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Original Research Article

A Study on Histogenesis of Thymus

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Abstract:

Background: The Thymus is a primary lymphoid organ, located in superior and anterior mediastinum. The blood thymic barrier in it provides an antigen free environment for maturation of thymocytes/ T lymphoctes. The thymus is well developed in foetuses and neonates. However, normal thymus gland is not frequently encountered in examination of adult histology or cadaver dissection, because of its fatty involution after puberty. Hence, a precise knowledge of its development, histogenesis & histo-differentiation of its various components is of utmost importance in understanding & analysing the structure of thymus and anatomical basis of many disorders like thymoma, Graves disease & other immunological disorders.

Aim of study: The present study aims to document the histological changes of thymus gland during different weeks of gestation in the human foetuses.

Materials and methods: The present study was carried out with 40 human foetuses of gestational age varying from 10 to 40 weeks in the Department of Anatomy, MKCG medical college, Berhampur, Odisha. Histogenesis of various components of thymus was studied after staining with Haematoxylin and Eosin.

Results: Lymphocytes were already present by 10th week. Lobulation started appearing by 12th week and completed by 16th week. Cortico-medullary differentiation started at 15th week, and became more distinct by 20th week. Broad connective tissue septae were observed in initial stage of development. Blood vessels were seen by 12th week. Hassaall's corpuscles appeared by 15th week. The Hassall's corpuscles were concentric whorl type in initial stage & become solid in later stage. The number and size of HC increased between 18 and 24 weeks.

Conclusion: The present study concludes that the lymphocyte colonization of thymus is established before 10th week, followed by lobulation major events like appearance of cortex, medulla, cortico-medullary junction & Hassall's corpuscles which take place between 15 – 20 weeks of gestational age. 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.

Keywords: Gestational Age, Histogenesis, Lobulation, Thymocytes, Cortico-Medullary Junction, Hassall's Corpuscles.

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Introduction

Thymus is an 'organ of Mystery' keeping the scholars in dark, still continues to elucidate the researchers till date. Unlike the other lymphatic organs, thymus does not filter lymphatic fluid rather it produces an array of histologically specialized cells vital to immune response. Thymus produces thymic hormones that support the growth and differentiation of T-cell progenitors and also provides a unique environment for the thymocytes to undergo development, differentiation and clonal expansion with in reticulum produced by epithelial reticular cells. The thymocytes or T lymphocytes are derived from haematopoietic stem cells in bone marrow & epithelial reticular cells are developed from 3rd pharyngeal pouch. Normal development of thymus is dependent on the interaction between the epithelium and the hematopoietic thymocytes.

Thymic corpuscles are whorls of flattened, concentrically layered cells, 30–100 μm in diameter that characterize the thymic medulla. Originating prenatally, and increasing in number throughout life, they perhaps remove dying thymocytes [1].

The thymus is also a part of the neuro-immunological and neuro-endocrine axes of the body, influenced by and influencing the products of

these axes. Its activity therefore varies throughout life under the influence of different physiological states, disease conditions and chemical insults, such as hormones, drugs and pollutants [1].

By the beginning of the third trimester, the lobule appears to be composed of equal thirds: one third cortex on one side, one third medulla, and one third cortex on the opposite side of the lobule. By term, it is expected that approximately 85% of the thymus is composed of cortex; the remainder is the medulla [2]. Dr Pitta venkata Chandrika et al [3] observed an increase in the ratio of cortex to medulla with the foetal age.

After birth, the thymus continues to develop and organize its cortical and medullary compartments, while it is being periodically seeded with bone marrow-derived hematopoietic progenitor cells. The organ has been observed to reach its maximum absolute weight during puberty. The thymus then goes through a slow and progressive process of involution with age, known as age associated or physiologic thymic involution, which is considered to be one of the hallmarks of the aging immune system. Physiologic thymic involution is characterized by gross regression in thymic size and microscopic alterations that eventually culminate in thymic atrophy. [2]

Multiple studies were attempted to establish the origin and functions of Hassall's corpuscles till date but a sequential study is still lacking which elucidate the morphological changes in Hassall's corpuscles. A precise knowledge of the histogenesis and histo-differentiation of various components of the normal thymus like appearance of thymocytes, epithelial reticular cells, lobulation, cortico-medullary differentiation & Hassall's corpuscles are essential in analysing the different pathologies like thymic neoplasia, myasthenia gravis and other autoimmune disorders. These findings can also be useful in forensic investigations for mutilated foetuses.

