Review / *Derleme*

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Development of the Esophagus and Stomach

Özefagus ve Mide Gelişimi

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ABSTRACT

Epithelial components of the organs of the digestive system are derived from the endoderm, whereas connective tissue and muscle components are derived from the mesoderm. At the 3rd-4th week of development, as a result of cephalocaudal and lateral foldings of the embryo, a portion of the endoderm-lined yolk sac cavity is incorporated in the embryo to form the primitive gut. Primitive gut is composed of four main regions: pharyngeal gut, foregut, midgut, and hindgut. The esophagus and stomach are derived from the foregut. The development of the esophagus is characterized by lengthening, widening, thickening, and histological changes. The development of the stomach is characterized by widening, thickening, and histological changes as well as positional changes.

In the present study, we tried to review the morphological and functional development of the esophagus and stomach with the aid of pictures obtained from various stages of prenatal and postnatal development of the organs of rats. Previous reviews lack information on both histological and functional development of the organs.

Keywords: Esophagus, development, stomach

ÖZ

Sindirim sistem organlarının bağ dokusu ve kas bileşenleri mesodermden köken alırken epitel bileşenleri endodermden gelişir. Gelişimin 3-4 haftalarında, embriyonun sefalokaudal ve lateral katlanması sonucunda endodermle döşeli yolk kesesinin bir kısmı primitif bağırsağı oluşturmak için embriyonun içinde kalır. Primitif bağırsak, sırasıyla faringeal bağırsak, ön bağırsak, orta bağırsak ve son bağırsak olmak üzere dört kısımdan oluşur. Özefagus ve mide ön bağırsaktan gelişir. Özefagusun gelişimi, uzama, genişleme, kalınlaşma ve histolojik değişikliklerle karaktirezedir. Midenin gelişimi, genişleme, kalınlaşma ve histolojik değişiklikler yanı sıra pozisyonel değişikliklerle karaktirezedir.

Biz derleme niteliğindeki bu makalede, sıçanların organlarının prenatal ve postnatal gelişiminin çeşitli aşamalarından elde edilmiş resimlerin eşliğinde özefagus ve midenin morfolojik ve fonksiyonel gelişimi ile ilgili bilgileri derlemeye çalıştık.

Anahtar Kelimeler: Özefagus, gelişim, mide

Development of the digestive tract

The digestive system consists of the digestive tube and its principal associated organs, namely, salivary glands, pancreas, liver, and gallbladder. It begins with the oral cavity and ends in the anal canal. The digestive tube is composed of the esophagus, stomach, small intestines (duodenum, jejunum, and ileum), and large intestines (cecum, ascending colon, transverse colon, descending colon, sigmoid colon, rectum, and anal canal). The liver and pancreas are accepted to be associated glands bound to the digestive tube by excretory ducts. Epithelial components of the organs of the digestive system are derived from the endoderm, whereas connective tissue and muscle components are derived from the mesoderm. The organs of the body are formed by the proliferation, migration, and differentiation of the stem/progenitor and mature cells.

The first 8 weeks of intrauterine development period is called as "organogenesis period" as well as "embryonic period". At the end of the 8th week, the embryo is approximately 30 mm in length and 2 g in weight. The heart is functional on the 4th week. Primary brain vesicles are formed, and primary brain waves are detectable. At the end of this period, all of the body systems are formed but are not mature in morphological and functional manner. The development and growth of the organs continue during the fetal period. Most of the organs are fully developed at the postnatal period; still, volume increase is obvious through the puberty period. It is a matter of fact that morphological and functional maturation period is not uniform for all of the cell types.

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In this review, we aimed to outline brief information about the histological features and prenatal and postnatal morphological and functional development of the esophagus and the stomach. Recent reviews lack information on both histological and functional development of these organs.

