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Original Research Article

HISTOGENESIS OF HUMAN LUNG - RETROSPECTIVE FETAL AUTOPSY STUDY.

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ABSTRACT

Histogenesis of human fetal lung was studied in 40 human fetuses under light microscope after sectioning and staining with hematoxylin & eosin stain, in fetuses with gestational age ranging from 10 weeks to fetuses above 30 weeks. Appearance of various levels of bronchi were identified with the changes in the epithelium at different levels of bronchi. The appearance of alveolar ducts and few alveoli were recognized after 25 weeks of gestation. Vascularisation of the fetal lung was observed as early as 10 weeks of gestation. Appearance of various levels of bronchi were identified with the changes in the epithelium at different ages of gestation

KEY WORDS: Fetal Lung, Bronchi, Respiratory Distress, Alveolar Ducts, Alveoli.

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INTRODUCTION

The process of histogenesis of lung is very significant as it determines the independent survival of fetus.

Lungs have a dual origin. The larynx, trachea, bronchi, bronchioles and respiratory bronchioles lined by cuboidal epithelium arise from the foregut diverticulum and the remaining respiratory bronchioles, alveolar ducts, alveolar sacs and alveoli arise from adjacent mesenchyme [1].

The maturation phase of the lungs can be divided into 4 stages-

(i)**Pseudoglandular stage** (6-16 weeks)- the developing lungs resembles exocrine glands. By 16 weeks all major elements of lungs are formed except those involved for gas exchange; (ii) **Canalicular stage** (16-26 weeks)- the lung tissue becomes highly vascular and the cranial segments of the lung mature faster than the caudal segments. Lung tissue becomes highly vascular and the lumina of bronchi and terminal bronchioles become larger. There is appearance of two or more respiratory bronchioles from terminal bronchioles by 24 weeks. Each respiratory bronchioles divides into three to six primodial alveolar ducts;

(iii) **Terminal sac stage** (26weeks till birth)- terminal sacs develop during this stage and their epithelium becomes very thin. Capillaries are seen bulging into these sacs. Blood air barrier is established which permits gas exchange;

(iv) **Alveolar stage** (32 weeks till 8 years)- sacs analogous to alveoli are present [2]. Studies [3] suggest a close association in the timings of development of blood vessels and the airways. A great variation in the number of completely

epithelialised bronchioles at all age groups and number of incompletely lined air tubes appeared to increase rapidly during the later stages of intrauterine life and the total number of airways showed an increase during the last trimester. The number of alveoli increased with increasing age throughout the childhood. Study also suggested an increase in the total number of air passages from 20th week of intrauterine life until upto one month after birth. The number of air passages with cartilages appeared to be of the adult by 20 weeks of gestation which was similar to another study, which demonstrated the appearance of cartilages at about 25th week of intrauterine life [4].

The development of lobar bronchi as small outgrowths from primary stem bronchus and further subdivisions of lobar bronchi into segmental bronchi can be traced as early as 5-6 weeks of gestation. Palmer [5,6] found 17 divisions between the trachea and terminal bronchioles in an 18 week old fetus and same number of division in 21 week fetus, but also detected capillaries between the epithelial cells of the last three generations at 21st week. Brenek [7] identified the appearance of cartilage by 10th week in the main bronchi, but didn't reach the level of segmental bronchi until 12 weeks. At 10th week the cartilage of main bronchi consisted of concentrations of large cells with round dark nuclei and palely eosinophilic cytoplasm. At 12th week the central cells of cartilage plate in the main bronchi were bigger and the nuclei appeared widely separated with the cell border slightly PAS positive and ground substance gradually appeared between the cells. At 13 and 14 weeks capsules were distinct featured in the proximal cartilage and at 16 weeks the ground substance at the proximal plate of cartilage stained slightly positive with PAS. Between 16th and 24th week the last few generations of bronchial tree partly loses the cuboidal epithelium due to ingrowth of capillaries and form the primitive respiratory bronchiole. Some authors [8] suggested that after birth, respiratory bronchioles were transformed again into fully epithelialised bronchioles by dealveolisation.

