Thymus gland Assessment and its Possible Relation with Fetal Growth Restriction

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Abstract

Although it is considered an endocrine gland, thymus gland is the main organ of the lymphatic system. Its primary function is to promote the development of specific white blood cells called T lymphocytes." The thymus is special in that, unlike most organs, it is at its largest in children. Once person reach puberty, the thymus starts to slowly shrink and become replaced by fat." Several methods for sonographic thymus measurement have been described. The thymus can be identified on the fetal three-vessel and tracheal view, between the great vessels posteriorly and the chest wall anteriorly. The thymus can be measured lengthwise and crosswise, its circumference and surface area can be measured. 8lThe nomograms for the analysis of the size of fetal thymus were developed in Canada (2007). A relationship was shown between the thymus transverse diameter and the gestational age, the fetal abdominal circumference and femoral length. The average transverse thymus diameter in mm was similar to the AC in cm, especially in the second trimester, which may be very useful information in day-to-day fetal sonography and echocardiography.

Keywords: Thymus gland, Fetal Growth Restriction

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Introduction

Although it is considered an endocrine gland, thymus gland is the main organ of the lymphatic system. Its primary function is to promote the development of specific white blood cells called T lymphocytes." (1)

The thymus is special in that, unlike most organs, it is at its largest in children. Once person reach puberty, the thymus starts to slowly shrink and become replaced by fat." (1)

Preprocessing of the T lymphocytes

Although all lymphocytes in the body originates from lymphocytes committed stem cells of the embryo (Pluripotent hematopoietic stem cells). These stem cells themselves are incapable of forming directly either activated T lymphocytes that provide "cell – mediated" immunity, or the B-lymphocytes, is responsible for forming antibodies that provide "humoral "immunity. These stem cells before they can do so, they must be further differentiated in appropriate processing areas as follows. **(1)**

Thymus Gland Preprocesses the T Lymphocytes.

The T lymphocytes, after origination in the bone marrow, first migrate to the thymus gland. Here they divide rapidly and at the same time develop extreme diversity for reacting against different specific antigens. **(2)**

That is, one thymic lymphocyte develops specific reactivity against antigen. Then the next lymphocyte develops specificity against another antigen. This continues until there are thousands of different types of thymic lymphocytes with specific re-activities against many thousands of different antigens. These different types of preprocessed T lymphocytes now leave the thymus spread by way of the blood throughout the body to lodge in lymphoid tissue everywhere. **(2)**

Such a process involves sequential expression of various proteins and rearrangements of the T-cell receptor (TCR) genes. The most immature thymocytes express neither the TCR complex nor the CD4 or CD8 accessory molecules; they are called double-negative thymocytes and represent 5% of total thymocytes. **(2)**

Maturation progresses with the acquisition of CD4 and CD8 markers, generating the CD4+CD8+ double positive cells, which constitute 80% of the whole population. In this stage, TCR genes are rearranged, and productive rearrangements yield the membrane expression of the TCR (complexed with the CD3) in low densities (TCRlow). **(2)**

Thymocytes that do not undergo a productive TCR-gene rearrangement die by apoptosis, whereas those expressing productive TCR will interact with peptides presented by molecules of the major histocompatibility complex (MHC), expressed on micro-environmental cells. **(3)**

This interaction will determine the positive and negative selection events, crucial for normal thymocyte differentiation. Positively selected thymocytes progress to the mature TCR highCD4+CD8 or TCRhighCD4CD8+ single positive stage, comprising 15% of thymocytes that ultimately leave the organ to form the large majority of the peripheral Tcell repertoire. **(3)**

The thymus also makes certain that any T lymphocytes leaving the thymus will not react against proteins or other antigens that are present in the body's own tissues; otherwise, the T lymphocytes would be lethal to the person's own body in only a few days. Thymus selects which T lymp tes will

be released by first mixing them with virtually all the specific "selfantigens" from the body's own tissues. (3)

If a T lymphocyte reacts, it is destroyed and phagocytized instead of being released. This happens to as many as 90% per cent of the cells. Thus, the only cells that are finally released are those that are nonreactive against body's own antigens—they react only against antigen from an outside source, such as from a bacterium, toxin, or even transplanted tissue from another person. (3)

Most of the preprocessing of T lymphocytes in the thymus occurs shortly before birth of a baby and for a few months after birth. Beyond this period, removal of the thymus gland diminishes (but does not eliminate) the T-lymphocytic immune system. However, removal of the thymus several months before birth can prevent development of all cell - mediated immunity. (2)

