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Prenatal thymus ultrasound – a new diagnostic tool for the assessment of immune efficiency

Prenatalna ultrasonografia grasicy płodowej w ocenie wydolności immunologicznej – nowe narzędzie diagnostyczne

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Summary

Recent years have seen significant advances in technology allowing the development of modern diagnostic tools, such as high resolution ultrasound equipment. This has enabled a dynamic development of prenatal diagnostics ensuring high-precision foetal imaging. Although most researchers focus on the search for potential structural pathologies, there is an increasing number of studies attempting to assess an impaired intrauterine foetal development due to adverse effects of potential 'toxic factors' associated with pregnancy pathologies such as intrauterine infection, spontaneous rupture of membranes, preeclampsia, trauma, malnutrition, chronic hypoxia, stress, etc. In this group, particular attention should be paid to reports on pathological involution of parenchymal organs, thymus in particular, by comparing the size of this organ in correlation with gestational age in both, physiological and complicated pregnancies. Recent reports supporting the relationship between the size of the central immune organ, i.e. the thymus, and the percentage of T regulatory cells in cord blood, are very promising. It seems that we are witnessing the emergence of novel tools for the assessment of the so-called 'immune potential of the foetus and newborn'.

Streszczenie

W ostatnich latach obserwujemy ogromny postęp technologiczny umożliwiający tworzenie coraz nowocześniejszych narzędzi diagnostycznych, takich jak aparaty ultrasonograficzne wysokiej rozdzielczości. Pozwala to na dynamiczny rozwój diagnostyki prenatalnej zapewniającej bardzo precyzyjne obrazowanie anatomii płodu. I choć większość badaczy koncentruje się na poszukiwaniu ewentualnych patologii budowy, pojawia się coraz więcej prac próbujących oceniać zaburzony rozwój wewnątrzmaciczny płodu – jako konsekwencji zadziałania potencjalnych „czynników toksycznych" towarzyszących patologiom ciąży takim jak: infekcja wewnątrzmaciczna, przedwczesne odpłynięcie płynu owodniowego, preeklampsja, uraz, niedożywienie, przewlekłe niedotlenienie, stres itp. W tej grupie na szczególną uwagę zasługują doniesienia dotyczące patologicznej inwolucji narządów miąższowych, a w szczególności grasicy, porównujące wielkość narządu w korelacji z wiekiem ciążowym w ciążach fizjologicznych oraz powikłanych. Bardzo obiecujące są najnowsze doniesienia potwierdzające zależność wielkości centralnego narządu immunologicznego, jakim jest grasica z odsetkiem limfocytów T regulatorowych we krwi pępowinowej. Wydaje się, że jesteśmy świadkami powstawania nowych narzędzi oceny tzw. „potencjału immunologicznego płodu i noworodka".

Conflict of interest
Konflikt interesów

None
Brak konfliktu interesów

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INTRODUCTION

Despite the enormous advances in understanding the pathogenesis of diseases in the immunological context, still little attention is paid to human immunity in relation to the central immune organ, i.e. the thymus.

Thymus is the primary and central lymphatic organ, which controls peripheral lymphoid tissues such as lymph nodes and spleen, during both in utero and postnatal periods. The thymus is involved in T-cell control. T-cell formation and maturation occurs in this organ,

which also stimulates their activity, and thus controls the functioning of the entire immune system; it can be said that thymus 'conducts the immune orchestra'. Preventing autoimmune diseases by immune-tolerance to self-antigens is another aspect. The thymus also has an endocrine function by producing thymosin, which stimulates lymphopoiesis. In conclusion, the thymus is essential for the development and maintenance of immunity (1).

Anatomically thymus is a bilobate gland located in the upper anterior thorax, between the sternum and the heart. 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 6 mm long. The thymus takes a bilobate shape and grows rapidly, reaching its maximum size in the perinatal period. The gland consists of the cortex and the medulla as well as fat tissue. 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 (2).

The thymus indeed shrinks after puberty, but the physiological atrophy of the thymus, during which a lymphatic organ weighing about 30 g turns into a lump of fat weighing a few grams, is very misleading. Of course, the atrophy has been scientifically confirmed and is inevitable... but can we put an equal sign between atrophy and the end of gland activity? The role of the thymus is underestimated and diminished as a result of a persisting hypothesis from years ago – that the function of thymus also disappears with age (3).

So how can we be certain that this is not the case?

There was a major breakthrough at the end of the last century. Professor Goldstein from the Washington University (USA) won the Nobel Prize for his discovery of the thymus hormone (thymosin).

