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Original Research Article

Histogenesis of human fetal liver from 12 weeks to 36 weeks of gestation

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ABSTRACT

Background: Fetal human liver developmental morphology is very important for diagnosis of congenital anomalies. The development of human liver is an ongoing process which begins after fertilization and continues into post-natal life. Liver is one of the organs of gastrointestinal tract having both exocrine and endocrine functions and capable of regeneration. Not only adult liver, the fetal liver is also an important organ with Haemopoietic functions. Pediatric liver transplants accounting for 10-15% of all liver transplants worldwide occur due to congenital defects.
Methods: The study is conducted on 50 livers procured from 50 aborted fetuses (34 males and 16 females) ranging from 12 to 36 weeks of gestation .After confirming their age through CRL they were grouped. Then processed to form sections and stained with hematoxylin and eosin and seen under light microscope.
Results: Histogenesis and development of human liver in prenatal period was observed under the microscope at various gestational age groups which was confirmed with lobular pattern, portal triad structures ,central vein and sinusoids showing fetal haemopoietic function which regress towards the term.
Conclusions: The present study gave emphasis on all physical parameters and a detail histogenesis and development of human liver in prenatal period from 12 to 36 weeks of gestation. This work agreed with previous studies.

Keywords: Central vein, Crown rump length, Haemopoisis, Hepatocytes, Histogenesis, Liver, Portal triad

INTRODUCTION

Liver is the largest gland in human body present in abdominal cavity. In fetal life liver is an important site of haemopoisis hence it is essential for all stages of life.[1] The main etiological factors behind liver transplantation are congenital liver defects. A better understanding of embryonic liver development would provide important treatment and preventive strategies for pediatric liver disease. It develops as ventral growth from gut endoderm in the region of anterior intestinal portal during 10-12 weeks of gestation.[2]

Ham and Cormack said that liver is a unique and the parenchymal cells(hepatocytes) that produce exocrine also elaborate endocrine secretion.[3] About 80% of liver volume and 60% of its cell population is formed by hepatocytes. Transport of nutrients across the hepatocytes is a key regulatory step in fetal growth and development.

Researchers have attempted to generate hepatocytes from adult, fetal liver and embryonic stem cells. These efforts particularly the recent success with embryonic stemcells, have been greatly facilitated by understanding embryonic liver development.[4]

As it is an important gland in prenatal and postnatal life, the present study of microscopic structure of human fetal liver at various gestational age groups has been done. This study may provide an insight to distinguish the

normal and pathological changes occurring in the liver during prenatal period.

METHODS

The present study was carried out in the Department of Anatomy, KAMSRC, LB Nagar; Hyderabad (Telangana), India. The materials of the present study were collected for a period of one year (October 2018 to October 2019).

Inclusive criteria

Total 50 fetuses taken were unclaimed, spontaneously aborted or still born ranging from gestational age 12 weeks to 36weeks (34 males and 16 females).

Exclusive criteria

The twins and the fetuses with congenital abnormalities were excluded. These fetuses were obtained from Department of Obstetrics and Gynecology, KAMSRC, LB Nagar; Hyderabad (Telangana), India.

Table 1: Gestational age can be estimated by crown rump length(CRL) in millimeters (mm) according to the human embryology textbook by hamilton, boyd and mossman.

Age (in lunar months /weeks)	Crown rump length in mm
3months (12 weeks)	54-56mm
4months (16 weeks)	98-102mm
5months (20 weeks)	148-152mm
6months (24 weeks)	198-201mm
7months (28 weeks)	228-232mm
8months (32 weeks)	264-266mm
9months (36 weeks)	298-302mm
10months (40 weeks)	334-336mm

Table 2: Gestational age can also be estimated in centimeters (cm) according to the standard chart.

