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Histogenesis of Fetal Small Intestine – A Cross Sectional Analytical Study

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Abstract

Introduction: Intestine is important during growth of the fetus in prenatal period. The intestinal mucosa is a highly differentiated structure and is capable of many of the physiological and biochemical processes that distinguish the small intestine mucosa of the adult by the time of birth. Hence understanding the histological changes taking place in the intestinal wall as it gets transformed from a primitive tube containing a stratified epithelium to a highly differentiated and organized structure during embryonic life is crucial.

Objective: To assess morphological changes and estimate the time period of appearance of various layers in the fetal small intestine.

Methods: The study was undertaken after getting approval from the Postgraduate Research Monitoring Committee (PGRMC) and Institute Ethics Committee (IEC). The human fetuses following abortion obtained from the Department of Obstetrics & Gynecology were used in the study. After formalin fixation, the fetal small intestine was dissected out. A segment of duodenum, jejunum, ileum was processed histologically and stained with Hematoxylin & Eosin. Microscopic features were noted.

Results: The epithelium of all the samples under study were simple columnar in nature. The muscularis mucosa was clearly differentiable after 20 weeks of gestational age. The appearance of Brunner's glands and Peyer's patches were noted from 18 weeks of gestational age.

Conclusion: The findings of the study correlated with the already established anatomical development of intestine. The understanding of the developmental

aspects of intestine in greater detail helps understand the pathogenesis of disease involving the intestine.

Keywords: Intestine, Development, Histogenesis.

Introduction

The endodermal gut tube is divided into four primary segments namely the esophagus, stomach, small and large intestine from rostral to caudal. These primary sections are further classified into secondary sections (from cranial to caudal): the esophagus; the stomach; the duodenum, jejunum and ileum; the large intestine. The transition of the histological features among the primary segments happen in an abrupt manner. At the same time, the secondary segments undergo a gradual transition in their histological appearance. While the morphological changes take place during the embryonic life, the differentiation of all the layers of gastrointestinal tract continues throughout the entire gestational period.[1]

The small intestine is mainly concerned with maintaining the fluid and electrolyte hemostasis, absorption of nutrients from the gastric contents and secretion of hormones. The overall area of small intestine available for carrying out these functions are increased to a great extent by three surface modifications: the plicae circulares, the villi and the microvilli. These factors bring about a 2, 7 and 13 times increase in the surface area of the intestine respectively. Hence, the total surface area is estimated to be an approximate 30 m^2. The segments that is mainly involved in the fluid and electrolyte absorption is the terminal part of ileum. Many nutrients including the carbohydrates, proteins, lipids, minerals such as calcium, phosphorus, iron, water and fat soluble vitamins (mainly vitamin B_{12}) and bile are absorbed in the various segments of small intestine.[2]

The goal of the present study is to have a better understanding of transformation from a primitive tube containing a stratified epithelium to a highly differentiated and organized structure during embryonic life. The current study aims to to assess morphological changes in epithelium of different segments of small intestine and estimate the time period of appearance of different layers in the fetal small intestine.

Materials & Methods

Study design

Cross Sectional Analytical Study

Subjects

The human fetuses following abortion obtained from the Department of Obstetrics & Gynecology were used in the study.

Inclusion criteria

- All fetuses more than 12 weeks of gestation following voluntary, spontaneous or therapeutic abortions.
- Stillborn

Exclusion criteria

- Fetal tissue with visible autolysis
- Fetus with obvious congenital anomalies such as intestinal atresia, malrotation, incomplete rotation, non-rotation, gastroschisis and omphalocele.

Methods

The study was carried out in the Department of Anatomy, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry from July 2022 to June 2024. The study was approved by the Departmental Postgraduate Research Monitoring Committee (vide approval No. JIP/D(R)/CIR-PGRMC(APRIL) 2022 dated 13.04.2022) and Institute Ethics Committee (vide approval no. JIP/IEC/2022/157 dated 13.07.2022). The gestational age of the fetuses

was assessed by measuring crown-rump length or crown-heel length. The second trimester fetuses were preserved using traditional method of cavity embalming while the third trimester fetuses and neonates were preserved by the procedure of arterial embalming. 10% Neutral Buffered formalin is used as the embalming solution in both the above mentioned methods.

The fetus was carefully dissected to remove the small intestine en bloc. Samples were obtained from each of duodenum, Jejunum and Ileum. The samples were dehydrated using descending grades of alcohol, cleared using xylene, impregnated and embedded with paraffin wax. The slides were then prepared and stained using Hematoxylin and Eosin. The slides thus prepared were then observed under Olympus CX41 RF bright field microscope.

