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Research Article

A HISTOLOGICAL OBSERVATION ON DEVELOPMENT OF HUMAN FETAL LUNG -A RETROSPECTIVE FETAL AUTOPSY STUDY

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Abstract

Background: This paper focuses on Lung histogenesis study in normal human foetuses ranging from 11 to 40 weeks of gestation age. The process of histogenesis is nothing but a series of events that occur during the development of a tissue. In this process undifferentiated cells attain full functional maturity.

Materials and Methods: The present study included 50 foetuses and abort uses received to the anatomy department from which the lung tissue was collected after they were fixed with formalin and observed for the cytoarchitecture under Light Microscopy after sectioning the lung and time sequence of appearance of various microscopic elements through H&E staining.

Results: In earlier weeks of gestation around 12 weeks mesenchymal tissue are abundant. Development Bronchial duct system well observed from 12 to 14 weeks onwards. At 14-16 weeks bronchi of varying sizes were seen. The lining epithelium in the bronchi varied between low columnar to pseudo stratified ciliated columnar and bronchioles showed simple cuboidal epithelium. The cartilage plates and interlobular septa were noted in mesenchyme around 16 weeks of gestation. The Glandular and lymphatic elements were seen developing around bronchial wall by 24 weeks. Respiratory bronchioles appeared by 24-28 weeks and their further division into alveoli by 32 weeks. Blood alveolar barrier was identified at 27 weeks of gestation. After the appearance of alveolar sac at 31 weeks of gestation, around 36-40 weeks alveoli were invaded by capillaries and hence were similar to the structure of an adult lung.

Conclusion: Abnormal or delay in embryogenesis of the lung has significant correlation with structural abnormalities. This prenatal developmental histology and morphology of human lung will definitely be a guiding light in the management of premature infants. This knowledge can be applied in lung resection surgery and during bronchoscopy for bronchoalveolar Lavage.

Key Words: Human foetal lung, Mesenchymal cells, Bronchi, Cartilages, Mucous and Serous glands.

INTRODUCTION

The lungs are the primary paired organs of the respiratory system in humans and most other animals. The two lungs are located near the backboneon either side of the heart.[1] Their function in the respiratory system is exchange of oxygen andcarbon dioxide between inspired air and the bloodstream. In humans, the main muscle of respiration that drives breathing is the diaphragm. The lungs also provide airflow that produces vocal sounds making human speech possible. Normal fresh lung is spongy in texture, floats in water and crepitates on touch. Due to absence of air within the alveoli in foetus and still born babies, lung is solid, sinks in water and does not crepitate during handling.[2,3]

Histogenesis - involves a series of integrated processes that occur during embryonic development, where in undifferentiated cells assume the characteristics of various tissues contained in human body and attain functional maturity. These undifferentiated cells comprise part of three primary germ layers- ectoderm, mesoderm, and endoderm. Process of histogenesis of lung is very significant as it determines independent survival of the foetus. This work has been taken up to comprehensively study the various aspects of histogenesis of lung in foetuses of Indian origin. This prenatal developmental morphology and histology of human lung is expected to be helpful for the management of premature infants. [4,5]

Congenital lung diseases most often from acquired developmental defects arising during gestation. Agenesis, accessory lung, ectopic lung, persistence of foetal lobulation, congenital lung cysts are some of the common developmental abnormalities. [6]

The lungs are foundational organ of the respiratory system. Basicfunction of lung is to facilitate gas exchange from the environment to blood and also helpful for tissue perfusion. Lung pathology is a significant cause of morbidity and mortality in worldwide. So, basic knowledge of histogenesis& anatomy of lung is essential for the clinician. Process of histogenesis of lung is very significant as it determines independent survival of the fetus. Although development of human lung has been widely studied and illustrated, most of the articles deal with few aspects of histogenesis. This present work was taken up for a comprehensive Histogenesis study of various aspects of lung development in foetuses ranging from 14 weeks to 40 weeks. Our study is significant for the neonatologist in the treatment of premature infants.

AIMS & OBJECTIVES

To observe the histological development of human foetal lung & its implication in cadaveric transplant & treatment of premature infants.

MATERIALS AND METHODS

This study about histogenesis of the lung was carried out in the histology laboratory of the Department of Anatomy at KAPV Government Medical College, Trichy. This study is a hospital based, observational and cross- sectional study. Study was done in association with the Department

of Obstetrics &Gynaecology, Mahatma Gandhi Memorial Hospital, Trichy from November 2020 to June 2022 on fifty aborted human foetuses without obvious congenital anomalies.