Development of the primitive gut

At the 3rd-4th week of development, as a result of cephalocaudal and lateral foldings of the embryo, a portion of the endoderm-lined yolk sac cavity is incorporated in the embryo to form the primitive gut. Primitive gut is composed of four main regions, namely, pharyngeal gut, foregut, midgut, and hindgut (Figure 1). The pharyngeal gut is separated from the primitive oral cavity by the buccopharyngeal membrane, whereas the foregut extends to the cloacal membrane that is the boundary between endoderm and ectoderm (1-9). The pharyngeal gut extending from the buccopharyngeal membrane to the tracheobronchial diverticulum consists of pharyngeal (branchial) archs, pharyngeal clefts, and pharyngeal pouches. Five pairs of pharyngeal pouches lined by the endoderm give rise to the middle ear cavity, auditory tube, tympanic membrane (first one), palatine tonsils (second one), thymus and inferior parathyroid glands (third one), superior parathyroid glands (fourth one) and finally, parafollicular cells of the thyroid gland (fifth one). The foregut lies caudal to pharyngeal tube and extends as far caudally as the liver outgrowth. The respiratory system, esophagus, stomach, proximal part of the duodenum, liver, pancreas, and gallbladder are derived from the foregut. The midgut begins caudal to the liver bud and extends to the junction of the right two-thirds and left third of the transverse colon in adult. Thus, the distal part of the duodenum, jejunum, ileum, cecum, appendix, and ascending colon and the proximal part of the transverse colon are derived from the midgut. Finally, the last part of the primitive gut that extends from the caudal end of the midgut to the cloacal membrane gives rise to the distal part of the transverse colon, descending colon, sigmoid colon, and rectum (Figure 1) (1-3, 5, 6).

Esophagus

Histology of the esophagus

The esophagus consists of the mucosa, submucosa tunica muscularis (muscularis externa), and adventitia/serosa. The mucosa is composed of the epithelium, lamina propria, and muscularis mucosa. In adults, the surface epithelium is nonkeratinized stratified squamous in type. Lamina propria, loose connective tissue, has some mucous glands called as "esophageal cardiac glands" at the proximal and distal ends of the esophagus. The muscularis mucosa is a longitudinally arranged smooth muscle layer. The submucosa, which is denser than the lamina propria, contains mucous tubuloalveolar esophageal glands proper. The nerve fibers and ganglion cells comprise the submucosal plexus (Meissner's plexus). The tunica muscularis is arranged as inner circular and outer longitudinal muscle layer. The upper one-third consists of striated muscle, the middle third consists of striated and smooth muscle, and the lower third consists of only smooth muscle. Another nerve plexus, the myenteric plexus (Auerbach's plexus), is present between the outer and inner muscle layers. The outermost layer is the adventitia above the diaphragm and the serosa below the diaphragm (10, 11).

Development of the esophagus

At the 4th week of development, the respiratory diverticulum (tracheobronchial diverticulum) appears at the ventral wall of the foregut. The tracheoesophageal septum formed between the respiratory diverticulum and the distal part of the foregut separates these two portions. Thus, the foregut is divided into the ventral respiratory primordium that gives rise to the respiratory system and the dorsal region that is the esophagus itself (2, 4, 6-9). At the beginning, the esophagus is short, but with the descent of the heart and lungs, it lengthens until the 7th week (2, 4, 6, 7). The development of the esophagus is characterized by lengthening, widening, thickening, and histological changes (9, 12).

Morphological & histological development

Epithelium: At the beginning, the epithelium is ciliated stratified columnar in type (2, 9). Menard et al. (13) reported ciliated stratified columnar epithelium at the 12th-16th week of intrauterine development. Sakai et al. (14) observed that ciliated cells were numerous at the esophagus epithelium of human fetuses at the 8th week but were decreased after the 14th week of development. At approximately the 8th week, the lumen of the esophagus is partially obliterated by proliferation of cells in its wall. However, the lumen is recanalized by the formation and coalescence of large vacuoles. During the recanalization, the stratified columnar epithelium transforms into the stratified squamous epithelium (2, 4, 7, 8). In general, it has been accepted that in humans, the esophagus epithelium becomes stratified squamous within the 4th month of development (2, 9); however, contradictory results have been reported about the exact time of this epithelial change in humans. Sakai et al. (14) observed an immature squamous stratified epithelium at the 14th week and fully mature one at the 21st week of development. Schaller et al. (15) observed the stratified squamous epithelium after the 23rd week. Some authors suggest that transformation from ciliated columnar to stratified squamous continues until birth. It has been suggested that the ciliated cells persist in the upper and lower ends of the esophagus until the advanced period of the pregnancy might give rise to the cardiac glands located in the lamina propria (1).

