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Original Research Article

A STUDY ON HISTOGENESIS OF THYMUS IN HUMAN FOETUSES

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ABSTRACT

Background: The Thymus is a lymphatic organ that exhibits certain unique structural features. The supporting reticular stroma arises from endodermal epithelium and produces a cellular reticulum. Lymphocytes are derived from haematopoietic stem cells.

Materials and methods: The present study was carried out with 20 human foetuses of gestational age varying from 10 to 31weeks in the Department of Anatomy,Thanjavur medical college, Thanjavur. Histogenesis of various components of thymus was studied after staining with Hematoxylin and Eosin.

Results: Lymphocytes appear by 10th week.Lobulation started appearing by 12th week and completed by 15th week.Corticomedullary differentiation started by 15th week, and become more distinct by18th week. Blood vessels were seen by 10th week and macrophages by 12th week. Hassall's corpuscles appeared by 15th week. The number and size of HC increased between 18 and 24 weeks.

Conclusion: Precise knowledge of the histogenesis and histodifferentiation of the various components of the normal thymus is essential in analyzing the different pathologies like thymic neoplasia, myasthenia gravis and certain other autoimmune disorder.

KEY WORDS: Histogenesis, thymus, lobulation, lymphocytes, Hassall's corpuscle, gestational age.

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INTRODUCTION

Thymus is a lymphatic organ that exhibits certain unique structural features. The supporting reticular stroma arises from endodermal epithelium and produces a cellular reticulum. The cells,designated as epithelioreticular cells serve as stroma. Lymphocytes come to lie in the interstices of the cellular reticulum, and these two cellular elements, the lymphocytes and the epithelioreticular cells, comprise the bulk of the organ. A Blood-thymus barrier is formed by sheathing of perivascular connective tissue of the thymus by the epithelioreticular cells. In addition, there are no afferent lymphatic vessels to the thymus. Thus it cannot react to circulating antigens [1].

Groups of medullary epithelial cells become characteristically arranged in the form of concentric whorls called thymic Hassall's corpuscles. The thymic components along with the micro environment of thymus gland are responsible for terminal T-cell differentiation

and the development and maintenance of cellular immunity. So there is a specific and characteristic histological alteration of thymus gland in the Acquired Immune Deficiency Syndrome (AIDS).

The concept of the thymus as an endocrine gland is now generally accepted and several of its biologically active substances have already been isolated. Among them three circulating peptides, thymosin,thymopoietin and thymulin have been chemically characterized and obtained in synthetic form. These thymic hormones were shown to play a major role in several intra and extra-thymic steps of T cell differentiation.[2,3] Awareness of the anatomical features and a precise knowledge of the histogenesis and histodifferentiation of the various components of the normal thymus are essential in analyzing the different pathologies like thymic neoplasia, myasthenia gravis and certain other autoimmune disorders.

MATERIALS AND METHODS

A total of 20 human foetuses of different groups ranging from 10 to 31 gestational weeks were procured from the Department of Obstetrics and Gynaecology, Raja Mirasudar Hospital, Thanjavur Medical College. These foetuses were the products of terminated pregnancies under the Medical Termination of Pregnancy Act of India, 1971 and stillbirths. Anomalous foetuses and twins were excluded from the study. The institutional ethical committee approval was obtained to perform the research work. Foetuses were obtained within 4-5 hours of birth to avoid postmortem changes and immediately fixed in 10% formalin. Gestational age of the fetus was calculated from first day of last menstrual age(LMP). Fertilization age was obtained by subtracting two weeks from gestational age. Fertilization age was also determined from crown rump length of fetus. The foetuses were dissected. The sternoclavicular joints were disarticulated and costal cartilages were cut. Thus the entire thoracic cavity was open and lower part of neck was also dissected for complete exposure of thymus in its natural location. The tissue sample was obtained , fixed and processed to prepare paraffin embedded blocks . 4-5 micron thick sections were cut from the blocks. The slides were stained with Haematoxylin and Eosin. The stained slides were studied under binocular research microscope.

OBSERVATION AND RESULTS

The foetal specimens were categorized into five groups: Specimens were divided into five groups according to the gestational age (weeks) based on the study of R.K.Ajita et al [8]. All the specimens were analyzed and plotted against age groups as given in Table 1.

Histogenesis of foetal thymus: The appearance of various cellular components and their period of development was noted and plotted against each group as mentioned by Ajita et al [8] in the table 2.