Whole lung specimens from 50 human foetuses of gestational age from 11 to 40 weeks of gestation were obtained. All the foetal lung specimens were examined and details recorded. The foetuses were collected from the labour ward after receiving the informed consent from the mother and legal guardians, either after spontaneous abortion or therapeutic legal abortions. Gestational age was calculated from LMP (last menstrual period). The collected foetuses were weighed using digital weighing scale and the gestational ages were confirmedby calculating CRL (crown rump length) using the inch tape &antenatal ultrasound records. Foetuses were immediately fixed in 10% neutral buffered formalin The foetuses were kept in formalin for 10-15 days. The lungs were studied after the dissection of fetuses. All the specimens were categorized into 5 groups based on gestational age. (A,B,C,D,E,) CRL of the 50foetuses (male 22 and female20) was noted beside the gestational age. [Table 1 & 2] The lung specimen were categorized into 5 groups (A,B,C,D, E) of 11-15 weeks(A group), 16-20 weeks (B group), 21-25 weeks (C group), 26-30 weeks (D group), 31-term (E group), according to the gestational age. From each group a sample of lung specimen was processed for histological examination. All the sections were taken on Rotatory microtome of 5-7 microns followed by embedding & paraffin block preparation. Staining was done with Haematoxylin and Eosin (H&E). Each section was observed for pulmonary maturation under light microscope and photomicrograph were taken relevantly

Inclusion criteria:

- Foetuses with informed consent of parents.
- Foetuses of spontaneous abortion, medical termination of pregnancy and still born
- Foetuses without congenital malformation.

RESULTS

Table1.Distribution of foetus in to groups

Groups	No.of foetuses	Gestational Age	Weight of fetus in Gms	Crown rump length
GroupI	10	11-15weeks	34-76	110-125mm
GroupII	10	16-20weeks	81-200	130-180mm
GroupIII	10	21-25weeks	198-214	190-210mm
GroupIV	10	26-30weeks	225-634	220-250mm
GroupV	10	31weeks –term	666-1940	260-400 mm

Group I: (11th-15thweek):

At 13 weeks of gestational age, the foetal lung specimen showed more amount of mesenchymal cells which were polygonal in shape with rounded nuclei (Figure 1). Few numbers of mucous glands were present. Dividing bronchi were lined by simple columnar epithelium (Figure 2). Cartilage plates were

not present. Blood vessels were also observed.

At late 13 weeks of gestational age, clusters of chondroblasts were seen around the dividing bronchi. Pale staining ill-defined connective tissuebronchial septa were seen dividing the lung parenchyma into lobules. Fewlayers of smooth muscles were present around the dividing bronchi. Few blood vessels were identified.

At 15thweeks ofgestational age, fewnumberofgoblet cells wereseen in betweentheepithelialcellsliningthebronchi.Meshworkofelasticfibreswere seen around the walls of blood vessels. (Figure 9)

Group II:(16th-20thweek):

At 16th weeks of gestational age, cartilage plates with few cell nestswere seen in the slide. I was able to observe that the lung appeared like a compound racemose gland, showing the features of pseudo glandular phase.

Pale staining connective tissue inter lobular septa were seen running from the pleura which was lined by flattened cells. These septa divided the lung parenchyma into number of lobules at 16 weeks of foetus. (Figure 3, 9)

At17th weeks of gestational age, condensation of mesenchymal cells was seen around the dividing bronchi which gradually decreased in amount in between the bronchial tubes. Numerous bronchi with various types (columnar, cuboidal, pseudostratified ciliated) of lining epithelium were observed.

The proximal bronchi were lined by pseudo stratified ciliated columnar epithelium and the distal bronchi showed simple columnar epithelium with cilia. (Figure 12)

At 20th weeks of gestational age, I observed the blood vessels around the dividing bronchi. Blood vessels were lined by flat endothelial cells and their walls showed polygonal cells and few spindles shaped cells. In this group the difference between artery and vein was delineated. (Figure 11)Mucous glands were identified during this week of gestation. Up to group II (20 weeks), I was not able to appreciate well-defined bronchioles. (Figure 4)

Group III (21-25weeks):

At 21 weeks of gestational age, well-defined secondary and tertiary bronchi surrounded by cartilage plates were observed and the smooth muscle layer around the bronchi were increased.

At 23 weeks of gestational age, the lamina propria of bronchi showed serous glands and blood vessels were present between the lining epithelium and cartilage plate. Few alveolar ducts and well- defined cartilage plates were visible. Blood vessels were also seen in increased number in the inter lobular septa which contained more collagen and some elastic fibres. Bronchi had folded columnar epithelium with irregularly arranged nuclei. (Figure 5,6)

At 25 weeks of gestational age, respiratory bronchioles lined by ciliated cuboidal epithelium were seen more distinctly. Lobular structure was not well defined due to the rapid division of the respiratory part of lung. The walls of respiratory bronchioles were interrupted at intervals by thin saccular out pouching which would form the future alveoli.

Group IV (26-30weeks):

At 26 weeks of gestational age, primitive alveoli were present. The capillaries were exposed into

the air space and some of them invaded the epithelium. In this group we were able to differentiate bronchi, bronchiole, true alveoli which were lined by flattened epithelium and surrounded by capillaries and smooth muscle layer.