Light microscopic study [9] of fetal lungs at 1-4 months showed tubular structure of the epithelial cells with columnar epithelium and in the older ones some cells were flat and cuboidal and glycogen was abundant. The structure of the tubuli became more irregular at 4-5 months and blood- air barrier appeared between the epithelial cells and at 5-6 months alveolar configuration appeared. During the 5th month epithelium changes from columnar or cuboidal to pseudocuboidal pattern.

Jeffery [10] stated that the human fetal airway mucosa is functional with mature cells by 24 weeks of gestation. The adult pattern of airway branching is complete by the 18th week but still after birth the tracheobronchial tree increases and the distal airways grow until atleast 8 years of life. Two types of surface secretory cells-the mucous and the serous cells were identified. Histochemically the presence of intracellular mucous has been demonstrated by 13th week of gestation and continued to extend along the bronchial tree upto 25th week after which no extension occured. The mucous secreting cells (MSC) were sparse or were gathered into small group of cells and their number peaked in the middle of the gestation and by the end of second term of gestation there was a decrease in the number of MSC. The submucosal glands appeared first in the proximal airways and progressed towards the periphery to reach the main carina 7 days later [11].

Authors [12] described the appearance of goblet cells by 13 weeks and in the proximal intrasegmental generation between 12-24 weeks, but their appearance in the distal generation was only after 32 weeks. Cilia were seen in the main bronchi at 10 weeks and in the most peripheral airways by 13 weeks [4,12] and by term the ciliated cells reached the terminal bronchiole.

At 12th week of gestation the epithelium in the adult bronchial tree was pseudostratified ciliated columnar with well developed basement membrance [4]. The basement membrane was identified by PAS reaction at 10 weeks of gestation. Some authors [13,14] described the histological appearance of lungs as tubular structure of epithelial ducts in the mesenchyme with smooth muscle fibres around some tubuli during the first half of 4th month. There was also presence of the bronchial artery at this stage.

In the later half of the 4th month the lung had glandular appearance with increased terminal buds. At the 5th month the lung began to loose its glandular appearance and many tubuli with rough surfaced and irregular lumen appeared. The epithelial lining of the terminal buds were low columnar or cuboidal with round vesicular nuclei and clear cytoplasm. The mesenchymal cells showed tendency to condense around the bronchus and expanded tubuli. The bronchus had ciliated columnar folded epithelium with irregularly arranged elongated or oval nuclei. At the 7th month the bronchial tree could be distinguished with the respiratory part of the lung by its deeper staining epithelial nuclei. At the 8th 9th and 10th month the epithelial cells became more flattened and the processes of the cytoplasm without nuclei increased in number. At the 10th month ciliated cells were observed at the terminal bronchi.

Although development of human lung has been widely studied and illustrated, most of the articles deal with few aspects of histogenesis. As the literature regarding the histogenesis of the fetal lung was scanty, the present study aims to analyse the development of lungs with the histological changes with increasing gestational ages. The study will establish the micro development of the human fetal lung in north-west Indian population.

MATERIALS AND METHODS

The present study was carried on 40 autopsied human fetuses of varying gestational ages in the Department of Anatomy, Government Medical College and Hospital, Chandigarh over a period of two years from 2014-2016. The fetus for the study was obtained from the Department of Obstetrics and Gynaecology of the same institute, which were sent for routine autopsy. Consent was taken from the parents as well as from the institutional ethics committee to perform autopsy and to carry out any additional studies.

Exclusion criteria:

1. Fetuses with congenital malformation.
2. Macerated fetuses
3. Maternal history of infection such as rubella, hepatitis, CMV, HIV.

Histological examination was done in 40 lungs of right and left side. The staining was done by the following methods.

1. Hematoxylin and eosin to demonstrate the normal microscopic structure of the lungs.
2. PAS to identify the presence of basement membrane.
3. Masson's trichrome for demonstration of the connective tissue.

OBSERVATIONS

10-15 weeks gestation: Mesenchymal cells were abundant at 10 weeks of gestation and cells appeared as clumps with large euchromatic nucleus. Nucleus appeared round to oval and oval to flat in cells surrounding bronchi. Mesenchymal cells started decreasing after 12 weeks. Dividing bronchi lined by columnar to pseudostratified columnar epithelium and few goblet cells were visible at 14+ weeks with smooth muscle fibres around the bronchus. Clustering of chondroblasts was seen surrounding the bronchi at 13 weeks and few PAS positive granules were identified at 14 weeks. Very few blood vessels started to appear at 10 weeks of gestation. Few vessels were visible in the interlobular septa also. Three to four layers of smooth muscle fibres were clearly identified around the developing arteries by Massons trichrome staining after 13 weeks of gestation. Few serous glands started to appear at 13 weeks of gestation.