Group I - The gland was seen to be composed of lymphocytes with a delicate capsule. The lobulation and corticomedullary differentiation were not seen. Trabeculae associated with blood vessels were observed .Spindle shaped epithelial cells were noted. No Hassall's corpuscles were observed.

Group II – Well-formed connective tissue capsule surrounds the gland. The lobulation of the gland was still advancing, with developing connective tissue trabeculae between lobules. Cortex and medulla were not recognizable. No Hassall's corpuscles were seen.

Group III - The number of lobules increased further. The peripheral part of each lobule is heavily infiltrated with lymphocytes, and are the darkly stained. The central parts of the lobule contain fewer lymphocytes, hence lightly stained. The cortex and medulla were differentiated from 15th week. Hassall's corpuscles were seen in some sections from 15thweek.

Group IV - Lobules, blood vessels, and connective tissues of its capsule become more extensive. The corticomedullary differentiation becomes distinct by 18th week. Hassall's corpuscles found to increase in size and number.

Group V - The thymic tissue of each lobule is continuous in the more central part of the adjacent lobule. The trabeculae were seen extending up to the cortex, leaving the medulla remain undivided. The parenchyma of thecortex

seen to be consisting of dense population of lymphocytes of all sizes, closely and uniformly packed. These cells occupy the spaces in the cytoreticulum and obscure it. The lymphocytes are less in number in medulla and hence cytoreticulum is seen well. There is a sharp demarcation between the cortex and medulla forming a clear corticomedullaryjunction.

Table 1: Categorization of specimen according to gestational age.

Group	Age(Weeks)	Number of fetuses
Group I	09-11	1
Group II	12-14	3
Group III	15-17	3
Group IV	18-24	9
Group V	25-31	4

Table 2: Appearance of various cellular components.

Group	Lobulation	Cortex	Medulla	CMJ	Trabeculae	HCs
I	Not seen	Not seen	Not seen	Not seen	Seen	Not seen
II	Started appearing	Not seen	Not seen	Not seen	Seen	Not seen
III	Increases further in number	Seen in some	Seen in some	Seen in some	Seen	Started developing
IV	Number increases	More densely packed lymphocytes seen	Less dense	Seen	More extensive	Number and size increase
V	Number increases	Densely packed with lymphocytes seen	HC with maturity	Clearly seen	More extensive	Number and size increases with maturity

Table 3: represents the various cellular components percentage in different gestational age groups, with reference to table 4

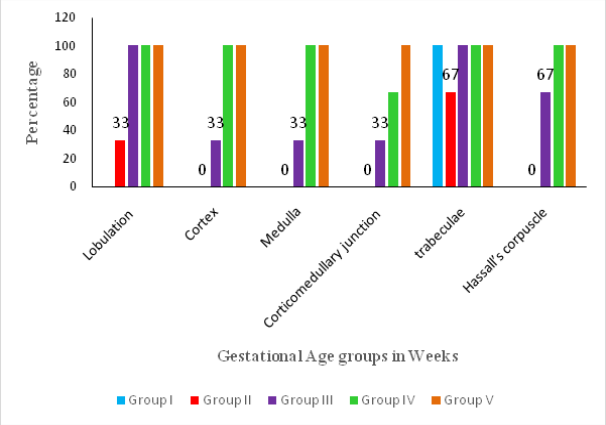


Table 4: Various cellular components percentage in different gestational age groups.

Group	Lobulation (%)	Cortex (%)	Medulla (%)	CMJ (%)	Trabeculae (%)	HCs (%)
Group I	0	0	0	0	100	0
Group II	33	33	33	0	67	0
Group III	100	100	100	33	100	67
Group IV	100	100	100	67	100	100
Group V	100	100	100	100	100	100

Table 5: Appearance of lobulation in different gestational age groups.

Group	Number of specimens	Number seen	Percentage (%)
Group I	1	0	0
Group II	3	1	33%
Group III	3	3	100%
Group IV	9	9	100%
Group V	4	4	100%

Table 6: Appearance of cortex in different gestational age groups.

Group	Number of specimens	Number seen	Percentage
Group I	1	0	0
Group II	3	0	0
Group III	3	1	33%
Group IV	9	9	100%
Group V	4	4	100%

Table 7: Appearance of medulla in different gestational age groups.