At 27weeks of gestational age, terminal sacs with thin cuboidal epithelium, capillaries beginning to bulge into the alveoli, intimate contact between epithelial and endothelial cells establishing the blood air barrier was observed. The foetus born at this stage would be able to survive independently. Function of blood-air barrier is gas exchange through diffusion. Very few mesenchymal cells were seen in the lung parenchyma and the number of serous glands in lamina propria decreased. (Figure 10)

Group V (31 weeks to up to term):

At 31 weeks of gestational age, clusters of alveolar sacs were seen opening from the alveolar ducts. The wall of the alveoli was thinned out and lined by simple squamous cells supported by fine smooth muscle fibres.

At 35 weeks of gestational age, I could appreciate the features of adult lung in foetal lung. All respiratory parts were well developed. The bronchi were lined by pseudostratified ciliated columnar epithelium, bronchioles lined by ciliated columnar or cuboidal epithelium, alveolar sacs by flattened cell lining and squamous epithelial lining of alveolar ducts. More number of vessels appeared in the interlobular septa. No glands were visible in the nearing term foetus and also mesenchymal cells were negligible. Cartilage plate were well defined around the bronchi. Smooth muscle covered the alveoli. (Figure 7,8)

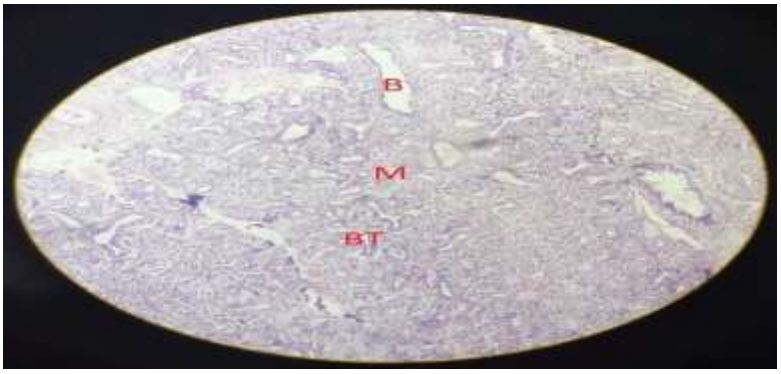

Fig.1.13weeks-10X: B-Bronchus, M-Mesenchymal cells, BT-Bronchial tubes. No cartilage

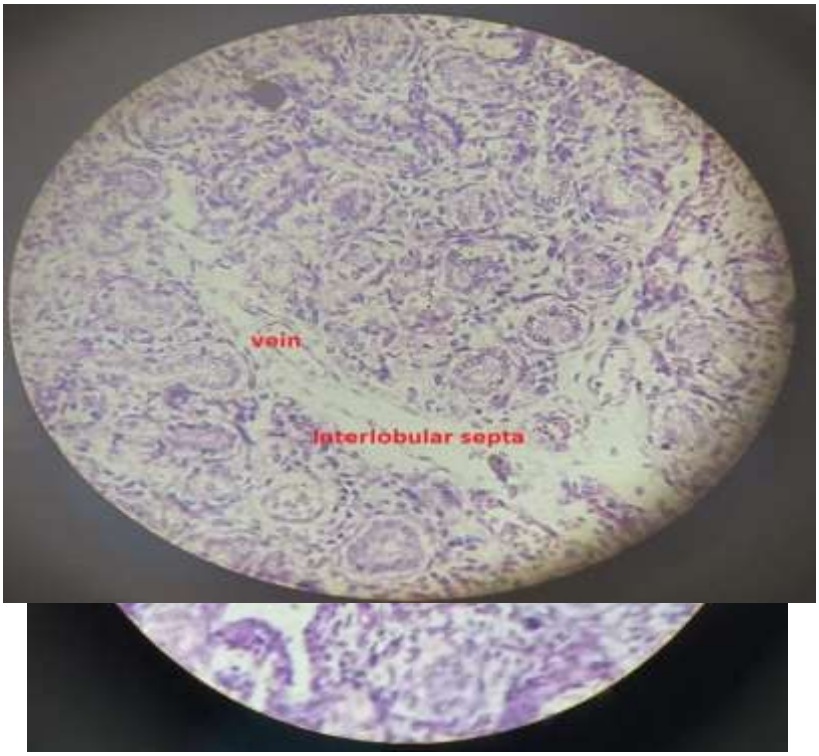

Fig.2.13weeks-40X: B-Bronchus,MT-Mesenchymaltissue,BT-Bronchial tubes.