Lamina propria: In human fetuses at the 19th-20th week, the glands have been rarely observed within this layer (16).

Muscularis mucosa: The muscularis mucosa, although very thin, has been detected at the 24th-26th week of the intrauterine development of human fetuses (16).

Submucosa: After the 27th week, the submucosal glands were observed (16). The submucosal plexus has been shown within

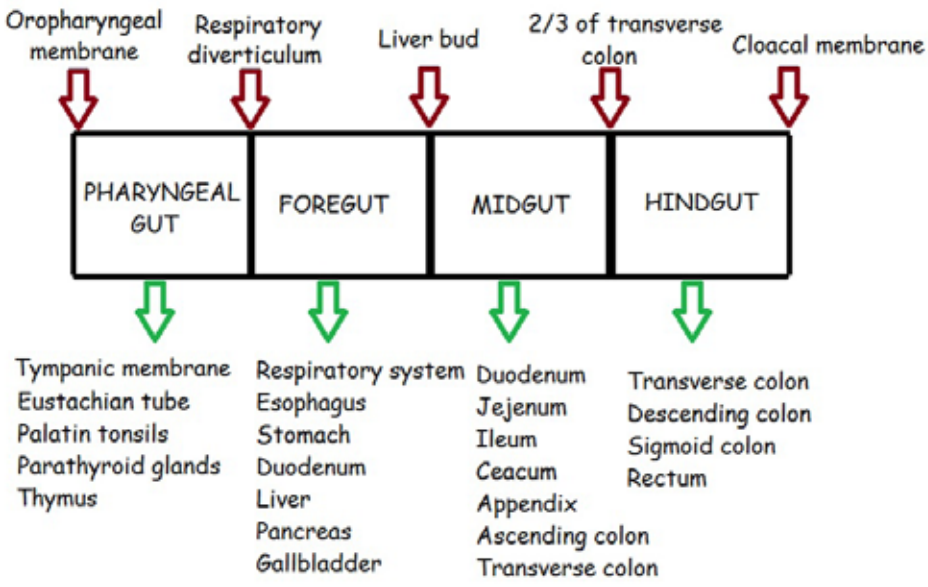


Figure 1. Main parts of the primitive gut tube and the organs derived from these regions are summarized (drawn by Esrefoglu M)

the 9th week (17).

Muscularis externa: In human fetuses, the circular inner muscle layer has been detected at the 5th week, whereas the outer longitudinal one has been detected at the 8th week (9). At the 9th week, both of the layers were arranged as uninterrupted muscle cell layers (18, 19). The myenteric plexus was detected within the 7th week of intrauterine development (17).

The esophagus continues to grow with elongation and thickening at postnatal period. It is approximately 8-10 cm at term, 12.5 cm at the end of the first year, 16 cm at the end of the 5th year, and 19 cm at the end of the 15th year. Its diameter is 5 mm at term and becomes 15 mm within the 5th year. Just after the delivery, within the first 4 weeks, the lumen of the esophagus rapidly enlarges, and thickening of the mucosa is obvious. The proportion of the thicknesses of the mucosa/submucosa increases until the end of the 2nd week (20).