Group	Number of specimens	Number seen	Percentage
Group I	1	0	0
Group II	3	0	0
Group III	3	1	33%
Group IV	9	9	100%
Group V	4	4	100%

Table 8: Appearance of corticomedullary junction in different gestational age groups.

Group	Number of specimens	Number seen	Percentage
Group I	1	0	0
Group II	3	0	0
Group III	3	1	33%
Group IV	9	6	67%
Group V	4	4	100%

Table 9: Appearance of trabeculae in different gestational age groups.

Group	Number of specimens	Number seen	Percentage
Group I	1	1	100%
Group II	3	2	67%
Group III	3	3	100%
Group IV	9	9	100%
Group V	4	4	100%

Fig. 1: No lobulation, no corticomedullary differentiation – 10 weeks, 40x

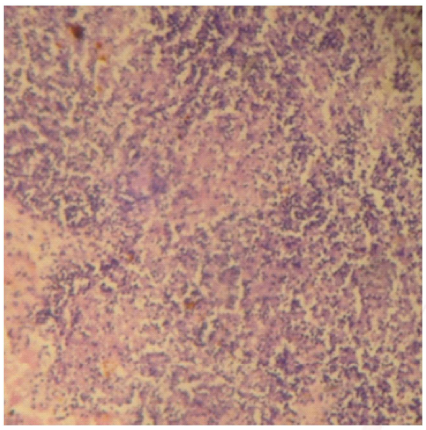


Fig. 2: Lobules begin to appear – 12 weeks, 40 x magnification

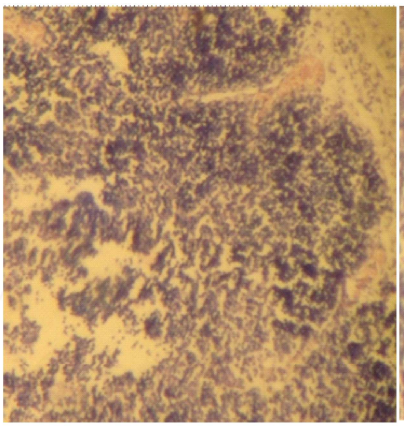


Fig. 3: Poorly formed lobules – 13 weeks, 40x magnification

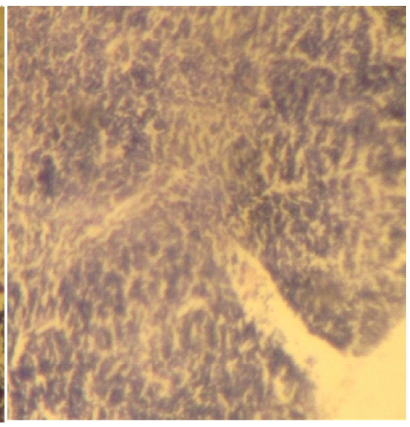


Fig. 4: Lobulations seen, no corticomedullary differentiation – 14 weeks, 100x magnification

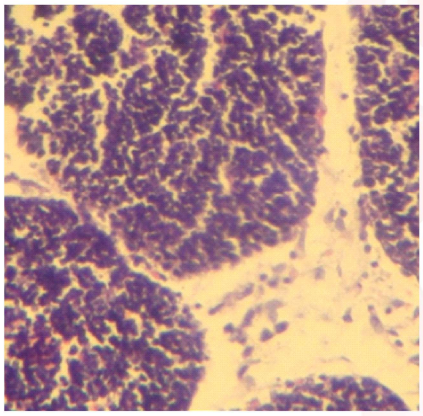


Fig. 5: Lobulations seen, corticomedullary differentiation ill defined – 15 weeks, 40 x

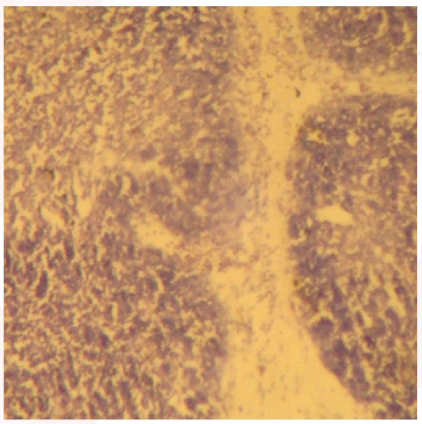


Fig. 6: Epithelial retinacular cells seen in trabeculae – 18 weeks, 40 x magnification

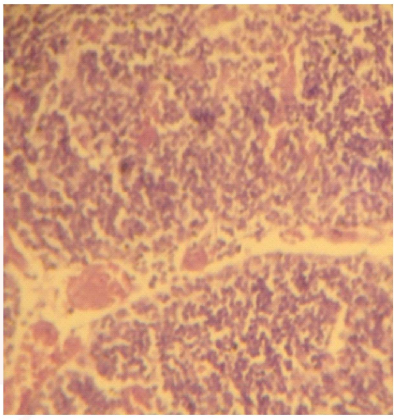


Fig. 7: Well formed lobules and blood vessels – 18 weeks, 40x magnification.