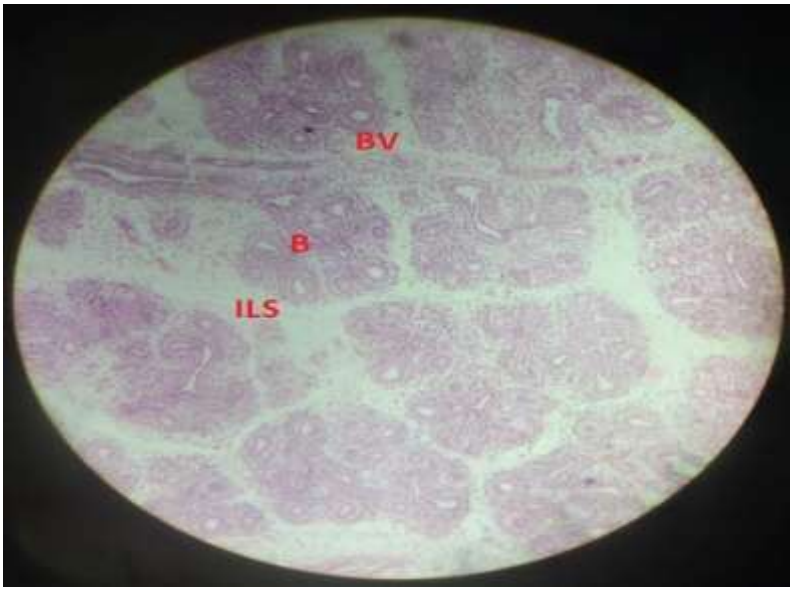

Fig. 3. 16 weeks-10X: B-Bronchus, ILS-Interlobular septa, BV-Blood vessel in ILS.