There are multiple types of T cells. They are classified into three major groups: 1) helper T cells, 2) cytotoxic T cells, and 3) suppressor T cells. The helper T cells are the most numerous of the T cells, usually constituting more than three quarters of all of them. They help in the functions of the immune system. They do this by forming a series of protein mediators, called lymphokines that act on other cells of the immune system as well as on bone marrow cells. (3)

Among the important lymphokines secreted by the helper T cells Interleukin-2,: Interleukin-3, :Interleukin-4, : Interleukin-5, : Interleukin-6, Granulocyte-monocyte colony- stimulating factor, Interferon. (3)

Cytotoxic T cells is a direct – attack cell that is capable of killing micro-organisms and, at times, even some of the body's own cells. For this reason, these cells are called killer cells. (3)

The thymus produces hormone- like proteins that help T lymphocytes to mature and differentiate. Thymic humoral factor increases immune responses to viruses. Some thymic hormones include thympoeitin and thymulin, thymosin, and thymic humoral factor (THF). thympoeitin and thymulin induce differentiation in T- lymphocytes and enhance T-cell function. (4)

Thymosin increases immune responses. It is also stimulating certain pituitary gland hormones (growth hormone, luteinizing hormone, prolactin, gonadotropin releasing hormone, and ACTH). (4)

Thymic hormones influence structure of the endocrine system, including the pituitary gland and adrenal glands, to assist in growth and sexual development. The thymus and its hormones also influence other organs including the kidneys, spleen, reproductive system, and central nervous system. (4)

Anatomy of the thymus gland

Positioned in the upper chest cavity, the thymus gland is actually a two – lobed structure that extends partially into the neck region. It is precisely located right about the, the thymus is situated

above the pericardium of the heart, in front of the aorta, between the lungs, below the thyroid, and behind of the sternum. (4)

The thymus has a thin outer covering called a capsule and consists of three types of cells. Thymic cell types include epithelial cells, lymphocytes, and Kulchitsky cells, or neuroendocrine cells. (4)

Epithelial cells – tightly packed cells that give shape and structure to thymus. Lymphocytes are immune cells. Kulchitsky cells are hormone- releasing cells. (3)

Each lobe of the thymus contains many smaller divisions called lobules. A lobule consists of an inner area called the medulla and outer region called the cortex. (3)

It originates from endodermal and mesodermal germ layers. The onset of thymus development occurs at the end of week 4, when the embryo is about 6mm long. The thymus takes a bilobate shape and grows rapidly, reaching its maximum size in the perinatal period. The thymus gland consists of the cortex and the medulla as well as fat tissue (2)

The tissue proportions change with age and, as a result, thymic tissue in adults is nearly replaced by adipose tissue and weighs less than a few grams. The thymus indeed shrinks after puberty, this is physiological atrophy, during which a lymphatic organ weighing about 30 g turns into a lump of fat weighing a few grams. (2)

At the of the last century, Professor Goldstein from the Washington University (USA) won the Nobel Prize for his discovery of the thymus hormone (thymosin). It was found that thymosin is released throughout life. So, two types of thymic involution were distinguished based on serum thymosin levels. (4)

Type one corresponds to normal natural process of 'physiological ageing' enabling survival to old age with normal hormone levels. Type two represents pathological, premature involution leading to immunity impairment, autoimmune diseases, cancer, etc. with very low thymosin levels. (4)

There are multiple causes of premature thymic involution and it may be difficult to identify the causative factor or to determine the timing of exposure in a given case. Therefore, since these 'toxic' factors can have effects already in the prenatal period, prenatal monitoring of thymus development and potential pathologies seems to be of great importance. (3)

The first article on the ultrasound assessment of fetal thymus was published by Felker et al. more than 25 years ago. (5) The thymus is visible on ultrasound as a roughly oval structure located within the superior mediastinum at the level of large heart vessels, between the heart and the sternum it's echo-structure is slightly smaller compared to surrounding lungs. It is clearly visible already at the end of the first trimester of pregnancy. (5)

Several methods for sonographic thymus measurement have been described. The thymus can be identified on the fetal three- vessel and tracheal view, between the great vessels posteriorly and the

chest wall anteriorly. The thymus can be measured lengthwise and crosswise, its circumference and surface area can be measured. 8lThe nomograms for the analysis of the size of fetal thymus were developed in Canada (2007). **(6)**

There are many published sets of measurement data for normal fetal thymic size in the literatures: that for anterior-posterior thickness, and that for perimeter. However, the anterior-posterior thickness of the thymus is difficult to define because its posterior extent varies significantly according to the size and arrangement of the great vessels. Also thymus perimeter measurement may be difficult and timeconsuming to measure, because the entire perimeter of the thymus is not always well defined. **(7)**