Results

A total of 25 fetuses were collected for the study purpose. Out of the 25 fetuses, 10 (40%) were male, 11 (44%) were female and 4 (16%) had indeterminate sex. The fetuses with any congenital anomaly including the gastrointestinal tract were excluded from the study. Both second and third trimester fetuses were collected. The gestational age of the fetus ranged from a minimum of 14 weeks (98 days) to a maximum of 40 weeks (281 days). The median gestational age was 21+3 weeks (150 days).

i) Mucosa

The **epithelium** in all segments of small intestine of all the collected samples were noted to be simple columnar with an oval basal nucleus. The apical surface of the simple columnar epithelium had brush border appearance. The goblet cells were interspersed along with the columnar cells. Their numbers were found to increase in sequential manner from proximal to distal end of small intestine (Figure 1 & 2).

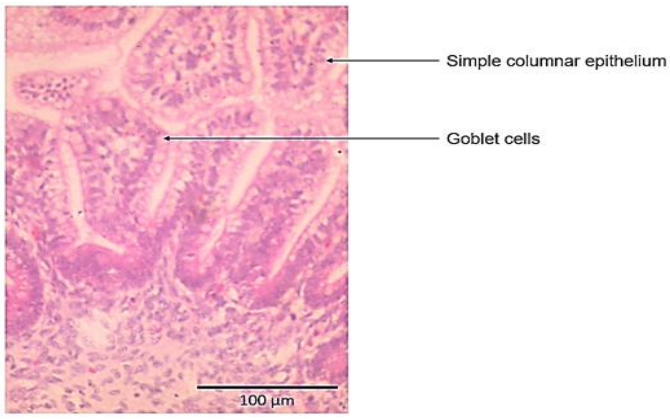

Figure 1: Duodenum of a fetus of gestational age 15 weeks showing goblet cells interspersed with simple columnar epithelium. Hematoxylin & Eosin stain. 40X magnification.

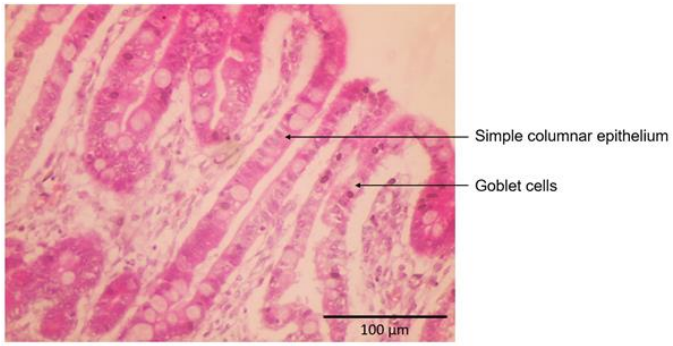

Figure 2; Duodenum of a fetus of gestational age 29 weeks showing increased number of goblet cells interspersed with simple columnar epithelium. Hematoxylin & Eosin stain. 40X magnification.

The **lamina propria** was composed of loose areolar connective tissue which extended into the core of the villus. Discrete aggregation of lymphoid tissue was seen in 7 fetuses (28%) of gestational age ranging from 14 to 18 weeks (Figure 3). The lymphoid tissue has started to form Peyer's patches from the gestational age of 18 weeks in 1 fetus (4%) (Figure 4). The distinguished Peyer's patches were observed in the remaining 17 fetuses whose gestational age is above 18 weeks (Figure

5). Tubular glands or crypts of Lieberkühn were seen in the lamina propria of fetuses of all gestational age.

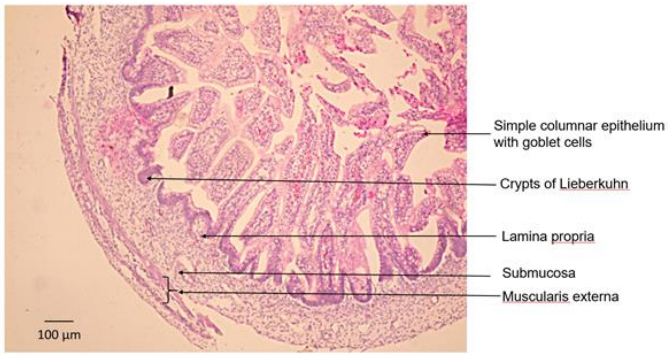

Figure 3: Ileum of 15 weeks old fetus showing discrete lymphoid tissue in lamina propria. Hematoxylin & Eosin stain. 10X magnification.