Materials and Methods

A total of 40 human foetuses of different groups ranging from 10 weeks to 40 gestational weeks were procured from the Department of Obstetrics and Gynaecology, MKCG Medical College& Hospital. These foetuses were the products of terminated pregnancies under the Medical Termination of Pregnancy Act of India, 1971 and stillbirths. 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 in10% formalin.

Gestational age was determined from crown rump length of foetus. The foetuses were dissected. The sternoclavicular joints were disarticulated and costal cartilages were cut. Thus, the entire thoracic cavity was opened 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.

Limitations of Study: Foetuses < 10 weeks could not be availed because of safe medications used for termination of unwanted pregnancies at home & these cases are not reported institutionally.

Exclusion Criteria: Anomalous foetuses and twins were excluded from the study.

Observation and Results

The foetal specimens were categorized into five groups: Specimens were divided into five groups according to the gestational age (weeks). All the specimens were analysed 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 in the Table 2.

Group I (9 -11wks): The lymphocytes were sparse and uniformly distributed in the gland with a delicate thin capsule. Spindle shaped epithelial cells and macrophages were also found. No Hassall's corpuscles & cortico-medullary junctions were observed.

Group II (12-14wks): Well-formed connective tissue capsule surrounds the gland. The lobulation of the gland was in advancing stage due to extension of connective tissue trabeculae into the gland. The lymphocytes increase in number. Blood vessels were found in the wide trabeculae. Cortex and medulla were not recognizable, but blood vessels appear at cortico-medullary junction. No Hassall's corpuscles were seen.

Group III (15-17wks): The trabeculae become thinner. The number of lobules increased further. The peripheral parts of some lobules are heavily infiltrated with lymphocytes and hence darkly stained; termed as cortex. The central parts of these lobules contain fewer lymphocytes and hence lightly stained; termed as medulla. The medullae of adjacent lobules are interconnected. Hassall's corpuscles were seen in some sections from 15th week.

Group IV (18-24wks): Lobules and connective tissue trabeculae become more extensive. The cortico-medullary differentiation becomes distinct by 17th week. Hassall's corpuscles increase in size and number.

Group V (≥ 25wks)- The trabeculae were seen almost extending up to the cortex, leaving the medulla remain undivided. Cortex and medulla are seen in all the lobules. The corticomedullary junction becomes more distinct. The numbers of Hassall's corpuscles further increases at a slower pace.

Table 1: Categorization of specimen according to gestational age.

Group	Age(Weeks)	Number of foetuses
Group I	≤ 10	2
Group II	11-14	7
Group III	15-17	13
Group IV	18-24	9
Group V	≥ 25	9

Table 2: Appearance of various cellular components.

Group	Lobulation	Infiltration of lymphocytes	Medulla	CMJ	Trabeculae/ Capsule	HCs
I	Not seen	Uniformly distributed	Not seen	Not seen	Thin capsule	Not seen
II	Started appearing	Uniformly distributed	Not seen	Not seen	Wide trabeculae with blood vessels	Not seen
III	Increases further in number	Densely packed at periphery of lobules	Seen in some	Seen in some	Narrower trabeculae	Started developing
IV	Number increases well formed	More densely packed lymphocytes seen	Less dense	seen	Well developed	Number and size increase
V	Number of mature lobules increases	Densely packed lymphocytes seen	HC with maturity	Clearly seen	Extends in some upto medulla	Number and size increases with maturity