15+-20 weeks gestation: Uneven distribution of mesenchymal cells with round to oval nucleus along with condensation of cells around few bronchi were visible. Numerous bronchi could be identified which were lined by cuboidal, columnar or pseudostratified ciliated columnar epithelium. Developing bronchioles were present which were lined by flattened epithelium. At 18+weeks formation of cartilaginous plates were identified. Clear distinction between artery and vein was established. Formation of cell nests seen with two to four chondrocytes were identified with PAS staining.

20+- 25 weeks gestation: Mesenchymal cells decreased in number which was more visible around bronchi with spindle shaped nucleus. Very few alveolar ducts were seen along with

dividing bronchi. Well defined cartilaginous plates were visible around the bronchi. Few cell nests were seen in the cartilaginous plate. Increased number of vessels were seen in the interlobular septa. More number of serous glands were observed. Collagen fibres in the interlobular septae were very well identified with Massons trichrome stain.

25⁺- 30 weeks gestation: Mesnchymal cells could be seen around bronchi as a single layer of cells. Differentiation could be made between larger bronchi and bronchioles. Glands became few in number.

>30⁺ weeks gestation: Mesenchymal cells were almost negligible. Bronchi, bronchioles and developing alveoli were identified. No glands were visible.

Fig 1: 11 weeks (H & E) Dividing bronchi with columnar epithelial cells with few goblet cells. No cartilage seen at this stage.

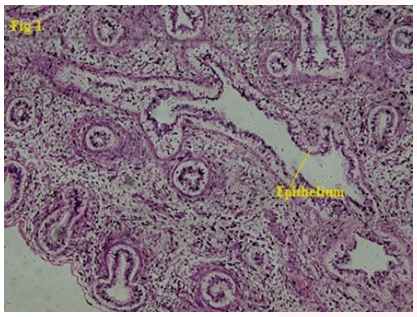


Fig. 2: 16 weeks (H & E) Appearance of cartilage plate and blood vessels visible. Prominent interlobular septae with bronchioles and less number of mesenchymal cells.

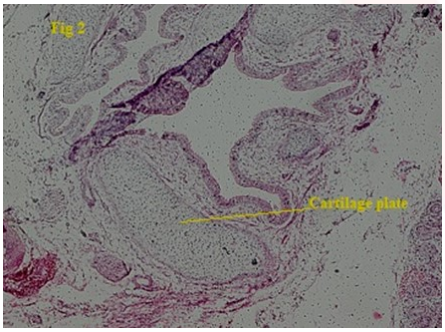


Fig. 3: 23 weeks (H & E) Cartilage plate visible along with secondary and tertiary bronchi.

Fig. 4: 25 weeks (H & E) Appearance of respiratory bronchioles with alveolar ducts

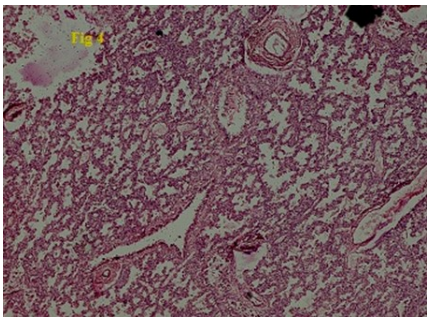


Fig. 5: 36 weeks (H & E) Appearance of numerous air sacs

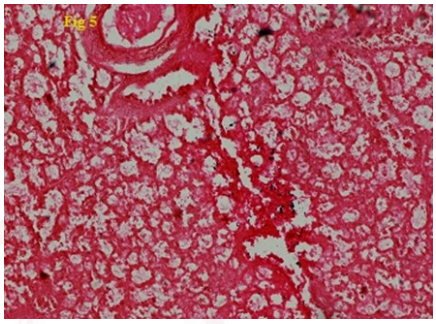


Fig. 6: 13+2 weeks MT Dividing bronchi visible with few interlobular septae.