Fig. 8: Many HCs seen – 19 weeks, 100x magnification

Fig. 9: Many HCs seen – 20 weeks, 40x magnification

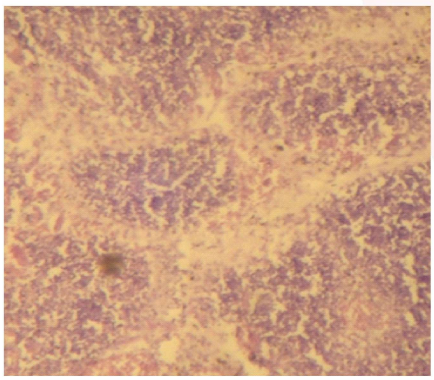


Fig. 10: Many developing HCs – 20 weeks, 40x magnification

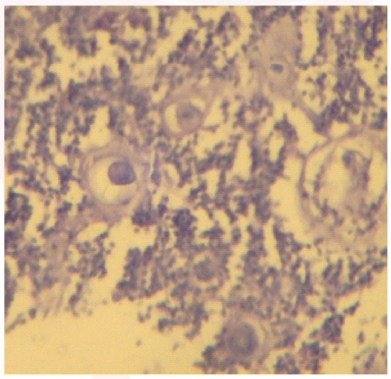


Fig. 11: Lobulation, HCs – 21 weeks, 40x magnification

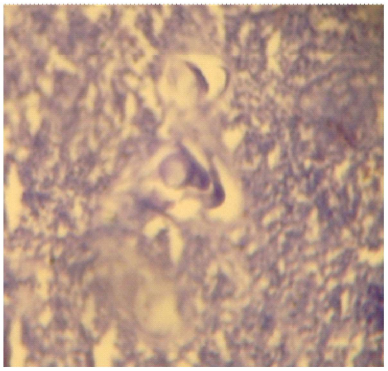
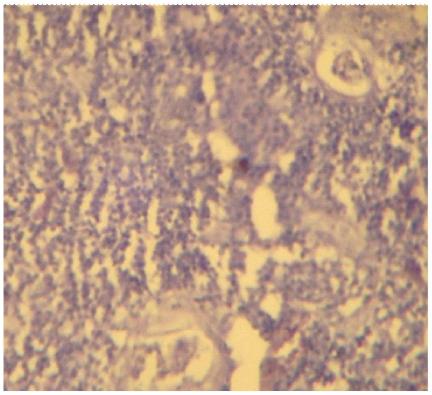
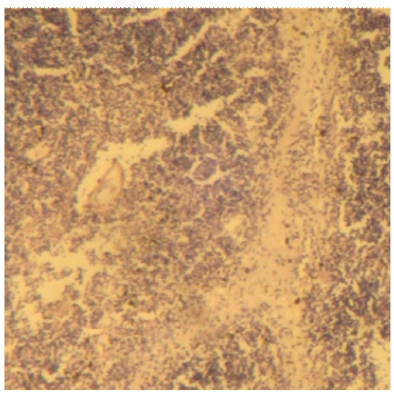


