower and middle thirds of the thyroid lobes – 14 % (7 cases); 4) in the parenchyma of the thyroid gland – 14 % (7 cases); 5) between the components of the neurovascular bundle of the neck – 4 % (2 cases). We found individual asymmetry of shape of left and right LPTG and UPTG.

We have identified cases of individual anatomical variability of the LPTG. In one case, a fetus with a PCL of 280.0 mm, the LPTG was observed to be displaced inferiorly and laterally in relation to the right lobe of the thyroid. The thyroid was butterfly-shaped. The right LPTG was located dorsally to the right common carotid artery and had a rounded shape with dimensions of 5.0 mm and 6.5 mm in height and width, respectively. It was located between the trachea and the right vagus nerve.

In all studied variants of the topography of the parathyroid glands, branches of the inferior thyroid artery were involved in their blood supply. In addition, the thyroid was supplied by branches of the superior thyroid artery and the arteries of the esophagus, trachea, and larynx. Venous drainage was provided by the thyroid venous plexus of the anterior surface of the neck of the trachea and thyroid gland, the cricoid arch, and the laminae of the thyroid cartilage. The right and left inferior thyroid veins form the brachiocephalic veins, and the right and left superior and middle thyroid veins form the internal jugular veins.

## Conclusions

1. The variants of the structure and topography of the thyroid gland, UPTG and LPTG, which we found, can be anatomical conditions for the development of both congenital pathology and variants of normal structure, which, however, can cause iatrogenic disorders during surgery.

2. In fetuses of 4-10 months of age, numerous variants of structure and topography of UPTG and LPTG are observed, which differ significantly from their typical structure.

3. The aplasia of the UPTG found in two human fetuses of 7 months of age is due to the peculiarities of their organogenesis and the formation of syntopia in the embryonic and prenatal period of prenatal morphogenesis.

4. The data obtained on individual anatomical variability of PTG should be regarded by endocrinologists and ultrasonographers when performing diagnostic and surgical procedures.

**Prospects for further research.** The study of prenatal morphogenesis of the parathyroid gland in fetuses of 4-10 months of age shows the need for further study and determination of its structural variants in newborns.

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## МОРФОГЕНЕЗ БРАНХІОГЕННИХ ЗАЛОЗ ШИЇ В ПЛОДОВОМУ ПЕРІОДІ ОНТОГЕНЕЗУ

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**Резюме.**

Бранхіогенні залози відіграють важливу роль у контролі за рівнем кальцію та йоду, і відповідно, мають безпосередній вплив на скорочення м'язів та нейротрансмісію. Варіанти будови та ектопічне розташування прищитоподібних та щитоподібних залоз підвищують складність оперативних втручань на щитоподібній та прищитоподібній залозах.

**Мета.** Дослідити варіанти будови та анатомічні особливості прищитоподібних та щитоподібної залоз на різних етапах плодового періоду розвитку людини.

**Матеріали та методи.** Для дослідження анатомічної мінливості бранхіогенних залоз шиї в плодовому періоді онтогенезу нами вибрано комплекс класичних методів морфологічного дослідження: морфометрія, тонке препарування під контролем мікроскопу, фотодокументування. Матеріалом для дослідження послужили 48 препаратів трупів плодів людини від 4-го до 10-го місяців внутрішньоутробного розвитку. Цифрові параметри органів та їх співвідношення з суміжними органами та структурами були згруповані у відповідні вікові групи та оброблені непараметричними методами варіаційної статистики з вираховуванням їх середньоарифметичного значення, його похибки та визначенням вірогідності різниць за t критерієм Стьюдента за допомогою програм MS «Excel» та «Біостатистика». Дослідження виконані з дотриманням основних положень Закону України № 1801-XII «Основи законодавства України про охорону здоров'я», ICH GCP (1996-2016 рр.), Гельсинської декларації Всесвітньої медичної асоціації про етичні принципи проведення наукових медичних досліджень за участю людини (1964-2013 рр.), Конвенції Ради Європи про права людини та біомедицину (від 04.04.1997 р.), наказу МОЗ України № 690 від 23.09.2009 р., на підставі чого дійшла висновку: запропоноване дослідження рекомендувати до публікування. Стаття є фрагментом НДР кафедри хірургії № 1 Буковинського державного медичного університету: «Розробка, обґрунтування і впровадження нових підходів до діагностики і лікування деяких гострих хірургічних захворювань, прогнозування їх перебігу та профілактики ускладнень», № держреєстрації – 0121U110501.

**Результати.** На початку плодового періоду онтогенезу людини відбувається інтенсивний розвиток паращитоподібної залози. У 15 досліджених плодів 4-5 місяців виявлена варіабельність морфології верхніх і нижніх прищитоподібних залоз. У даний період нам траплялись наступні їх форми: видовжена, овальна, бобоподібна, півмісяцева форми. При дослідженні 15 плодів 6-7 місяців встановлені такі різновиди форми верхніх і нижніх прищитоподібних залоз: овальна, видовжена, округла, півмісяцева, сочевицеподібна та бобоподібна. Топографічно нами виявлено такі варіанти розташування верхніх прищитоподібних залоз: 1) між верхньою та середньою третинами часток ЩЗ; 2) на рівні верхньої третини щитоподібної залози; 3) на рівні середньої третини щитоподібної залози; 4) в паренхімі щитоподібної залози; 5) над частками щитоподібної залози – 40 % (20 випадків), 36 % (18 випадків), 10 % (5 випадки), 8 % (4 випадки), 6 % (3 випадки) – відповідно. Стаття є фрагментом НДР кафедри хірургії № 1 Буковинського державного медичного університету: «Розробка, обґрунтування і впровадження нових підходів до діагностики і лікування деяких гострих хірургічних захворювань, прогнозування їх перебігу та профілактики ускладнень», № держреєстрації – 0121U110501. терміни виконання: 01.2021-12.2025 рр.

**Висновки.** 1. Встановлені нами варіанти будови та топографії щитовидної залози, верхньої прищитоподібної залози і нижньої прищитоподібної залози можуть бути анатомічними умовами розвитку як природженої патології, так і варіантів нормальної будови, які тим не менш можуть стати причиною ятрогенних порушень під час оперативних втручань. 2. У плодів 4-10 місяців спостерігаються численні варіанти будови та топографії верхньої прищитоподібної залози і нижньої прищитоподібної залози, що значно різняться з їх типовою будовою. 3. Виявлена у двох плодів людини 7 місяців аплазія верхньої прищитоподібної залози обумовлена особливостями їх органогенезу і становлення синтопії у ембріональному та передплодовому періодах пренатального морфогенезу. 4. Отримані дані щодо індивідуальної анатомічної мінливості прищитоподібних залоз слід враховувати хірургам-ендокринологам та лікарям ультразвукової діагностики під час виконання діагностичних і оперативних маніпуляцій.

**Ключові слова:** щитоподібна залоза; прищитоподібні залози; шия; анатомія; плід.

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