Functional development

It has been shown that peristaltic capacity has been gained at the 1st trimester of pregnancy (21). Three types of movement within the wall of the esophagus at the 2nd trimester have been detected. These are the spontaneous opening of the lumen throughout the length of the esophagus, peristaltic contractions, and reflux from the stomach (22). Although peristalsis has been observed by ultrasonographic examination at the 2nd trimester, spreading of peristalsis throughout the esophagus and at the lower esophageal sphincter has been found to be immature at term. Consequently, reflux of breast milk to the esophagus is very common. The pressure of the lower esophageal sphincter becomes equal to that of adults at approximately postnatal 3rd-6th week (23). Thus, 75%-80% of newborns suffer from regurgitation within the first 2 weeks of their life. This problem almost completely (95%) improves without intervention until the end of the 1st year (24).

Figure 2 summarizes the prenatal and postnatal developmental changes of the esophagus in rats.

Stomach

Histology of the stomach

The stomach consists of the mucosa, submucosa muscularis (muscularis externa), and serosa. The mucosa is composed of the epithelium, lamina propria, and muscularis mucosa. The epithelium, which is simple columnar epithelium, functions as both lining and also secretory epithelium. The covering epithelium also protects the mucosa against acidic content of the stomach by producing mucus. The mucosa and submucosa together make longitudinal folds and ridges called 'rugae'. Under light microscope, the surface of the stomach contains numerous and relatively deep depressions called gastric pits (or foveola) that are formed by the surface epithelium. The underlying loose connective tissue, lamina propria, is largely occupied by gastric glands that open into the bottom of the gastric pits. The gastric glands are composed of five cell types, including the chief cells, parietal cells, mucous neck cells, enteroendocrine cells, and undifferentiated adult stem cells. The muscularis mucosa is composed of two layers, usually arranged as an inner circular and outer longitudinal layer. The submucosa is composed of dense connective tissue containing the nerve plexus of Meissner. The tunica mucosa is traditionally described as consisting an inner oblique, a middle circular, and an outer longitudinal layer. The myenteric nerve plexus is present between muscle layers. The outermost layer is