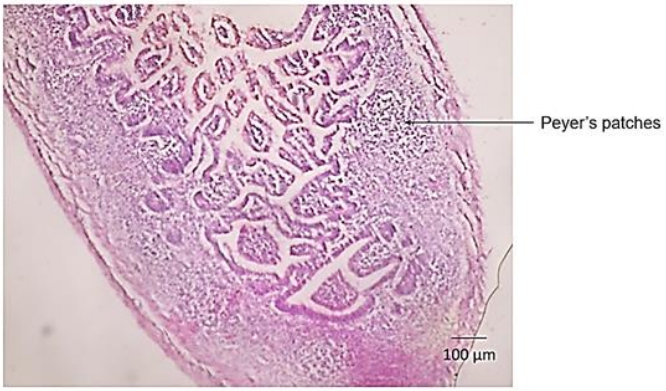

Figure 4: Ileum of fetus of gestational age 18 weeks showing appearance of Peyer's patches. Hematoxylin & Eosin staining. 10X magnification

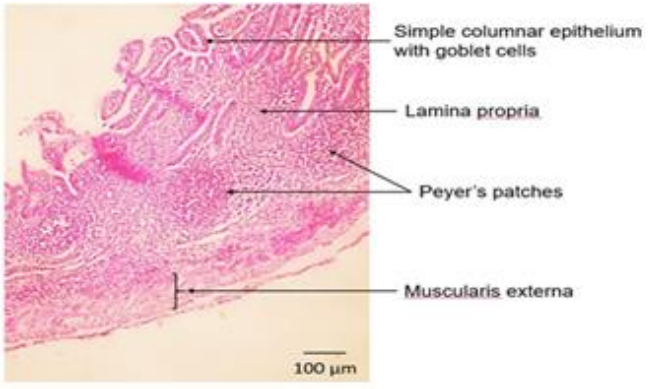

Figure 5: Ileum of a fetus of gestational age 29 weeks showing presence of Peyer's patches. Hematoxylin & Eosin stain. 10X magnification.

The **muscularis mucosa** layer was not distinguishable in 8 fetuses (32%) whose gestational age was less than 20 weeks. It was clearly differentiated consisting an inner circular layer and an outer longitudinal layer of smooth muscle cells in 14 fetuses (56%) (Figure 6 & 7). The muscularis mucosa was seen to be branching into the core of the villus in the fetuses where it was clearly differentiated.

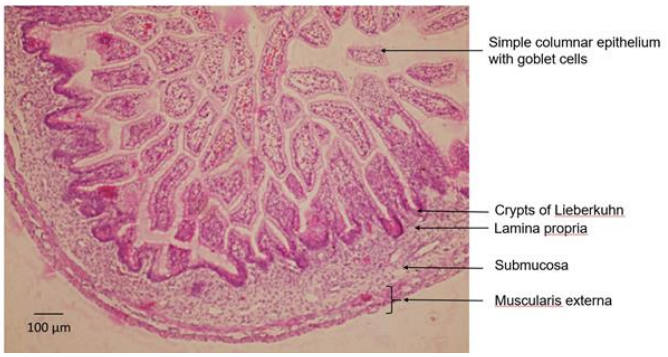

Figure 6: Jejunum of 15 weeks old fetus. Hematoxylin & Eosin stain.

10X magnification.

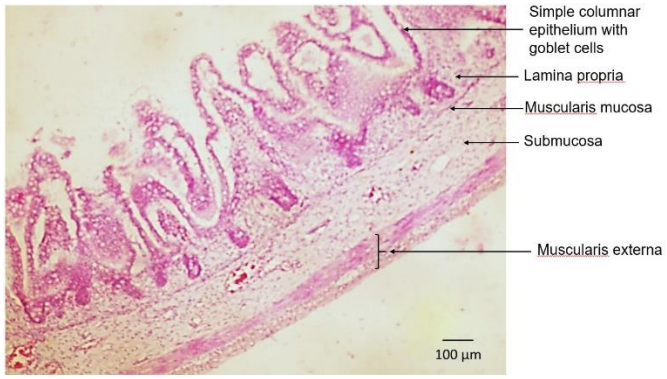

Figure 7: Jejunum of a fetus of gestational age 29 weeks showing presence of muscularis mucosa. Hematoxylin & Eosin stain. 10X magnification.

Submucosa

The submucosal layer was irregular dense connective tissue with nerves, blood vessels, and lymphoid tissue. The Brunner's glands were found in 18 fetuses (72%) whose gestational age was above 18 weeks. In the remaining 7 fetuses (28%) of gestational age less than 18

weeks, Brunner's glands were not differentiable (Figures 8,9 & 10).