Table 3: various cellular components percentage in different gestational age groups:

groups	Total numbers	Lobulation		CMJ		Trabeculae		Hassall's corpuscle	
		Number	%	Number	%	Number	%	Number	%
I	2	0	0	0	0	0	0	0	0
II	7	3	43	0	0	3	43	0	0
III	13	12	92	10	77	12	92	3	23
IV	9	9	100	9	100	9	100	7	78
V	9	9	100	9	100	9	100		100

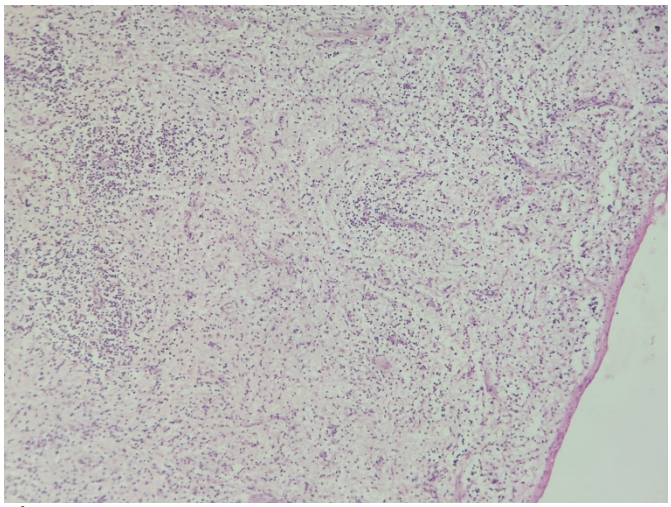

Figure 1: Thymus at 10th wk of gestation showing thin capsule without any trabeculae and blood vessels

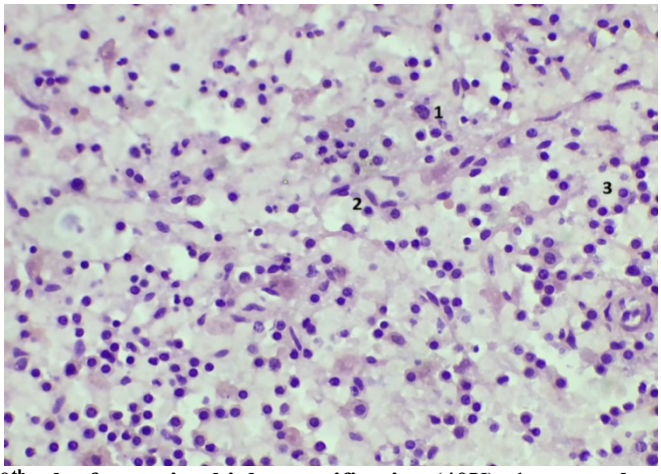

Figure 2: Thymus at 10th wk of gestation high magnification (40X): 1.macrophage, 2.epithelial reticular cells, 3. Lymphocytes

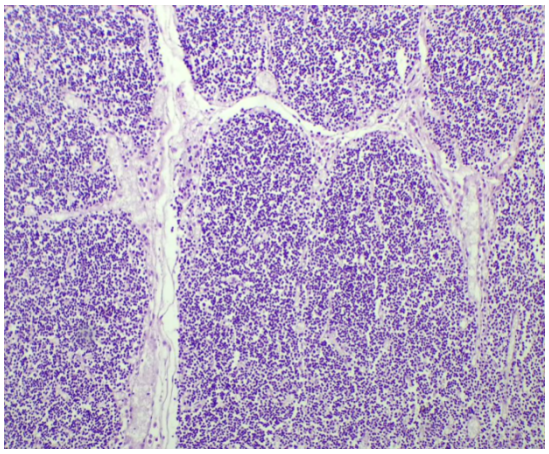

Figure 3: Thymus at 12th wk of gestation, trabeculae with blood vessels begin to appear, lymphocytes are uniformly distributed.