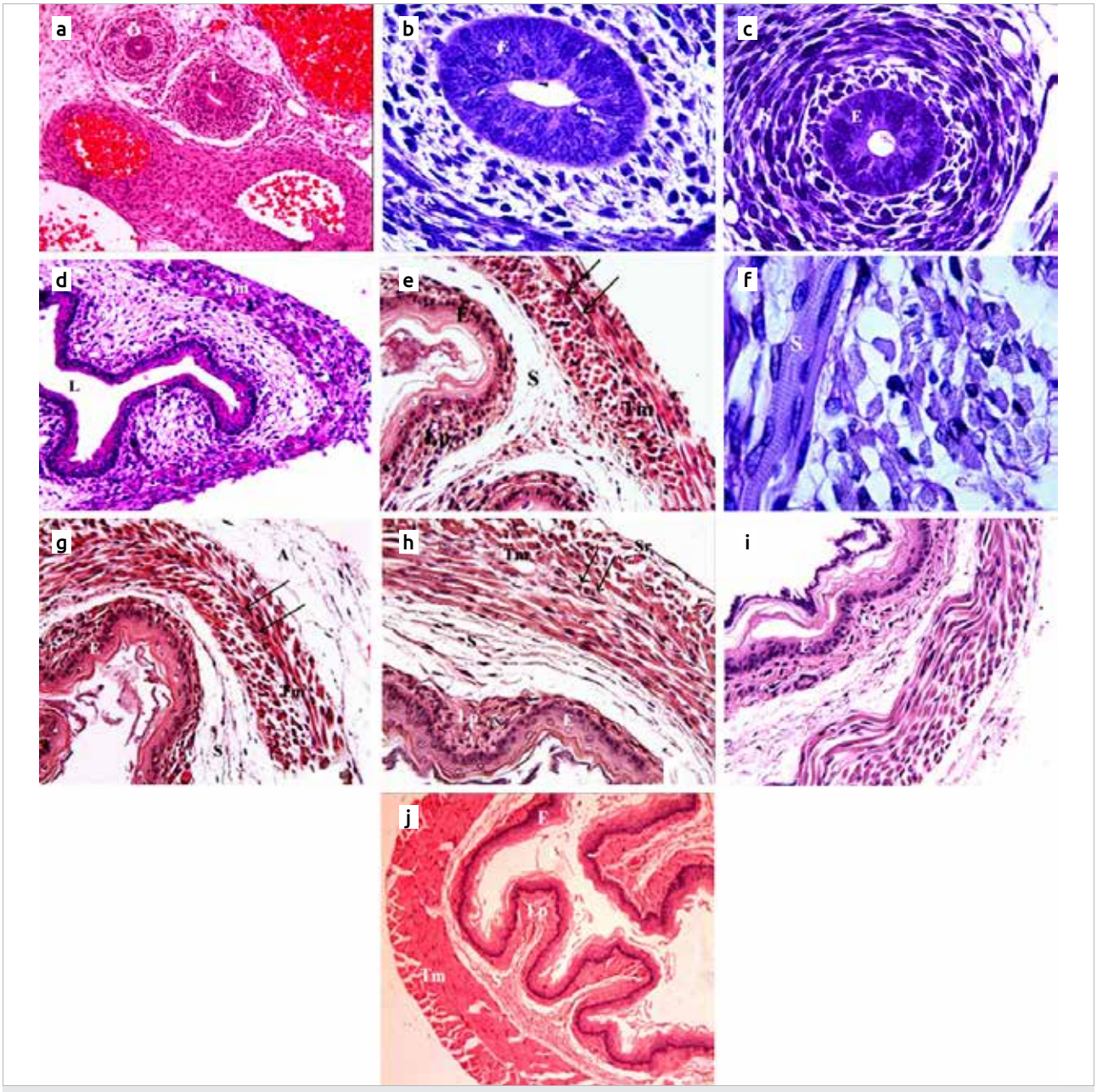


Figure 2. The prenatal changes within the features of the esophagus are shown in rats. A-B. Intrauterine 7th day. The esophagus (Ö) and trachea are located together in the mesenchymal connective tissue. The epithelium (E) of the esophagus, stratified columnar in type, is surrounded by the mesenchymal connective tissue. A circular muscle layer (K) around the mesenchymal connective tissue is obvious. H&E, X20; PAS, X100. C. Intrauterine 17th day. In general, histological features of the esophagus are similar to those of the previous period; however, the muscle layer (K) is highly thickened. H&E, X100. D. Intrauterine 20th day. Histological features of the esophagus are now similar to those of adult rats. The lumen (L) is highly enlarged; moreover, the wall of the esophagus has folds as a result of muscular contraction. Additionally, the epithelium (E) is stratified squamous in type, and the mesenchymal connective tissue (M) around the epithelium is thickened. The tunica muscularis (Tm) is now composed of two layers, namely, inner circular and outer longitudinal muscle layers. H&E, X40. E-J. The postnatal changes within the features of the esophagus are shown in rats. E-F. Postnatal 5th day. Stratified squamous epithelium (E), lamina propria (Lp), submucosa (S), tunica muscularis (Tm), and myenteric plexus between muscle layers (arrows) are seen. Occasionally, there are striated muscle fibers within circular (S) and longitudinal (L) muscle layers. H&E, X40; PAS, X100. G. Postnatal 10th day. The epithelium (E), lamina propria (Lp), submucosa (S), tunica muscularis (Tm), and, additionally, adventitia (A) are obvious. The myenteric plexuses between muscle layers are marked with arrows. H&E, X40. H. Postnatal 15th day. The layers of the wall of the esophagus are thickened. The outermost layer is here the serosa (S). H&E, X40. I. Postnatal 20th day. Maturation of the layers is obvious. For example, now epithelium is keratinized stratified squamous in type (keratinization is expected in rodents). H&E, X40. J. Young adult rat. Stratified squamous epithelium (E), lamina propria (Lp), submucosa (S), and tunica muscularis (Tm) are seen. The wall of the esophagus is highly thickened. H&E, X10.

the serosa, which is composed of the mesothelium and underlying thin, loose connective tissue (10, 11).