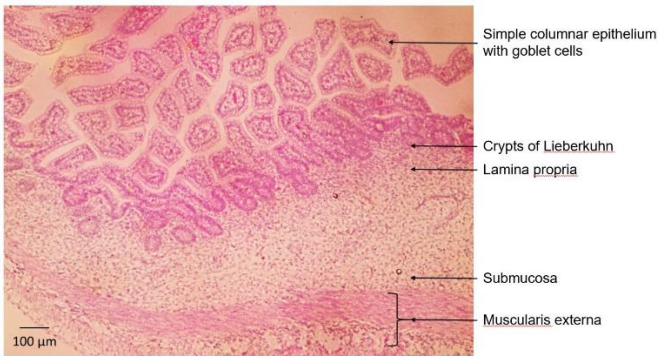

Figure 8: Duodenum of 15 weeks old fetus. Hematoxylin &Eosin stain.

10X magnification.

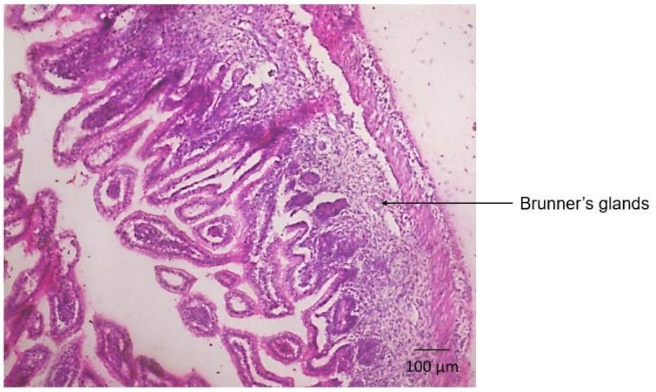

Figure 9: Duodenum of fetus of gestational age 18 weeks showing appearance of Brunner's glands. Hematoxylin & Eosin staining. 10X magnification

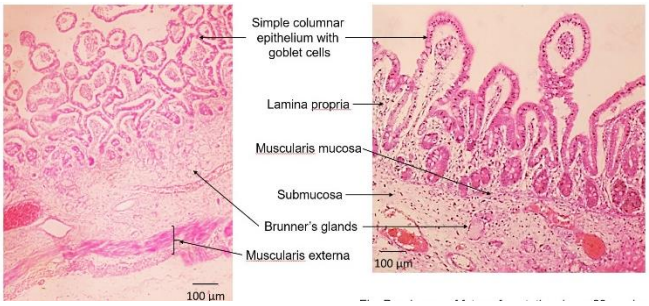

Figure 10: Duodenum of fetus of 29 weeks' gestation showing presence of Brunner's glands and muscularis mucosa. Hematoxylin & Eosin stain. 10X magnification

Muscularis externa

In all the samples, the layer of muscularis externa was differentiated into an inner circular layer and outer longitudinal layer of smooth muscles. Outside the muscularis externa, the intestinal segments had a layer of loose areolar tissue with blood vessels embedded in it.

Table 1 summarises the histological findings in each layer of small intestine.

Table 1: Histological findings in each layer of small intestine

Layer of small intestine	Findings
Epithelium	Simple columnar in nature with interspersed goblet cells.
Lamina propria	Discrete lymphoid tissue in 7 fetuses (28%) Peyer's patches started to form in 1 fetus (4%) Distinguishable Peyer's patches in 17 fetuses (68%)
Muscularis mucosa	Absent in 8 fetuses (32%) Clearly differentiated in 14 fetuses (56%)
Submucosa	Brunner's glands present in 18 fetuses (72%) Brunner's glands absent in 7 fetuses (28%)
Muscularis externa	Differentiated into inner circular and outer longitudinal smooth muscle layers

Discussion

i) Epithelium

According to the results of the study conducted by Pamela Colony Moxey and Jerry S. Trier, the epithelium

in a fetus of gestational age 9 to 10 weeks is of a stratified nature which is up to two to six cell layer thickness. They described sub epithelial mesenchymal aggregations which then projected into the central lumen with the overlying stratified epithelium. Later there was reduction in the degree of stratification of the epithelium. The epithelium lining the apex of the developing villi morphed into a columnar epithelium while the stratified epithelium remained in the sides of the villi by 10 weeks of gestation. After the 10th week, the authors noted the presence of stratified epithelium confined to the intervillous spaces.[3] In a study conducted by Pfoze K and Rajshree H, the epithelium in samples of 9 weeks of gestation were found to be pseudostratified in nature and from 10 weeks of gestation, the epithelium was simple columnar in nature.[4] The minimum gestational age of the sample collected in the present study was 14 weeks of gestation. The epithelium of all the samples was simple columnar in nature.