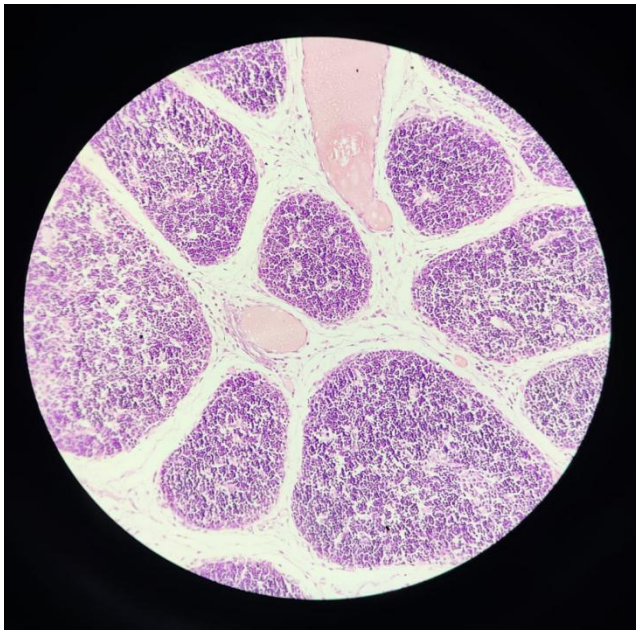

Figure 4: Thymus at 13 wk of gestation, wide trabeculae with blood vessels and lobulations.

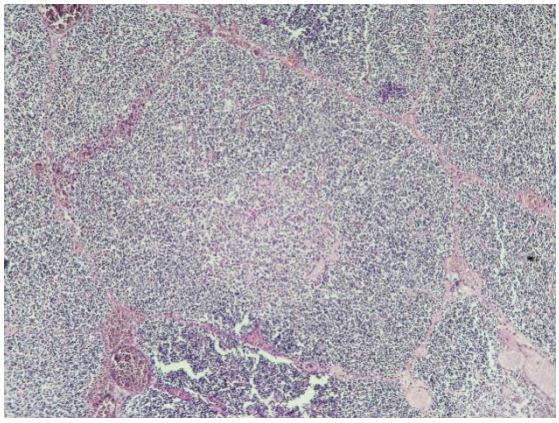

Figure 5: Thymus at 14th wk of gestation, with inconspicuous medulla. Blood vessels at cortico-medullary junction.