Fig. 12: Solid and cystic type of HCs – 24 weeks, 40 x magnification





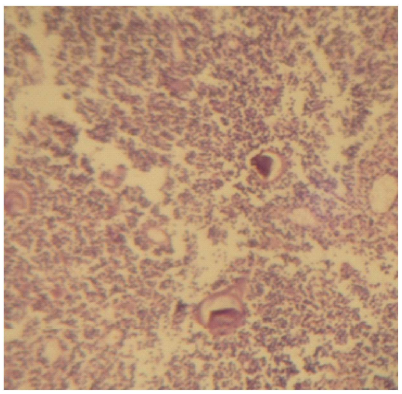


Fig. 13: Lobulation, solid and cystic type of HCs – 25 weeks, 40x magnification

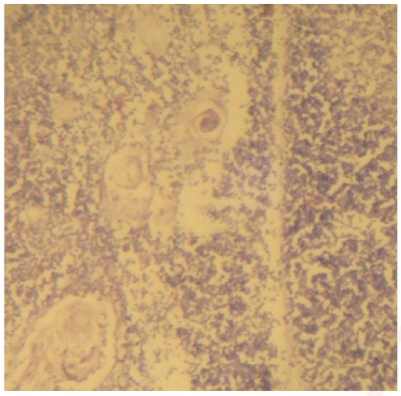


Fig. 14: Well formed compound type of HC – 26 weeks, 100x magnification

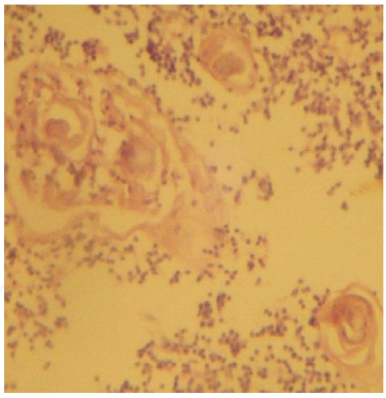


Fig. 15: Lymphocytes – 27 weeks, 400x magnification

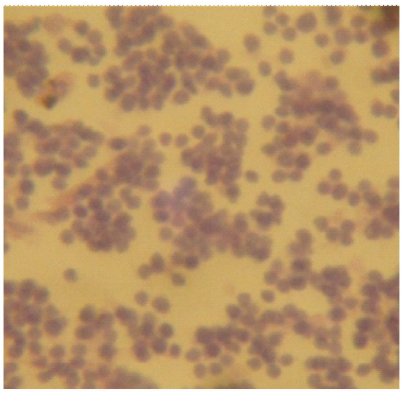
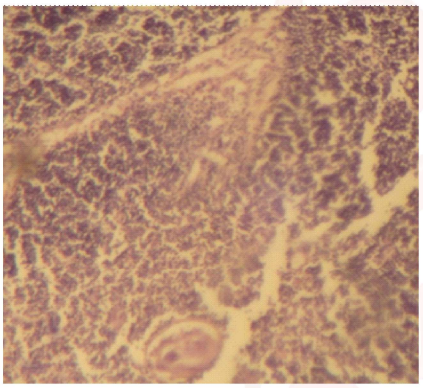


Fig. 16: HCs, blood vessels in trabeculae – 31 weeks, 100x



DISCUSSION

Appearance of lymphocytes: The time at which the lymphocytes were present in the thymus varies in different studies. It appears by 8thweek according to Standring S [9]. Reported to appear by 9thweek according to Hamilton and Mossman [10], Von Gaudecker, Ritter and Lampert [11],Ajita et al [8], prabhavathy [12], Bashir khan and Sanobar sheikh [13].

In the present study the lymphocytes were observed from 10th week which have round purple nuclei with basophilic cytoplasm. It could not be ascertained whether lymphocytic infiltration occurs from 8th week onwards, since the present study examined foetuses from 10 weeks of gestational age.

Lobulation: The epithelial cells grow as thumb like protrusions into the mass of mesenchyme, which later forms a thin capsule around the organ. In the region between epithelial protrusions, the mesenchyme remains and forms thin incomplete septa, to give the lobular appearance.

Ghali et al [14], Bashir khan and Sanobar sheikh[13] reported lobulation at 10thweek,

Table 10: Appearance of Hassall's corpuscle in different gestational age groups.

Group	Number of specimens	Number seen	Percentage
Group I	1	0	0
Group II	3	0	0
Group III	3	2	67%
Group IV	9	9	100%
Group V	4	4	100%

while Haar [15] reported appearance of lobulation at 12thweek. In the study conducted by Ajita et al [8] and Prabhavathy[12] lobulations started at 9th week and completed by 12th week. According to Vijayalakshmi et al[16] lobulations appeared by 16th week.

In the present study lobulation started by 12th week and completed by 15thweek.

Corticomedullary junction: The cells of lymphatic series are more concentrated towards the borders of each lobule. Hence, at the periphery of the lobules lymphocytes are numerous and densely packed forming darkly stained cortex, whereas the medulla is lightly stained due to less number of lymphocytes.