Now that we know that the gland produces thymosin, we can monitor its levels. Interestingly, it was found that thymosin is released throughout life (4). Two types of thymic involution were distinguished based on serum thymosin levels.

Type one corresponds to a normal, natural process of 'physiological ageing' enabling survival 'to the age of 100' – with normal hormone levels. Type two represents pathological, premature involution leading to immunity impairment, autoimmune diseases, cancer, etc. – with very low thymosin levels (5).

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 (6, 7).

The first article on the ultrasound assessment of foetal thymus was published by Felker et al. more than 25 years ago (8). Significant interest of researchers in foetal thymus did not occur until the emergence of modern ultrasound equipment ensuring high resolution images essential for the differentiation between parenchymal organs of similar structure as well as Doppler techniques for blood flow detection.

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 echostructure is slightly smaller compared to surrounding lungs. It is clearly visible already at the end of the first trimester of pregnancy (9).

Several methods for sonographic thymus measurement have been described. The thymus can be identified on the foetal 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 also be measured (10, 11). The TT-ratio (thymic-thoracic ratio) proposed by Chaoui et al. can also be used. Its usefulness is due to the fact that the value remains stable during pregnancy between week 15 and delivery term; its average value is approx. 0.4. The ratio is particularly useful in the diagnosis of thymic hypoplasia in heart defects (12).

The first nomograms for the analysis of the size of foetal thymus were developed in Israel (2002) and Canada (2007) (9, 10). A relationship was shown between the size of the thymus and the gestational age, the foetal abdominal circumference and femoral length (10). Numerous reports on the usefulness of foetal thymus assessment focused on the issues related to thymic hypoplasia, which was usually linked to 22q11.2 deletion. The usefulness of foetal thymus evaluation in heart defects with arterial cone anomalies was emphasised. Thymic hypoplasia was considered as a strong guideline for geneticists to identify or exclude DiGeorge syndrome. This is a congenital hypoplasia of the thymus associated with the occurrence of defects and primary immunodeficiency. Structural abnormalities primarily 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).

According to Chaoui, thymic hypoplasia in heart defects indicates 80% risk of DiGeorge syndrome (only 50% risk according to Bataev). However, the assessment of thymus in heart defects is essential from a clinical point of view (13, 14).

A number of studies demonstrate a proportional growth of thymus in physiological pregnancy, regardless of gender. Also, similar thymic development in observed in multiple pregnancy.

Precise biometric tables for organ size in relation to pregnancy size are available. Conveniently, it can be remembered that the transverse dimension of the thymus is 12 mm at an average of 19 weeks gestation, while the size of the thymus corresponds to the num-

ber of gestation weeks at 33 weeks gestation, i.e. an average of 33 mm. In the perinatal period, the thymus is slightly larger than the foetal age counted in weeks. This growth pattern is analogous to the growth of other foetal parenchymal organs such as the liver, kidneys or thyroid gland (9-11).

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) (15).

Modern high-resolution ultrasonography theoretically allows to see and measure everything – but for what purpose?

First of all, when examining the thymus more attention is paid to the mediastinum, which makes it easier to detect heart defects, particularly those with congenital thymic hypoplasia (12-14).

Secondly, 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.

Thirdly, 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. 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 (16).

An increasing number of publications in the recent 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 (17, 18).

Similar observations about the premature involution of the thymus were presented in studies investigating pregnancies complicated by intrauterine growth restriction. In these cases, the size of the thymus is referred to as a prenatal marker for the foetal immunoendocrine response to malnutrition. Such cases often result in different forms of immune insufficiency, also throughout later life (19-21).

One report on the assessment of foetal thymic involution in the context of predicting the potential occurrence of clinical preeclampsia, is also very promising. Also in this type of pregnancy pathology, early markers for the occurrence of complications are lacking (22).

CONCLUSIONS

The natural process of thymic involution is a physiological phenomenon. We should remember that even an organ weighing a few grams, which undergoes physiological involution, i.e. normal atrophy, is able to ensure normal functioning of the immune system from birth until old age. If the process of involution of the organ starts too early, especially in utero, it can lead to immune system pathology in both newborns and infants, as well as the occurrence of potential autoimmune disorders in adulthood.

It seems that the prenatal thymus ultrasound may be of key importance for the assessment of the so-called immune potential in the process of pathological thymic involution, which can result from an exposure to a toxic agent. This immune potential is essential not only for the foetus and newborn but throughout life.

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