Fig. 4. 16 weeks-40X: B-Bronchus, ILS-Interlobular septa, BV-Blood vessel

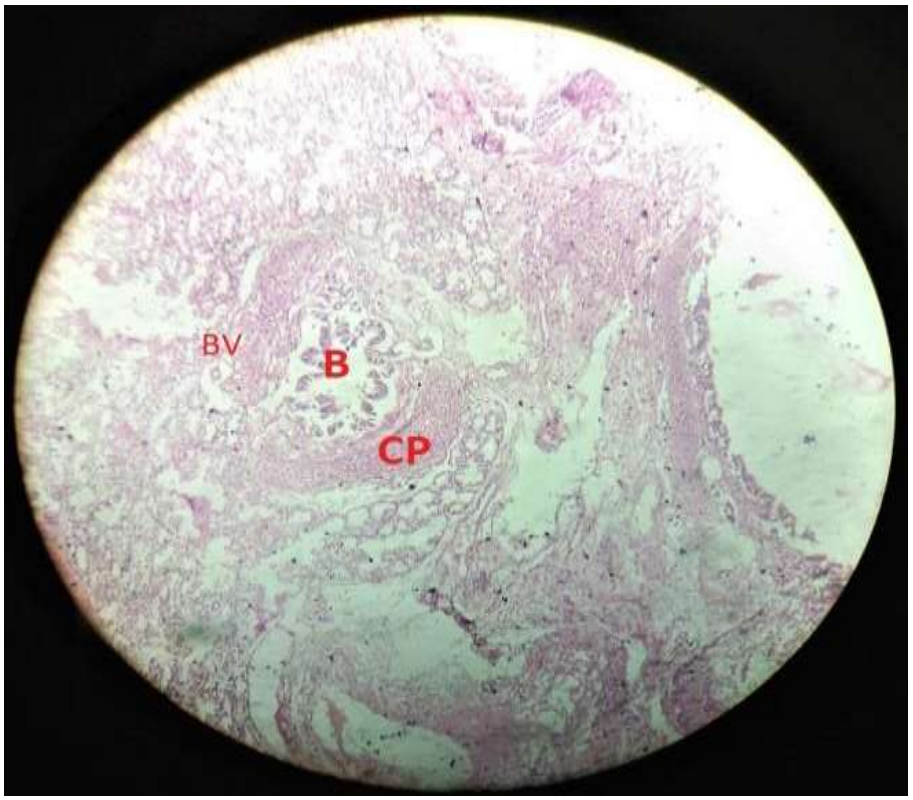

Fig.5.23weeks-10X:B-Secondary Bronchus,CP-Cartilageplate, BV-Blood vessels

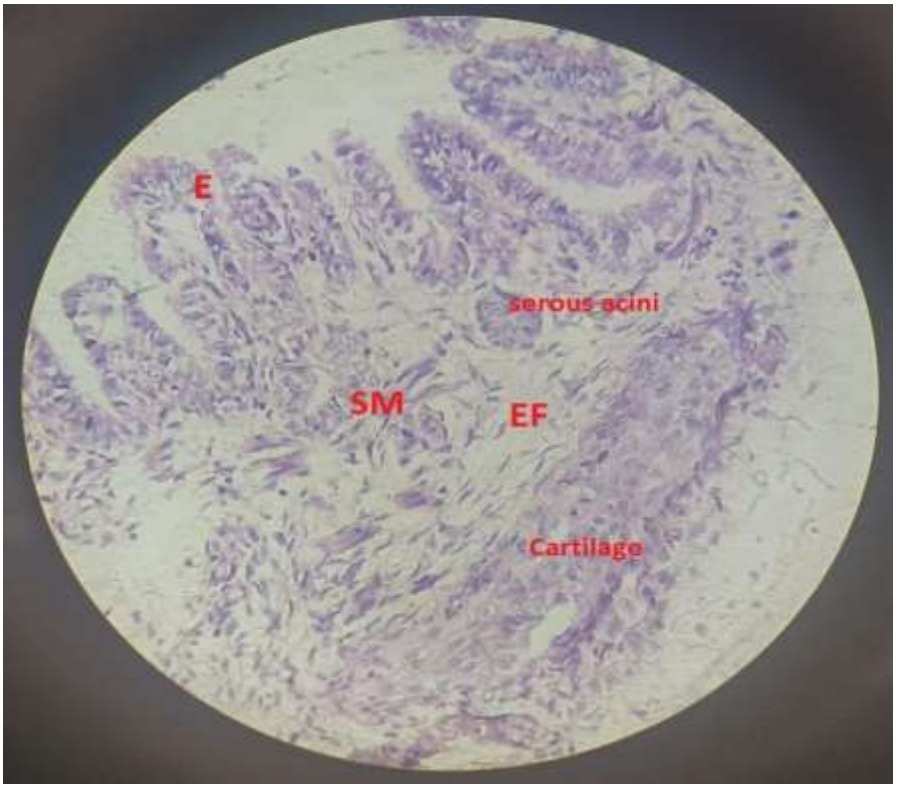

Fig.6.23 weeks-40X:E-Bronchialepithelium,SM-Smoothmuscle, EF-connective tissue elastic fibres.

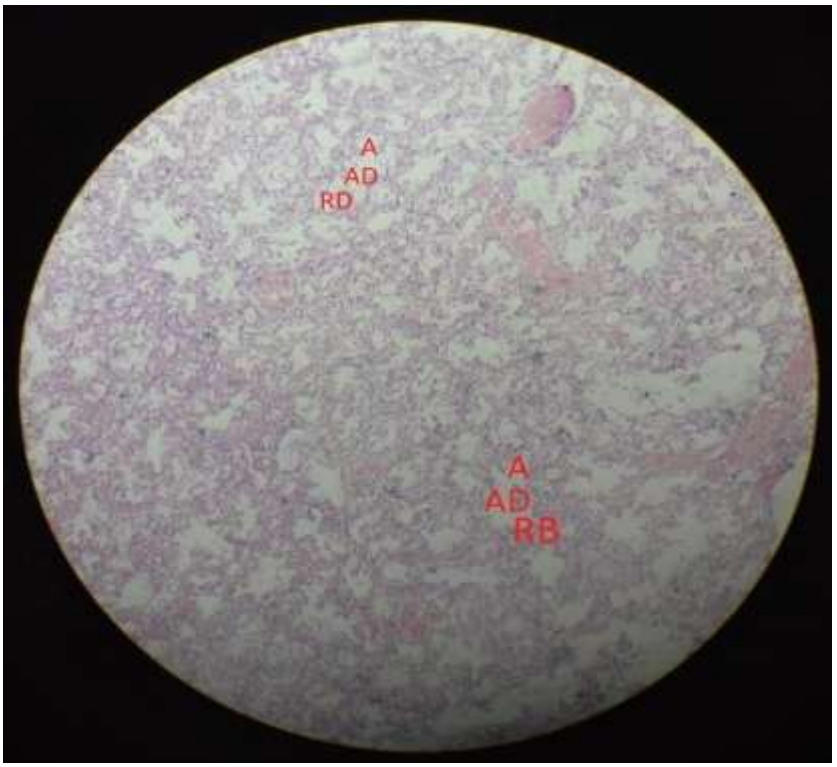

Fig.7.36weeks-10X:RB-RespiratoryBronchioles,AD-Alveolar duct, A-Alveoli.