Development of the stomach

The development of the stomach is characterized by widening, thickening, and histological changes as well as locational and directional changes. The stomach appears as a fusiform dilatation of the foregut at the 4th week of development (2-8). The growing stomach rotates 90° clockwise around the longitudinal axis (2, 4-8). The rotation causes its left side to face anteriorly and its right side to face posteriorly. Additionally, during this rotation, the original posterior wall of the stomach grows faster than the anterior portion, forming greater and lesser curvatures. Before the rotation, the cephalic and caudal ends of the stomach originally lie in the middle, but during further growth, the stomach rotates around the anteroposterior axis. Thus, the caudal pyloric part moves to the right and upward, and the cephalic or cardiac portion moves to the left and slightly downward (2-8). At the 14th week of development, the anatomical features including greater and lesser curvatures, fundus, corpus, and pylorus are formed in human fetuses (25). The diameter of the stomach increases as the fetus swallows amniotic fluid. At the 20th week of development, the macroscopical and microscopical features of human fetuses are similar to those of newborns (26). In fact, at the 32nd-34th week of development, all of the layers including the mucosa, submucosa, muscularis, and serosa become more and more similar to those of the adult stomach (27). Cell differentiation within the stomach continues from early to late fetal period (9). It has been suggested that swallowed amniotic fluid influences cell proliferation and differentiation (28).

Epithelium: At the beginning, gastric epithelium is a stratified epithelium in type. It has the characteristics of stratified or pseudostratified epithelium at the 4th week of development (7, 29), whereas pseudostratified epithelium at the 8th-20th week of development in human fetuses (30). Transition from stratified or pseudostratified epithelium to simple epithelium takes place at the 11th-17th week of development (31, 32). Some patchy areas of pseudostratified epithelium have been observed at the 12th week of development in humans. Thus, epithelial transition may continue until the 20th week (33). Chimalgi et al. (27) reported a simple cuboidal epithelium at the 15th-20th week of development, but a simple columnar epithelium at the 21st-22nd week of development. The exact mechanism of the epithelial transition is unknown. Nevertheless, the cells of the stratified epithelium might migrate to other parts of the body or undergo necrosis or apoptosis and finally disappear (28).

Gastric pits: For the first time, gastric pits begin to appear at the 8th week at the fundus and corpus regions of the stomach (34). Kerry et al. (26) detected gastric pits at the 14th week of development. However, they become similar to those of adults at the 15th-16th week of development.

Gastric glands: Although the mucosa has been formed until the 15th week, between the 21st and 24th week and at the 18th week, mucosal thickening is obvious (27). For the differentiation of the gastric glandular cells, various signals (35), hormones, and local growth factors derived from the mesenchyme are necessary (36). Morphological features of the glands become similar to those of adults at the 15th-16th week of development. It has been reported that the glands, which are acinar in type at the 15th-20th week, branch at the 21st-22nd week and later lengthen and become tubular at the 23rd-28th week of development. After the 28th week, they continue to lengthen and become coiled (27).

Parietal cells: In fact, the cells of the fundic glands with high succinic dehydrogenase activity are parietal cells at the 8th week of development (37). Nevertheless, the parietal cells with acidophilic cytoplasm can be recognized at the 12th-15th week of development (27, 33). These cells also observed within the pyloric glands at the 13th week express intrinsic factor and hydrogen-potassium activity (38). It is now known that hydrochloric acid begins to be secreted at approximately the 32nd week of development in humans (9, 39). On the other hand, intrinsic factor has been detected at the 14th week, its level increases seven times until the 25th week of development (40). The level is the factor that becomes equal to that of adults within postnatal first 10 days (41).

Chief cells: The chief cells can be recognized at the 13th week of development (42). Chimalgi et al. (27) observed this cell type at the 22nd week. Some researchers reveal that these cells have pepsinogen activity at the 16th week of development (39), whereas some of the others report that they do not have that activity until birth (42).

Mucous neck cells: Mucous cells can be detected at the 13th week for the first time. They can produce mucus at the 16th week of development (42). Chimalgi et al. (27) detected the mucous neck cells at the 22nd week of development.