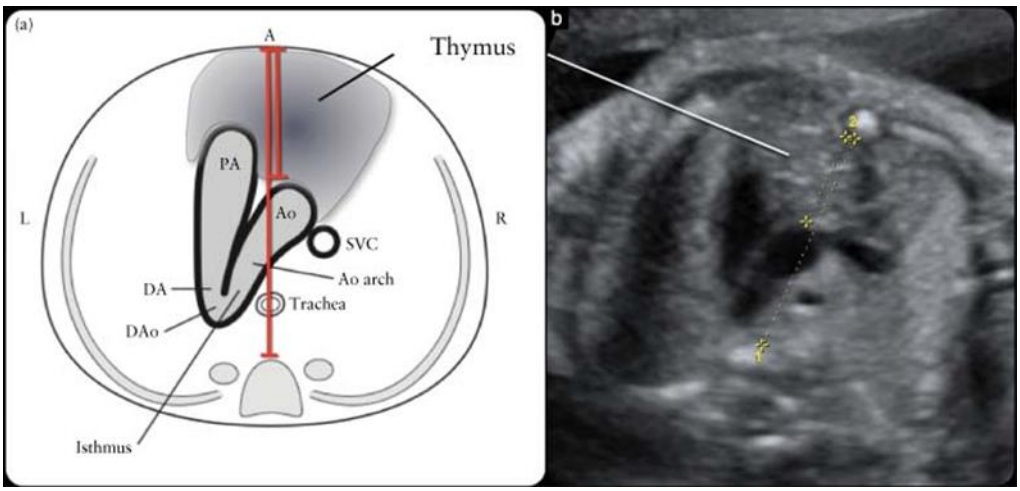

Figure (1): Three-vessel-trachea view shown on gray scale ultrasound

Measurement of the transverse diameter is easier than that of the perimeter because the interface with the lungs, demarcating the lateral margins of the thymus. The transverse diameter of the thymus can be defined more consistently and is therefore readily measurable. **(6)**

The transverse diameter of the fetal thymus increased according to the fetal GA, BPD, FL and AC in a linear manner. $1 The transverse dimension of the thymus is 12 mm at an average of 19 weeks gestation, while the transverse diameter of the thymus corresponds to the number of gestation weeks at 33 weeks gestation, i.e. an average of 33mm. In the perinatal period, the thymus is slightly larger than the fetal age counted in weeks. This growth pattern is analogous to the growth of other fetal parenchymal organs such as the liver, kidneys or thyroid gland. **(5)**

A relationship was shown between the thymus transverse diameter and the gestational age, the fetal abdominal circumference and femoral length. The average transverse thymus diameter in mm was similar to the AC in cm, especially in the second trimester, which may be very useful information in day-to-day fetal sonography and echocardiography. **(8)**

In case of difficulty in visualizing the thymus, particularly in the second trimester, when the echogenicity of the thymus is similar to that of the lungs, Doppler techniques may be used – then

the borders of the thymus are delineated by the internal mammary arteries, which clearly separate the gland from the lung tissue, resulting in an image of vascular contours resembling a box – hence the name of technique – thymus box (THY-BOX). **(9)**

Since the thymus is highly susceptible to different intrauterine "toxic' factors, such as hypoxia, infection, trauma, malnutrition and stress, assessment of thymic size seems particularly important in these cases. An increasing number of researchers demonstrate a correlation between the thymic size and the percentage of T cells, complement and thymosin levels in cord blood. **(10)**

This aspect is particularly interesting and promising as it seems that a new non-invasive prenatal diagnostic tool is being developed for the detection of secondary immunodeficiency. **(11)**

Numerous reports on the usefulness of the fetal thymus assessment focused on the issues related to thymus hypoplasia, which was usually linked to 22q11.2 deletion. The usefulness of fetal thymus evaluation in heart defects with arterial cone anomalies was emphasized. Thymus hypoplasia was considered as a strong guideline for geneticists to identify or exclude DiGeorge syndrome. **(12)**

This is a congenital hypoplasia of the thymus associated with the occurrence of defects and primary immunodeficiency. Structural abnormalities involve heart defects, facial dysmorphia with cleft palate and parathyroid aplasia. There are also publications describing the coexistence of atrophic thymus and heart defects in genetic syndromes, such as Down syndrome, Edwards syndrome and Patau syndrome. **(13)**

An increasing number of publications in the last years have demonstrated the coexistence of thymic involution as a response to intrauterine infection, which seems very promising in the search for an effective tool to monitor pregnancies with premature rupture of the membranes, when, as we all know, maternal biochemical parameters, such as CRP, procalcitonin and leukocytosis are simply insufficient. **(14)**

Similar observations about the premature involution of the thymus were presented in studies investigating pregnancies complicated by fetal growth restriction. **(15)**

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