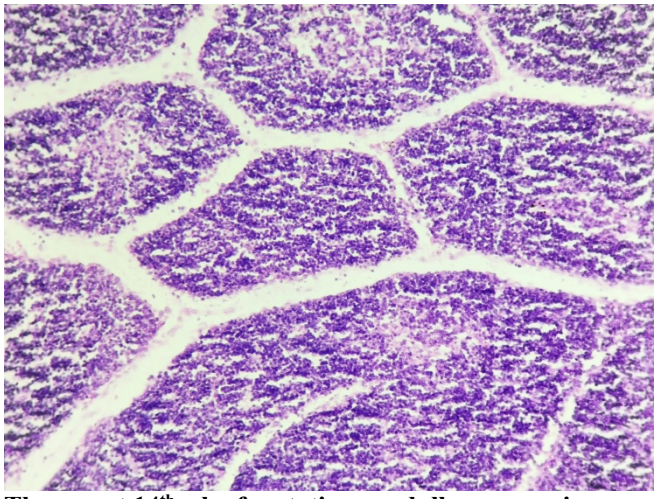

Figure 6: Thymus at 14th wk of gestation, medulla appears in some of lobules

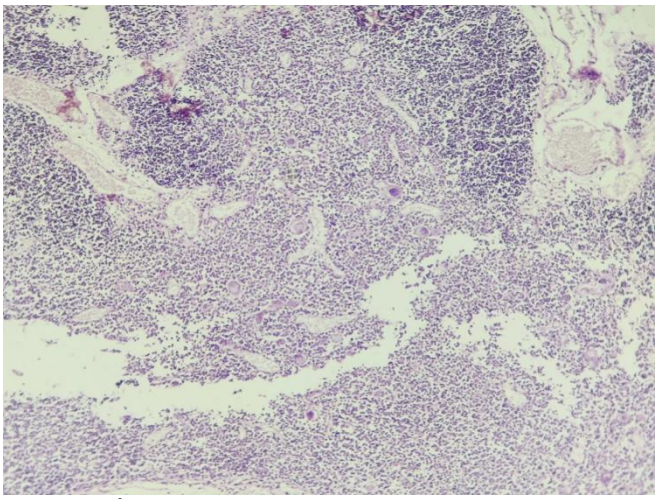

Figure 7: Thymus at 17th wk of gestation, Hassal's corpuscles appear in some lobules.

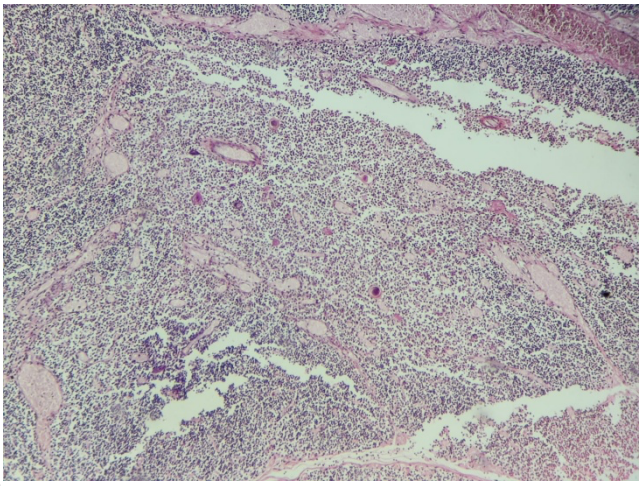

Figure 8: Thymus at 18th wk of gestation, blood vessels at cortico-medullary junction, Hassal's corpuscles in progression.

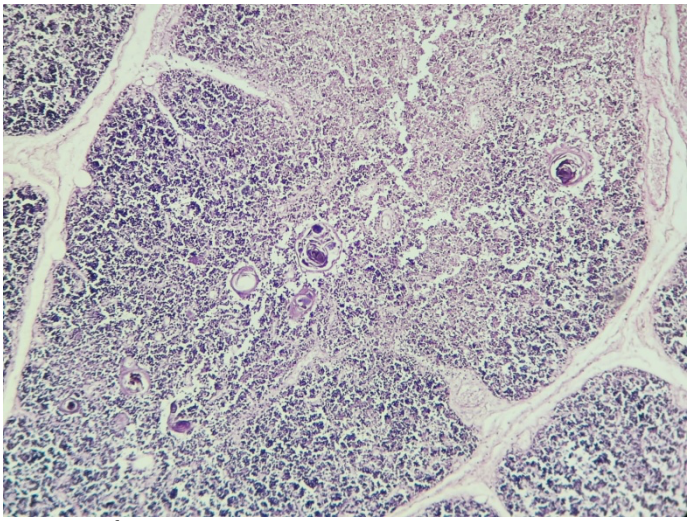

Figure 9: Thymus at 23rd wk of gestation, Hassal's corpuscles increase in number and size

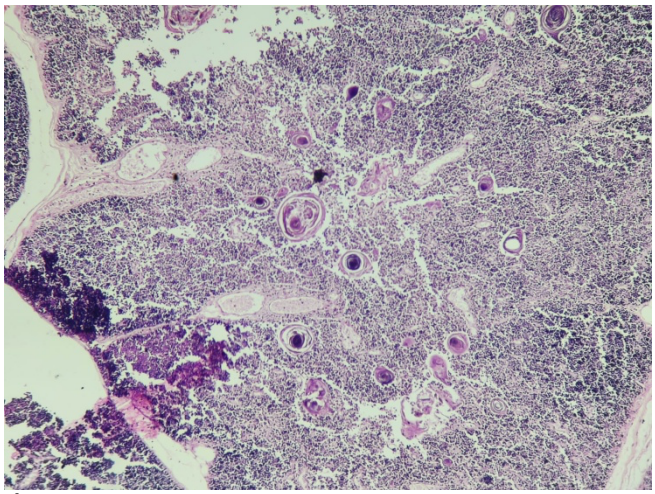

Figure 10: Thymus at 30th wk of gestation, Hassal's corpuscles fetal / whorl type at periphery and become mature type at centre.