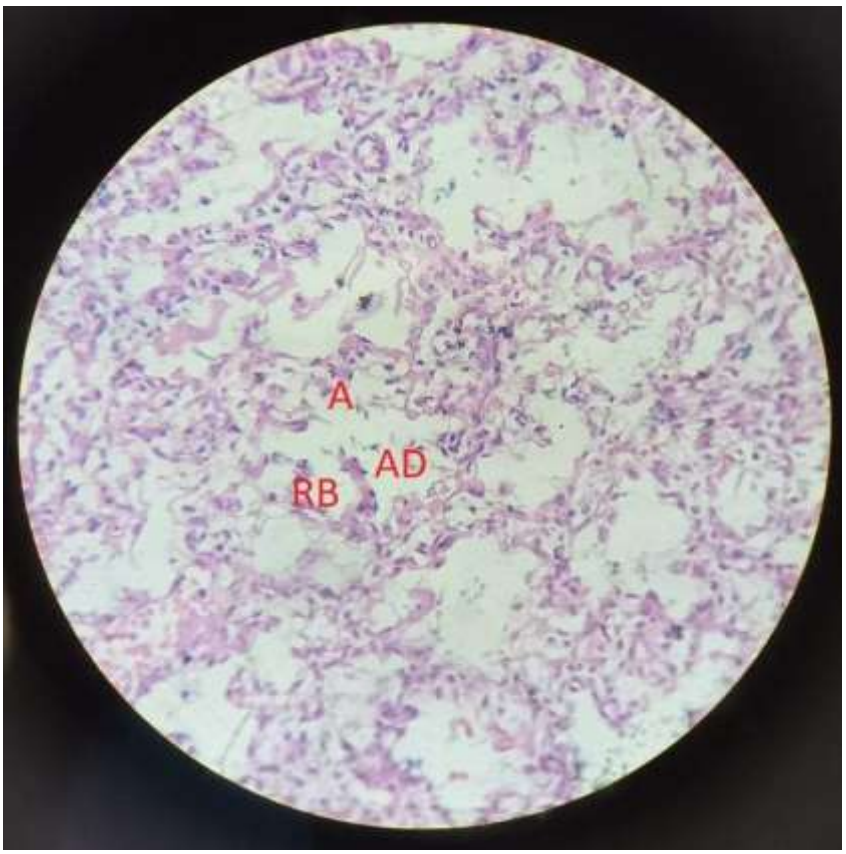

Fig.8.36weeks-40X:RB-RespiratoryBronchioles,AD-Alveolar duct, A-Alveoli.

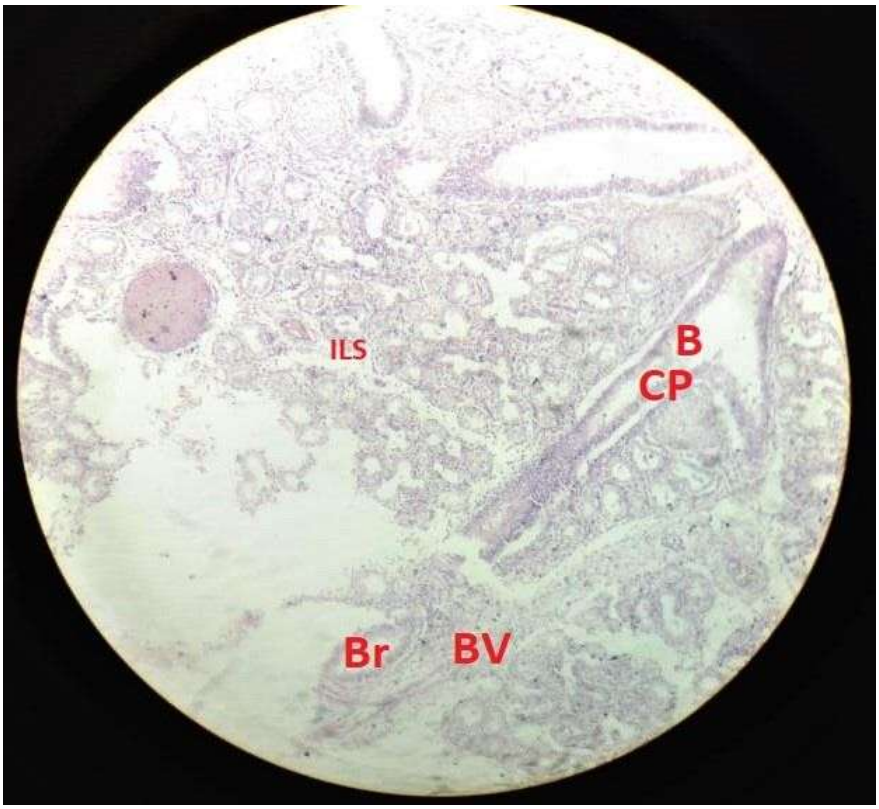

Fig.9.15 weeks -10X B-Bronchus,Br-Bronchioles CP-Cartilageplate, BV-Blood vessels, ILS-Interlobular septa.