Enteroendocrine cells: It has been accepted that for the first time, enterochromaffin cells appear at the 11th week of development (43, 44). Oberg et al. (45) observed these cells in the surface epithelium at the 9th-10th week. Additionally, they detected a new and interesting peptide function in food intake and growth hormone release at the 10th week of development (46). The enteroendocrine cells containing gastrin and somatostatin have been detected at the 8th week, glucagon and ghrelin at the 10th week, and serotonin at the 11th week of development (47, 48). G cells, another type of the endocrine cells, have been detected at the 18th week of development (38). Throughout the fetal period, fetuses have a gastrin concentration of 10% of adults (49). Following birth, newborns in their first couple of days have higher serum gastrin levels than adults (50, 51).

Muscularis mucosa and submucosa: The muscularis mucosa appears at the 22nd week of development. The submucosa is

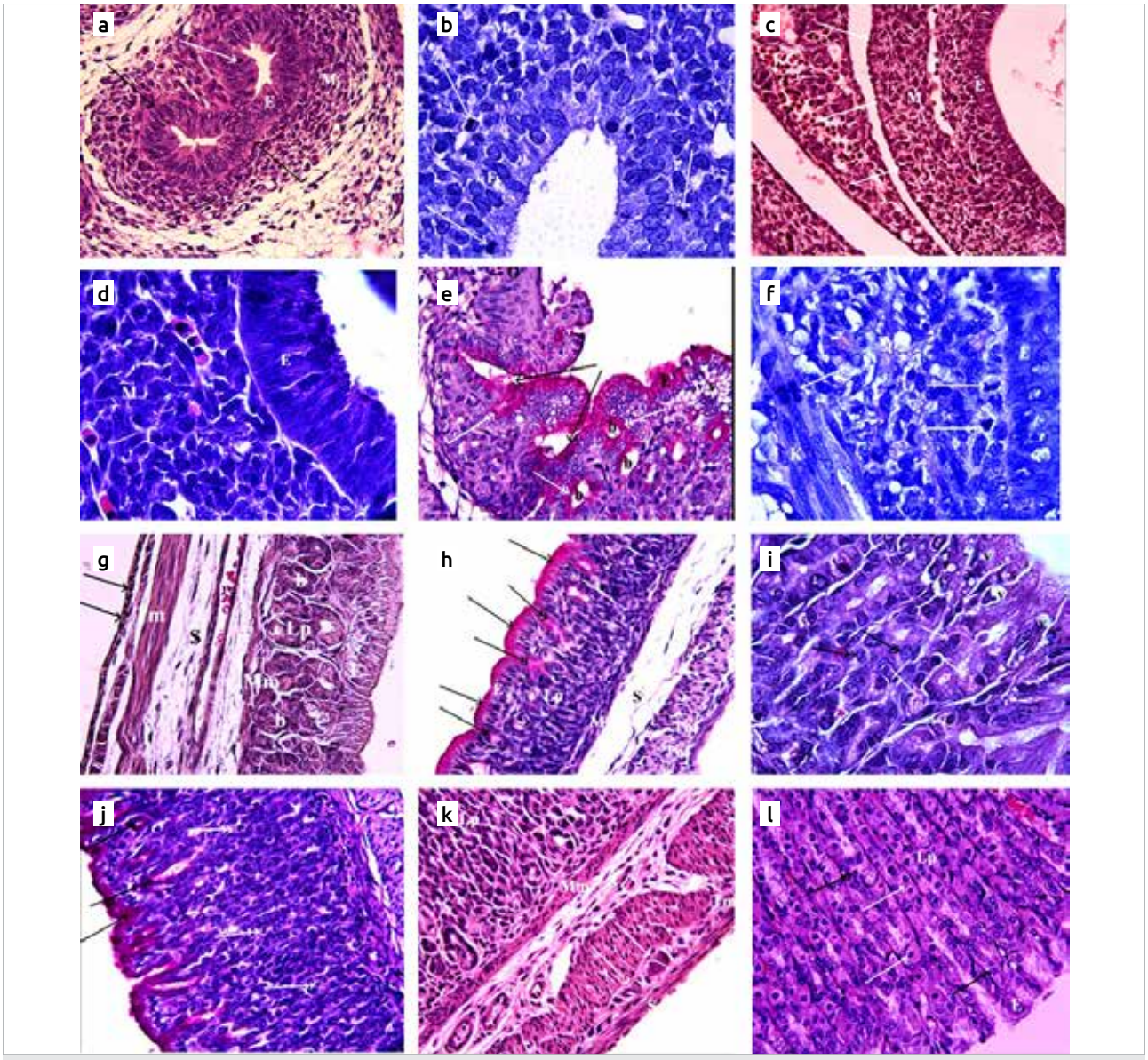


Figure 3. The prenatal changes within the features of the stomach are shown in rats. A. Intrauterine 7th day. Pseudostratified columnar epithelium (E) and surrounding mesenchymal connective tissue (M) are observed. Basement membrane (black arrows) and mitotic figures within the epithelium (white arrows) are marked. PAS, X40. B. Intrauterine 10th day. Pseudostratified columnar epithelium (E) and surrounding mesenchymal connective tissue (M) are observed. Mitotic figures within the epithelium and connective tissue are marked. H&E, X100. C-D. Intrauterine 14th day. Still, the wall of the stomach is composed of pseudostratified columnar epithelium (E) and surrounding vascular mesenchymal connective tissue (M). Hematopoietic cell groups within the liver are marked by white arrows. H&E, X40; H&E, X100. E-F. Intrauterine 20th day. Foveola (black arrows) and glands (b) are formed. PAS positive mucus can be observed at the surface epithelium and glandular epithelium (white arrows). Additionally, a circular muscle cell layer (K) is now obvious at the periphery of the mesenchymal tissue. Mitotic figures within