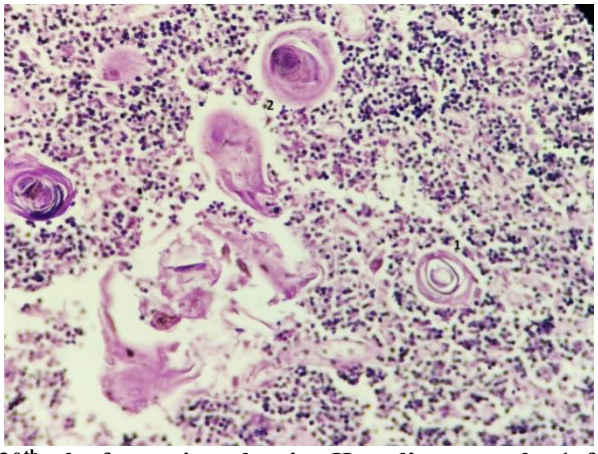

Figure 11: Thymus at 30th wk of gestation, showing Hassal's corpuscles 1. fetal / whorl type and 2. mature type.

Discussion

Appearance of lymphocytes: The time at which the lymphocytes were present in the thymus varies in different studies. It appears by 8th week according to Standring S [1]. Reported to appear by 9th week according to Ajita et al [4], Hamilton [5], Von Gaudecker B [6], Prabhavathy [7], Bashir khan [8]. J Gayathri et al [9] observed the lymphocytes at 10th week. Vaishali S K [10] reported presence of lymphocytes at 12th week.

In the present study the lymphocytes were already present by 10th weeks; corroborative with earlier works.

Lobulation: Thumb like protrusions from the thin capsule into the gland give the later a lobular appearance. In the study conducted by Ajita et al [4], Prabhavathy [7] and J K Sarkar [11] lobulations started at 9th week and completed by 12th week. Bashir khan [8], Ghali et al [12] reported lobulation at 10th week while Haar [13] reported appearance of lobulation at 12th week. According to Vijayalakshmi et al [14] lobulations appeared by 16th week. In the study conducted by J Gayathri et al [9]; lobulation started by 12th week and completed by 15th week. Vaishali S K [10] reported distinct lobulations at 18th week. Srinivasa Rao Y [15] reported lobulation at 19th week. Sandhya V Y [16] observed lobulation at 19th week.

In the present study lobulation started by 12th week and completed by 16th week, corroborative with findings of J Gayathri et al [9] and Haar [13].

Corticomedullary junction:

The Corticomedullary differentiation noted in the embryos of 40 mm crown- rump length (age 11 wk gestation) by Hamilton [5] and Ghali et al [10] by 11th week. Ajita et al [6] and J K Sarkar [11] stated that the differentiation started at 9th week and more distinct between 12 to 14 weeks. According to Bashir khan [8], the differentiation started at 12th week and more distinct by14th week. Arey [17] and Hayward [18] noted the CMJ differentiation by 12th week, Prabhavathy[7], Haar [13], Lobach D F [19] found by 14th week. In the study conducted by J Gayathri et al [9]; the cortico medullary differentiation started at 15th week, became more distinct by 18th week. Vijayalakshmi et al [14] reported at16th week. According to HariKrishna N S [20] CMJ become distinct at 22nd week. Vaishali S K [10] reported distinct CMJ at 18th week. Srinivasa Rao Y [15] reported at 19th week. Sandhya V Y [16] and Helen Suban M G [21] observed CMJ at 17th week.

In the present study the cortico medullary differentiation started at 15th week, become more distinct by 20th week. Initially the cortex was thin, becomes thicker in later stage. Almost corroborative to earlier researchers.