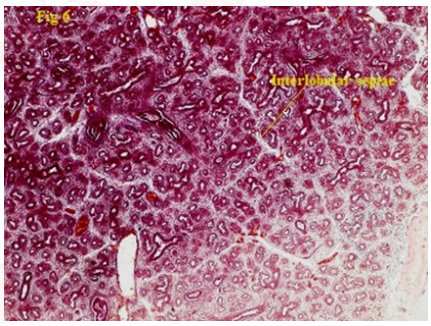


Fig. 7: 14+3 weeks MT Blood vessels in the interlobular septae.

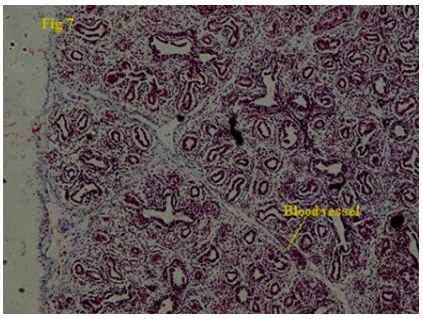
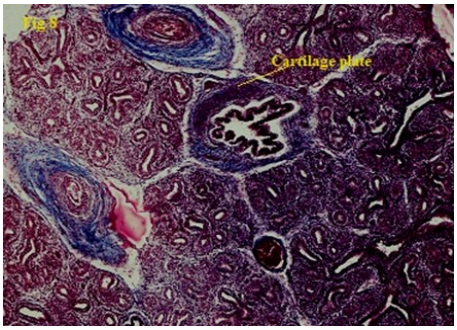


Fig. 8: 16 weeks MT Well defined cartilage plate with few cell nest.



Histological changes in lung with increasing gestation

Features	10-15 weeks	15^{+}-20 weeks	20^{+}-25 weeks	25^{+}-30 weeks	30^{+} weeks
Mesenchyme	· Mesenchymal cells abundant at 10 weeks. · Cells appeared as clumps with large euchromatic nucleus · Nucleus round to oval; oval to flat in cells surrounding bronchi. · Cells started decreasing after 12 weeks.	· Un evev distribution of cells with round to oval nucleus. · Condensation of cells seen around few bronchi.	· Mesenchymal cells decreased · More visible around bronchi with spindle shaped nucleus.	· Could be seen around bronchi as a single layer of cells.	· Almost negligible.
Bronchus	· Dividing bronchi seen lined by columnar to pseudostratified columnar epithelium. · A few goblet cells visible at 14^{+} weeks. · Smooth muscle fibres seen around bronchus.	· Numerous bronchi could be identified. · Lining epithelium varied from cuboidal, columnar or pseudostratified ciliated columnar.	· Pseudostratified ciliated columnar epithelium demonstrated around various levels of bronchi. · Presence of goblet cells verified. · Bronchioles were seen lined by flattened epithelium. · Very few alveolar ducts seen.	· Differentiation could be made between larger bronchi and bronchioles. · Presence of alveolar ducts identified.	· Bronchi, bronchioles and developing alveoli seen. · Alveolar ducts identified in large numbers.
Cartilage	· Clustering of chondroblasts seen surrounding the bronchi at 13 weeks.	· Formation of cartilaginous plates identified at 18^{+} weeks.	· Few cell nests seen in the cartilaginous plate.	· Cartilage plate with cell nests seen around the bronchi.	· Cartilage plate well defined around the bronchi.
Blood vessels	· Very few blood vessels started to appear at 10 weeks of gestation. · Blood vessels increased in number after 13 weeks of gestation. · Few vessels started to appear in the interlobular septa.	· Few blood vessels were seen surrounding the dividing bronchi. · Clear distinction between artery and vein identified.	· Blood vessels increased in number. · Few arterioles and capillaries identified. · Increased number of vessels in the interlobular septa.	· Numerous arteries and veins identified. · Numerous blood vessels surrounding the bronchi visible.	· Blood vessels increased in number. · More number of vessels appeared in the interlobular septa.
Glands	· Few serous glands started to appear at 13 weeks of gestation.	· Serous glands identified. · Mucous glands absent.	· More number of serous glands observed.	· Glands became fewer in number.	· No glands were visible.