the connective tissue and muscle layer are marked with white arrows. PAS, X40; H&E, X100. G-L The postnatal changes within the features of the stomach are shown in rats. G. Postnatal 5th day. Stratified columnar epithelium (E), lamina propria (Lp), muscularis mucosa (Mm), submucosa (S), tunica muscularis (Tm), and serosa (arrows) are obvious. Lamina propria is occupied by gastric glands (b) containing acidophilic parietal cells. H&E, X40. H. Postnatal 10th day. Epithelium (E), lamina propria (Lp), muscularis mucosa (Mm), submucosa (S), tunica muscularis (Tm), and serosa (arrows) are observed. Gastric pits begin to appear (two-headed arrows). At the surface of the epithelium and lumen of the glands, PAS positive mucus is seen. PAS, X40. I. Postnatal 10th day. Epithelium is still stratified. Some vacuoles (v) within the epithelium are seen. The parietal cells (white arrows) and chief cells (black arrows) are detectable. H&E, X100. J. Postnatal 15th day. Mucosa is thickened, gastric pits are clearly recognizable, and PAS (+) mucus is increased (arrows). Many mitotic figures are present within the glandular epithelium (white arrows). K. Postnatal 20th day. All of the layers are thickened. Between the muscle layers, the myenteric nerve plexus is seen (arrows). H&E, X40. L. Young adult. Simple columnar epithelium (E), lengthened glands in lamina propria (Lp), and increased number of the chief (black arrows) and parietal cells (white arrows) are observed. H&E, X40.

the thickest layer of the wall within the 15th-20th week and 25th-27th week (27).

Muscularis externa: The circular muscle layer appears at the 15th week, and the longitudinal muscle layer appears at the 28th week of development. Muscle layer becomes thicker especially between the 21st and 24th week and between the 28th week and birth (27). Gastric motility can be detected approximately at the 20th week of development (52).

Serosa: The serosa layer has been formed until the 15th week of development (27).

Figure 3 summarizes the prenatal and postnatal developmental changes of the stomach in rats.

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