The Cortico medullary differentiation noted in the embryos of 40mm crown-rump length by Hamilton and Mossman [10] and Ghali et al[14] by 11th week .Arey [18] and Hayward [17] noted the CMJ differentiation by 12th week, Haar, Lobach& Haynes[15]and Prabhavathy [12] by 14th week. Ajita et al [8] stated that the differentiation started at 9th week and more distinct between 12 to 14 weeks. According to Bashir khan and Sanobar sheikh, the differentiation started at 12th week and more distinct by 14th week .Vijayalakshmi et al [16] reported at 16th week.

In the present study the cortico medullary differentiation started at 15th week, become more distinct by 18th week. This coincides with the study of Vijayalakshmi et al [16].

Appearance of blood vessels: According to Haar[15], Hamilton and Mossman[10], Ajita et al[8], Bashir khan and Sanobar sheikh[13] vascularization started at 9th week. Medullary vessels were seen at 12th week.

Vascularity was reported by Williams et al by 10thweek, and Ghali et al[14] at by 11thweek. In the present study blood vessels were seen by 10th week in the trabeculae. Since the fetus prior to 10th week was not examined, it could not be ascertained whether blood vessels were present at early stages.

Appearance of macrophages: Haynes reported macrophages by 10th week, while the appearance of macrophages was reported at 12th week by Ajita et al [8].

Stranding S [9] ,Bashir khan and Sanobar sheikh [13] reported its appearance at 14th week. In the present study macrophages were seen from 12th week, which coincides with the study of Ajita et al [8].

Appearance of epithelial reticular cells: Hamilton and Mossman[10], Von Gaudeck[11] and Standring S [9] have described the appearance of epithelial reticular cells by 8th week. Ajita et al[8] observed the cells at 9th week. Hayward [20], Arey [18] and Bashir khan and Sanobar sheikh [13] reported at 10th week. Vijayalakshmi et al[16] reported the epithelial cells at 12th week of gestation.

In the present study the epithelial cells were observed at 10th week. Since the foetus prior to 10th week was not examined, it could not be ascertained whether the epithelial cells were present at an earlier stage.

Appearance of Hassall's corpuscles: The time of appearance of Hassall's corpuscles varies in different studies; Fawcett [19], Hamilton and Mossman [10] reported its appearance as early as 8th week while Stranding S [9] and Arey [18] at 10th week. Ajita et al and Krishnamurthy et al [23] noted its appearance by 15th week. Lobach and Haynes [21] reported it between 15th and 16th week while Liberti et al[22] noted at 16thweek. Vijayalakshmi et al [16] reported it at 18th week of gestation.

In the present study the Hassall's corpuscle was observed from 15th week onwards, which coincides with the study of Ajita et al[8].

Liberti et al [22] mentioned that the mean area of Hassall's corpuscle increased with the foetal age with greatest difference between 16th-19th week and 20th-23rd week. Ajita et al [8] and Krishnamurthy et al [23] observed the increase in number and size during 17th- 24th weeks. Bashir khan and Sanobar sheikh [13] reported the growth to occur during 18th- 24thweek.

In the present study the number and size of the Hassall's corpuscle increased during 18th- 24th week, which coincides with the study of Bashir khan and Sanobar sheikh [13].

Hassall's corpuscles of varying shapes and sizes, immature solid to mature cystic types seen. The number increases with gestational age. The gland during this stage had an internal architecture similar to that seen in the adults.

CONCLUSION

The present study concludes that in the histogenesis of human foetal thymus, significant cellular events like lobulation, corticomedullary differentiation and the appearance of Hassall's corpuscle all takes place between 15th and 18th week of gestational age. Thereafter the microscopic growth and maturity takes place in the form of increase in size of lobules, blood vessels and increase in size and number of Hassall's corpuscle. Hence the period of gestation between 15 and 18 weeks is critical for the development of foetal thymus. Any insult occurring to the developing thymus in the form of radiation or drugs can affect its histogenesis leading to impaired immunity.

The clinical implication of this study is to provide the basis for more accurate interpretation of the histogenesis of foetal thymic cellular components in relation to gestational age. Individuals in whom there is a persistence of myeloid cell beyond 28 weeks of gestation, suggest they are prone for myasthenia gravis.

ABBREVIATIONS

CMJ – corticomedullary junction

HC – Hassall's corpuscles

Conflicts of Interests: None

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