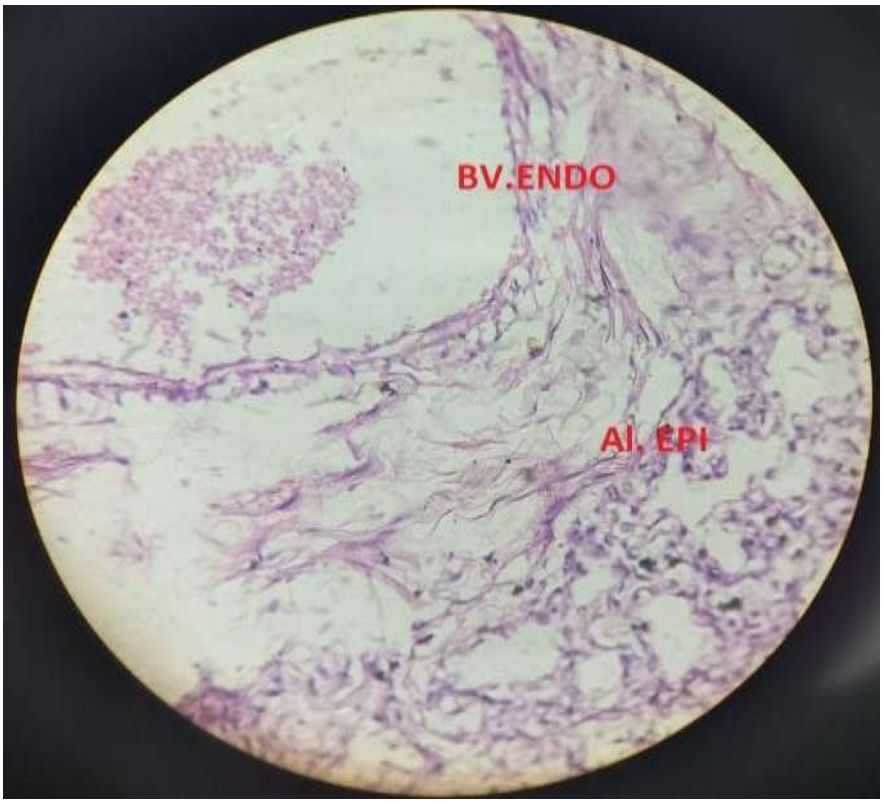

Fig. 10. 27 weeks -40X Blood air barrier, BV.ENDO-Endothelium ofblood vessels, Al.EPI-Alveolar epithelium

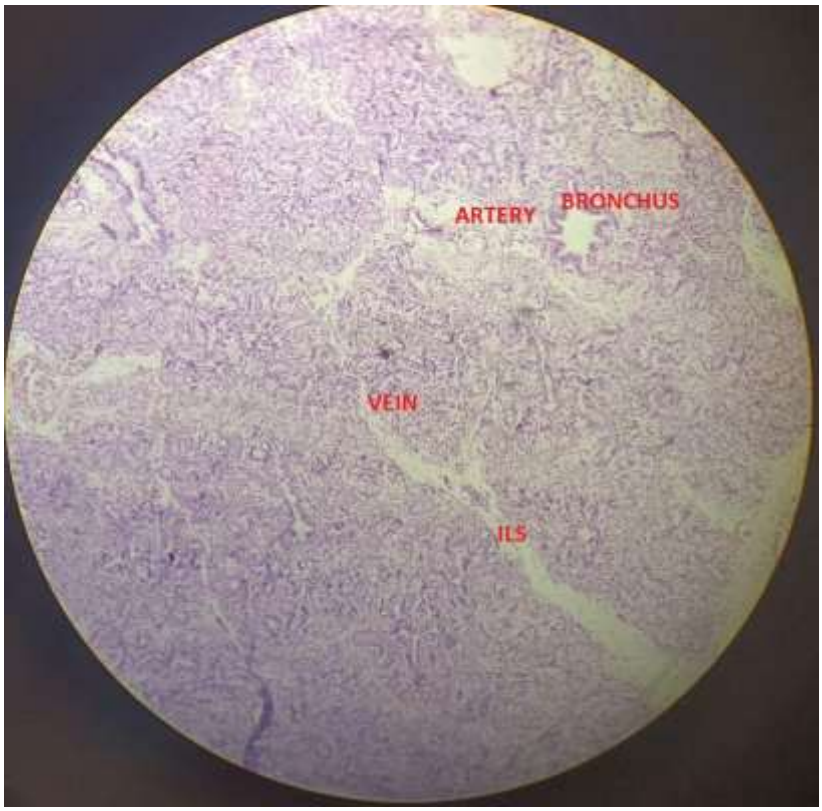

Fig.11.18Weeksofgestation-10Xshowedwelldistinctionbetween artery and vein.

Fig.12.17weeks-40x showed pseudostratified ciliated columnar epithelium

DISCUSSION

MESENCHYMAL CELLS

In the present study, at 13th weeks of gestational age, foetal lung specimen shows more amounts of mesenchymal cells which is polygonal cell with rounded nuclei. At 17th weeks of gestational age, condensation of mesenchymal cells is seen around the dividing bronchi and gradually decreased in their amount in between the tubes. At 27weeks of gestational age, very few and almost absence of mesenchymal cells was seen in the lung parenchyma.The present study findings are similar to Tanaka et al (1980) [7] and Jessy J P (2019),[8] but delayed presentation according to SanjuktaSahoo in 2018. [9]. More amount of mesenchyme was seen at 8 weeks in SanjuktaSahoo, 10 weeks in Jessy J P, 12 weeks Tanaka et al, 13 weeks in present study. Condensation of mesenchymal cells were seen at sixth month of gestational age in Tanaka et al, after 15 weeks of gestational age in JessyJP,in present study at 17 weeks of gestational age. Absence of mesenchymal cells was seen inTanaka et al at seventh month of gestational age, after 20weeks of gestational age in Jessy JP, in present study at 27 weeks of gestational age.