Fig. 9: 26 weeks MT Well defined blood vessels. Cartilage plate around bronchi with cell nest.Alveolar ducts visible.

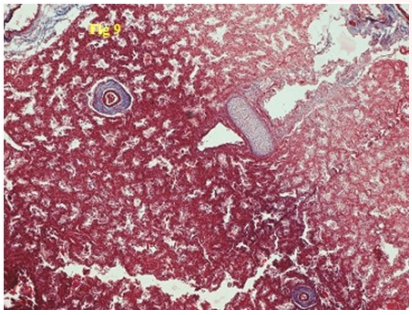


Fig. 10: 11 weeks (PAS) Dividing bronchi visible.

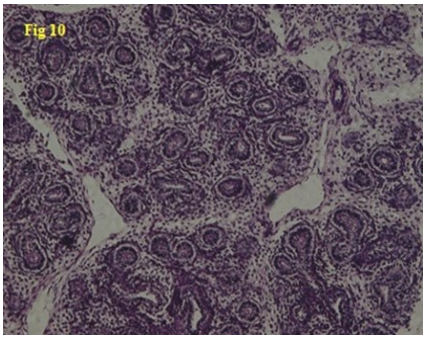


Fig. 11: 16 weeks (PAS) Bronchi with pseudostratified ciliated columnar epithelium with cartilage plate.

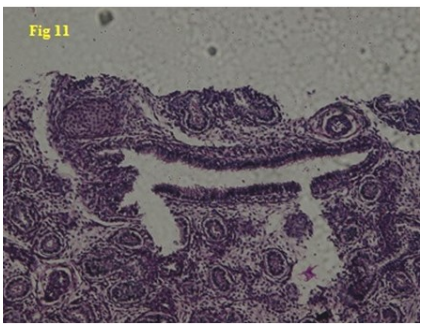


Fig. 12: 20 weeks (PAS) Bronchi with well defined epithelium and blood vessels.

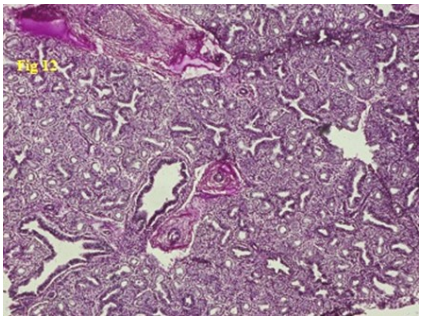
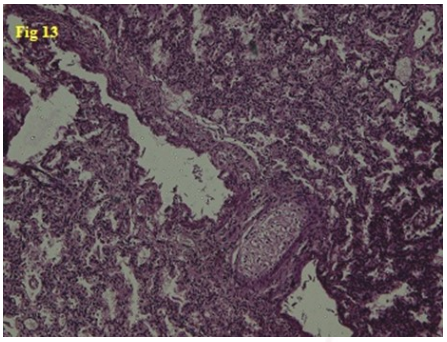


Fig. 13: 25 weeks (PAS) Bronchi with well defined epithelium and cartilage plate.



DISCUSSION

Various authors have studied the histogenesis of lung in fetal specimens and have tried to define a timeline for the appearance of various distinct features.

Bucher and Reid [4] described the appearance of basement membrane at 10 weeks by pale pink stain with PAS positive which did not appear continuous. The author also commented that the basement membrane was well developed by 12 weeks of gestation. Eugenia [15] also described the thin limiting membrane lining the cavity reflected over the mesodermic mass which represented the visceral pleura. Only few authors have mentioned about the pleural membrane or the lining.

In the present study the pleural layer which formed the outermost covering of the lung tissue was identifiable at 10 weeks of gestation. The layer was continuous with one layer of flat endothelial cells having oval to flattened nuclei. Few collagen fibres were present in this layer. There was no extension of this layer into the parenchyma of the lung at 10 weeks of gestation. After the 15th week of gestation, some fibres from the layer were seen extending into the parenchyma of the lung giving the lung lobular appearance. After 20 weeks of gestation more and more number of fibres were seen extending into the parenchyma of the lung leading to the well defined lobular appearance of the lung.