Appearance of blood vessels: Vascularity appears by 10th week according to Standring S1. Linda M [2] reported blood vessels in thymus at 18th weeks gestation. According to Ajita et al [4], Hamilton [5], Bashir khan [8], Haar J L [13] vascularization started at 9th week. J Gayathri et al [9] observed blood vessels by10th week in the trabeculae. Ghali et al [12] reported at 11th week. Harikrishna N S [20] reported blood vessels at 24 week.

In the present study, blood vessels appeared in trabeculae at 12th weeks and and at cortico-medullary junction and in medulla at 14th week.

Appearance of macrophages: Haynes [22] reported macrophages by 10th week, while the appearance of macrophages was reported at 12th week by Ajita et al [4], J Gayathri et al [9] and J K Sarkar [11]. Stranding S [1], Bashir khan [8] reported its appearance at 14th week.

In the present study macrophages were seen at 10th week, which coincides with the study of Haynes [22].

Appearance of epithelial reticular cells: Standring S [1], Hamilton [5], Von Gaudeck [6] have

described the appearance of epithelial reticular cells by 8th week. Ajita et al [4] observed the cells at 9th week. Bashir khan [8], J Gayathri et al [9], Hayward [18] and Arey [17] reported at 10th week. Vaishali S K [10], Vijayalakshmi et al [17] reported the epithelial cells at 12th week of gestation. Sandhya V Y [16] found Hassall's corpuscle at 19th week.

In the present study the epithelial reticular cells were present by 10th weeks; corroborative to earlier workers not agreeable to Vaishali S K [10], Vijayalakshmi et al [14] and Sandhya V Y [16]

Appearance of Hassall's corpuscles: The time of appearance of Hassall's corpuscles varies in different studies. Hamilton [5] and Fawcett [23] reported its appearance as early as 8th week while Stranding S [1] and Arey [17] at 10th week. Ajita et al [4], J Gayathri et al [9] and Krishnamurthy et al [24] noted its appearance by 15th week. Ajita et al [4] and Krishnamurthy et al [24] also observed an increase in number and size during 17th- 24th weeks. Lobach D F [19] reported it between 15th and16th weeks while Liberti et al [25] noted at 16th week. Vijayalakshmi et al [14], Harikrishna N S [20] reported it at 18th week of gestation.

Bashir khan [8] reported the growth to occur during 18th- 24th week. J K Sarkar [11] found Hassall's corpuscles at 14th week and their number and sizes increased between 15-24 weeks of gestation.

Vaishali S K [10] found miniature Hassall's corpuscle at 12 week. Srinivasa Rao Y [15] reported the Hassall's corpuscle at 19th week. Sandhya V Y [16] observed Hassall's corpuscle at 17th week.

In the present study, the Hassall's corpuscle started to appear at 16th week. The number & size increased during 18th- 24th week, which coincides with the study of Bashir khan [7]. Hassall's corpuscles of varying shapes and sizes, immature solid to mature cystic types seen. The number increases with gestational age. The thymic corpuscles at the periphery is whorl type, towards centre is mature type. At term the thymic corpuscles become more adult mature type.

Conclusion

The present study concludes that the lymphocyte colonization of thymus is established before 10th week, followed by lobulation (12 - 16 weeks). But major events like appearance of cortex, medulla, corticomedullary junction & Hassall's corpuscles take place between 15 – 20 weeks of gestational age. Thereafter the histogenesis occurs at a slower pace towards the puberty. Hence first 20 weeks of gestation is considered as high risk period, when any external or internal injury to thymus is detrimental to the normal growth of the thymus.

Most of the events that took place in our study are much similar to the findings of J. Gayathri. It may be due to the fact that both our populations share similar geographic and genetic factors.

The clinical implication of this study is to provide the basis for more accurate interpretation of histogenesis of foetal thymic cellular components in relation of gestational age restricted to the effect of genetic & environmental factors of southern Odisha.

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