DEVELOPMENTOFBRONCHIANDBRONCHIOLES

In the present study, in 15th week of gestation bronchi were lined with simple columnar epithelium with few goblet cells. The proximal bronchi were lined by pseudo stratified ciliated columnar epithelium and the distal bronchi showed simple columnar epithelium with cilia at 17th week of gestation. At the 23rd week of gestational age, bronchus showed folded columnarepithelium with irregularly arranged nuclei. At 25th week of gestational age, respiratory bronchioles were seen more distinctly and lined by ciliated cuboidal epithelium.

Similar findings were noted in study done by Jeffery etal, wherein respiratory bronchioles were seen branching and at its end, were alveoli lined by flattened epithelium. [10]

At 26th week of gestational age, we were able to differentiate bronchi, bronchiole, true alveoli lined by flattened epithelium and also surrounded by capillaries and smooth muscle layer. The present study findings were similar to the studies done by Tanaka et al, JessyJp, and Deepali. R. Kate.[7,8,4]

CARTILAGEANDSMOOTHMUSCLE

In the present study, in 13 weeks of gestational age, cartilage plateswere not able to be appreciated. After 13th week of gestational age, cluster of chondroblasts were seen around the dividing bronchi. At 16 weeks ofgestational age, cartilage plates with few cell nests were seen in the slide. According to Edward et al,[11] by 4th week of IUL cartilage was in the trachea and extended to lobar and segmental bronchi by 12-16 weeks. At 21 weeks of gestational age, well-defined secondary and tertiary bronchi surrounded by cartilage plate was observed and the smooth muscle layer around the bronchus increased. The present study finding correlates with Bucher U and Reid L[12], and SatheshNaik et al, [13] closely corresponding toJessy JP, delayed presentation compared to SanjuktaSahoo (2018) and early presentation compared to Deepali. R. Kate (2013).

BLOOD VESEELS AND INTERLOBULAR SEPTA

In the present study, few blood vessels were identified at late 13 weeks of gestational age. Meshwork of elastic fibres were seen around the walls of blood vessels during 15th weeks of gestational age. Pale staining connective tissue inter lobular septa were seen running from the pleura which was lined by flattened cells. These septa divided the lung parenchyma into number of lobules in 16 weeks foetus and few blood vessels were identified in the septa. Reid and Hislop,[14,15] observed preacinar blood vessels at 16-17 weeks of gestation and intracinar vessels developed later with the development of respiratory airways .

At 20 weeks of gestational age, blood vessels were lined by flat endothelial cells and their walls showed polygonal cells (invades mesenchyme) and few spindles shaped cells (Smooth muscle layer) and the difference between artery and vein was delineated. At 23 weeks of gestational age, the lamina propria of bronchi showed serous glands and blood vessels were present between the lining epithelium and cartilage plate. The capillaries were exposed into the air space and some of the invaded the epithelium in the 26th week of gestational age. At 27 weeks of gestational age, terminal sacs with thin cuboidal epithelium, capillaries beginning to bulge into the alveoli and intimate contact between epithelial and endothelial cells establishing the blood air barrier were observed. At 35 weeks of gestational age, a greater number of vessels appeared in the interlobular septa. The findings of present study were not corresponding with other studies as delayed presentation according to Sanjukta, JessyJp; early development according to Tanaka et al, Deepali, Sathesh Naik,[13].

MUCOUS AND SEROUS GLANDS

In present study, we observed that at 20 weeksof gestation mucous glands were present. At 23 weeks of gestational age, the lamina propria of bronchi showed serous glands and also mucous glands were reduced. The number of serous glands in lamina propria decreased at 27weeks of gestation. No glands were visible in the nearing term foetus. The present study findings were correlate with studies done by Bucher u et al and Tos M. According to them serous glands started decreasing in number after 25 weeks of IUL and not visible by 30 weeks.[16,17]

CONCLUSION

According to the present study of histogenesis of human foetal lung, the viability and maturation of the lung was achieved during 27 weeks of gestation. Demonstration of surfactant producing cells and lamellar bodies could not be demonstrated by light microscopic study. The lungs are foundational organ of the respiratory system. Basic function of lung is to facilitate gas exchange from the environment to blood and also helpful for tissue perfusion. Lung pathology is a significant cause of morbidity and mortality in worldwide. So, basic knowledge of histogenesis& anatomy of lung is essential for the clinician. This prenataldevelopmentalhistologyandmorphology ofhumanlungwilldefinitely be a guiding light in the management of premature infants. This knowledge can be applied in lung resection surgery and during bronchoscopy for bronchoalveolar lavage.

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