A few studies described the mesenchymal cells, their appearance and their transformation into any other cells. Tanaka et al [13] observed that the mesenchymal cells near the bronchial tree had spindle shaped nuclei with rich chromatin and other areas had oval vescicular nuclei; during the first half of the 4th month single layer of mesenchymal cells was observed around the tubuli which did not condense. The study also noted that the mesenchymal cell near the bronchial tree were different from those present in the other areas, and the cells showed a tendency to condense around the bronchus and expand the tubuli at 6th month of gestation. The authors also described that the mesenchymal cells gradually reduced after 25 weeks of gestation [16].

In the present study at 10 weeks of gestation the lung parenchyma was occupied by abundant mesenchymal cells of varying size. Out of these mesenchymal cells some dark and light stained cells could be seen containing few granules. At 12 weeks the mesenchymal cells were still abundant but the parenchyma was also occupied by dividing bronchi. The mesenchymal cells started moving from each other after 15 weeks of gestation, as most of the parenchyma became occupied by the developing and dividing bronchi. After 20 weeks of gestation the mesenchymal cells became much sparse to almost absent. As described by previous authors, the present study also observed that the mesenchymal cells near the bronchi had spindle shaped nucleus and the rest had oval to round nucleus.

In the present study, after 12 weeks of gestation most of the lung tissue were occupied by the bronchi and various stages of dividing bronchi. As the age advanced more number of bronchi appeared which were differentiating into the various levels of division. More number of air spaces appeared in the parenchyma as the age advanced.

Bucher and Reid [4] described that at 10 weeks of gestation plates of cartilage were found developing in the zones of precartilage in the main bronchi. It consisted of concentrations of large cells with round dark nuclei with palely eosinophilic cytoplasm. At 12 weeks the central cells of the plates of cartilage in the main bronchi were bigger and the nuclei apperared more widely separated from each other. The cell borders also showed slightly PAS positive reaction. As the development advanced the ground substance gradually appeared between the cell and at 13-14 weeks the capsules were a distinct feature in the proximal bit of cartilage.

The ground substance near the proximal plates of cartilage stained slightly positive with PAS stain at 16 weeks of gestation.

In the present study no cartilage plate could be identified at 10 weeks of gestation. Accumulation of large pale cells could be identified around the bronchus which were the precursors for the development of future cartilaginous plate. At around 13 weeks of gestation clustering chondrocytes surrounding the bronchus were seen developing into small cartilaginous plate. The cartilage plate surrounding the bronchi was observed developing around the main or the primary bronchus at 13 weeks of gestation which was a little later than compared to that of study by Bucher and Reid [4].

Few authors [7] described more advanced development of cartilage in the left lung than the right by 10 and half to 11 weeks of gestation. But in the present study no cartilage plate was identifiable at 10 weeks or at 11 weeks both in right and left lung. Other authors [14,4] identified 4-5 islands of developing cartilage with appearance of cell nest in lacunae by 15-18 weeks of gestation and cartilage continued to appear until about 25 weeks of intrauterine life. In the present study well developed cell nest could be identified by 20 weeks of gestation which was contradictory to the study done by above authors. In the present study the use of special stains identified the appearance of well defined cartilage plate at 14 weeks of gestation. Few bronchial tubules were lined by plates of cartilage after 15 weeks of gestation which were identified as the primary bronchus and smaller bronchial tubules were lined by large chondroblastic cells which could be the developing secondary bronchi. After 18 weeks of gestation well formed cartilage as noticed in larger bronchi and few smaller bronchi.

Study also showed some of the smaller bronchial tubules lined by well formed cartilage plate which was identified as the secondary bronchus. After 25 weeks of gestation, well defined cartilage plate observed, and in few larger bronchial tubules the plates were seen uniting with each other. Some authors [13] described the appearance of smooth muscle fibres around the tubuli after 15 weeks of gestation and few authors described the smooth muscles in the walls of the tubuli at 23 weeks of gestation [14].

In the present study smooth muscle cells around the bronchus could be identified as a single or two layered around the bronchus with few collagen fibres at around 12-14 weeks of gestation. After 20 weeks of gestation the smooth muscle layer around the bronchus increased. The bronchi were surrounded by smooth muscle layer even when the cartilage plate was absent, which were classified as the respiratory bronchioles during later weeks of gestation.