ii) Villi

Pamela Colony Moxey and Jerry S. Trier conducted a study that reconfirmed the craniocaudal direction of formation of villus. They also noted that after 10 weeks of gestation, the epithelium in the intervillous region were stratified in nature and the villi continued to increase in length.[3] Lacroix B et al studied the development of human small intestine using scanning electron microscopy and brush border enzymology. They have observed that villi appeared as rounded projections during the 8th week of gestation before which the luminal side of the intestine remained flat. There is a progressive increase in the height of villi between 10th and 14th week of gestation. According to them, the appearance of villi follows a proximodistal gradient. At 11 weeks of gestation, the villi start to appear as protuberances in the precaecal region while the proximal part of the intestine.[5] In a study conducted by Pfoze K and Rajshree H, the authors noted a progressive increase in the number of villi in accordance with increase in gestational age.[4] The presence of finger like villi throughout all the segments of small intestine was noted in all the specimens in the current study.

iii) Goblet cells

Pamela Colony Moxey and Jerry S. Trier concluded that the goblet cells were observed even when the epithelium was stratified in nature by 9 weeks of gestation. The authors opined that the number of goblet cells increased relatively with the advancement of gestational age.[3] Pfoze K and Rajshree H conducted a study to determine the time of appearance of goblet cells in the small intestine of human. There was an increasing number of goblet cells observed in few samples at 10 weeks of gestation. Goblet cells were absent in a few samples at 10 weeks of gestational age. Goblet cells were present invariably in all the examined specimen at 12 weeks of gestational age.[4] Goblet cells were seen interspersed with the enterocytes lining the epithelium of all samples in the present study. The amount of goblet cells was also found to be increasing with an increase in gestational age.

iv) Brunner's glands

Pamela Colony Moxey and Jerry S. Trier observed the presence of Brunner's glands in the proximal part of small intestine from 14 to 15 weeks of gestation.[3] Salva MN et al conducted a study in which they concluded in their study that there were no Brunner's glands seen in both 1st and the 2nd trimester. They began to develop in the submucosa of duodenum during the third trimester.[6] In the present study, the presence of Brunner's glands were noted from 18 weeks of gestational age.

v) Peyer's Patches

Salva et al in their study observed the formation of Peyers patches during the third trimester. According to them there were discrete lymphoid tissues present in the 1st and 2nd trimester. They have noted that the lymphoid tissue was less in the first trimester and gradually increased in size in the subsequent trimesters.[6]

In the study conducted by Jo spencer at al investigated the terminal ileum of human fetus for the development of gut associated lymphoid tissue. They also used immunohistochemistry to characterize the phenotype of lymphoid cells forming the Peyer's patches in ileum. Their study comprised of paraffin sections of 27 fetuses with gestational age ranging from 14 to 19 weeks and cryostat sections of ileum from 9 fetuses of gestational age ranging from 11 to 19 weeks. In fetuses of gestational age 11 and 12 weeks, there were no lymphoid aggregates noted. They first observed the formation of lymphoid tissue aggregates infrequently at 14 weeks of gestation and larger consistent aggregates were noted from 16 weeks of gestation. They also studied the phenotypical composition of the lymphoid aggregates. Their findings were that at 14 weeks, the follicles mostly contained T cells. At 16 weeks, they were made up of both B and T cells with no cellular zonation. At 19 weeks of gestation, the follicles had a distinct zonation with B and T cells.[7]

J S Cornes conducted a study counting the number of Peyer's patches with the small intestine specimens obtained from necropsies of 14 premature infants and 24 full term infants and children up to 14 years of age. The number of Peyer's patches ranged from 45 at 24 weeks of gestation to 305 patches at 12 years of age. They concluded that the patches had a tendency to increase in both number and size with increasing age.[8] The Peyer's patches were noted from 18 weeks of gestation and discrete lymphoid tissues were seen in the lamina propria of samples less than 18 weeks of gestation.

Conclusion

Intestine undergoes a complex development to perform the function of absorption of nutrients while keeping the primary line of defence intact. The time of appearance of the layers and the segmental modifications of intestine has been observed and documented in the present study. Understanding of the developmental aspects of intestine in greater detail helps understand the pathogenesis of disease involving the intestine.

Acknowledgement

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