In the present study the few bronchi were lined by columnar to pseudostratified epithelium with two to three goblet cells at few spaces with few infoldings at 11 weeks and there were so many tubule lined by columnar epithelium which was similar to a study at 16 weeks of gestation [14]. But other authors described simple columnar epithelium at the first half of fourth month [13]. Present study also identified few bronchi lined by columnar to cuboidal epithelium in the age group 20±25 weeks and some of the tubules lined with columnar epithelium, were also surrounded by cartilage plate. Few tubules lined by columnar epithelium also showed the appearance of cilia. Another author [14] described fully differentiated bronchi at 23 weeks of gestation and a few cuboidal bronchi lined by low cuboidal cells. The study [14] also described the appearance of respiratory bronchioles by 25 weeks of gestation which were lined by ciliated cuboidal epithelium. In the present study we could find few respiratory bronchioles and alveolar ducts lined by simple cuboidal epithelium. In the present study few alveolar sacs were seen developing at 25 weeks of gestation which were lined by flattened epithelium. Study done by Kate et al [14] identified alveoli at 28 weeks of gestation and more amount of primitive alveoli were seen in abundance with alveolar ducts noted at 29 weeks. In the present study, adult appearance was seen only after 30 weeks with more number of air spaces and the developing alveoli lined by squamous cells.

Palmer [6] also described a similar finding in his study in fetuses between 21st and 22nd week with 1-5 generation lined by pseudostratified ciliated columnar epithelium, 8th generation with ciliated columnar epithelium, 9-10th generation with epithelia of lower height with cilia and 11th gen-

eration with ciliated low columnar cells with few cuboidal cells.

Few serous glands were visible in the present study by 13 weeks of gestation which increased in number with increasing gestational age, but in the present study, presence of mucous glands could not be identified at any stage. The serous glands started decreasing in number after 25 weeks of gestation and were not visible by 30 weeks. This was similar to the observation by few authors [12,10,11], but the author[12] observed mucous glands also. Some authors [11] observed male superiority in gland number but other studies described no sex differences in the gland density during development. Present study could not differentiate any such sexual dimorphism in the number or density of glands, but revealed absence of mucous glands at all stages of gestation.

Present study appreciated the development of few small blood vessels by 10 weeks of gestation with increased number of vessels after 13 weeks of gestation. Few vessels were seen in the interlobular septa also. Few vessels were seen developing around the developing bronchi after 15 weeks of gestation. After 15 weeks clear distinction between artery and vein could be identified as the muscular layer around the artery increased in number. Few arterioles and capillaries started to appear after 20 weeks of gestation. Numerous blood vessels were seen surrounding the principal and few secondary bronchus. This observation was comparable with the studies done by other authors [14,5,17-20].

SUMMARY AND CONCLUSION

The presence of visceral pleura of the lungs could be established as early as 10th week of gestation which were lined by squamous epithelium.

Between 10-11 weeks of gestation the parenchyma of the lung consisted of large number of undifferentiated mesenchymal cells, with few dividing bronchial tubules. After 11 weeks of gestation few mesenchymal cells near the dividing bronchi were seen differentiating into large chondroblastic cells. The number of mesenchymal cells started decreasing proportionately after 12 weeks of gestation and became almost negligible after 30 weeks of gestation.

As the age advanced number of dividing bronchi increased, few bronchi lined by pseudostratified columnar epithelium, few by columnar and cuboidal epithelium. Few developing bronchioles were visible at 18 weeks of gestation. Alveolar ducts became visible after 20 weeks of gestation. Differentiation could be made between larger bronchi and bronchioles after 25 weeks of gestation. Serous glands were identified after 13 weeks of gestation and goblet cells started to appear after 14 weeks. The serous glands decreased after 25 weeks of gestation. No mucous glands could be identified at any gestational ages. Cilia started to appear in the epithelium after 15 weeks of gestation.

Few blood vessels appeared at 10 weeks of gestation and the number of blood vessels increased with increasing gestation with their appearance in the interlobular septa also.

Well formed cartilage plate around the principal bronchi was observed only after 18 weeks of gestation.

According to the present study, histogenetically the lungs can be considered viable and mature after 25 weeks of gestation which can result in independent survival of the fetus. This assumption is based on the fact that by this age the alveolar ducts and alveoli have started to develop and mature.

Conflicts of Interests: None

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