Gestational age (weeks)	BPD(cm)	HC(cm)	AC(cm)
12-16	2.1-3.5	7.0-12.4	5.6-10.5
17-20	3.9-4.9	13.7-17.5	11.7-15.2
21-24	5.2-6.1	18.7-22.1	16.4-19.7
25-28	6.4-7.2	23.2-26.2	20.8-24.0
29-32	7.4-8.2	27.1-29.6	25.0-28.0
33-36	8.4-9.0	30.4-32.4	29.0-31.8

Methodology of this study is the materials for present study were 50 fetuses (34 males and 16 females) with gestational age ranging from 12- 36weeks. The known gestational age of fetuses was then correlated with the respective CRL according to Textbook of Embryology by Hamilton, Boyd and Mossman (Table 1) with an osteometric board having mm scale. Gestational age can also be estimated in cms by a standard chart. (Table 2). It helped to confirm their registered gestational age, to rule out any IUGR and conveniently grouped them into 6 groups according to their gestational age (Table 3).

Table 3: Groups of fetuses according to their gestational age.

Groups	Gestational age in weeks	Number of fetuses
A	12-16weeks	5
B	17-20weeks	10
C	21-24weeks	9
D	25-28weeks	11
E	29-32weeks	8
F	33-36weeks	7

The fetuses were embalmed and then kept in 10% formalin for 24 hours. The Livers were dissected. Next after embedding the paraffin blocks were prepared. Seven micrometer sections were taken with rotary microtome and stained with hematoxylin and eosin. These were observed under the microscope and then micro-photographed.

This process was followed after taking permission from the Kamineni Institutional Ethics Committee (Registration No. ECR/58/Inst/AP/2013/RR-16) at KAMSRC and Kamineni hospitals, LB Nagar, Hyderabad, India.

RESULTS

Group A (12 - 16 weeks)

The section shows Mesenchymal cells having an irregular anastomosis with sinusoids entrapped between the anastomosing cords. The Parenchymal ells are arranged as irregular clumps and cords (Figure 1 and 2).

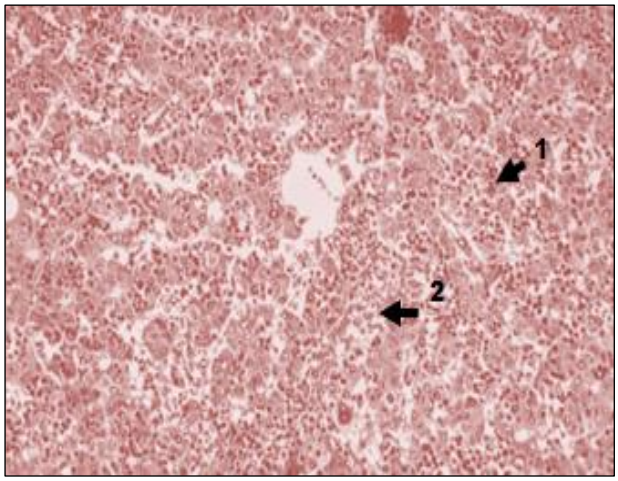

Figure 1: Photomicrography 10x H and E (1): parenchymal cells (2): Hematopoietic cells.

At places hematopoietic cells were observed in sinusoids. At the same time Central vein and Portal triad were not observed clearly.

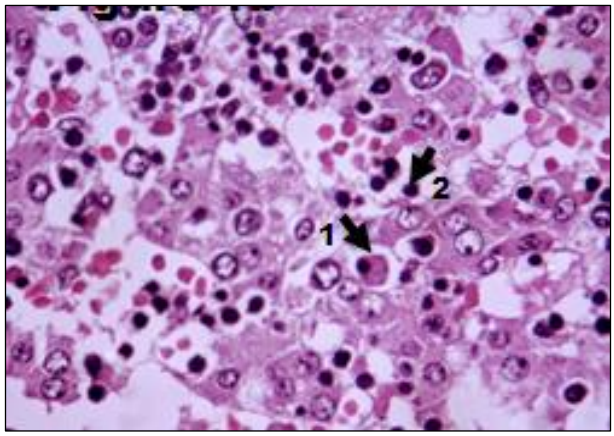

Figure 2: Photomicrography 40x;H and E; (1): hematopoietic cells (2): parenchymal cells.

Group B (17-20 weeks)

The Parenchymal cells of hepatocytes are in the form of irregular anastomosing cords. The Lobular pattern was not defined, and primitive blood cells were identified in sinusoids. The Central veins were clearly seen at this stage. The Portal triads (tributary of Portal vein, branches of Hepatic artery and Bile ductule) were surrounded by connective tissue during this gestational period (Figure 3 and 4).

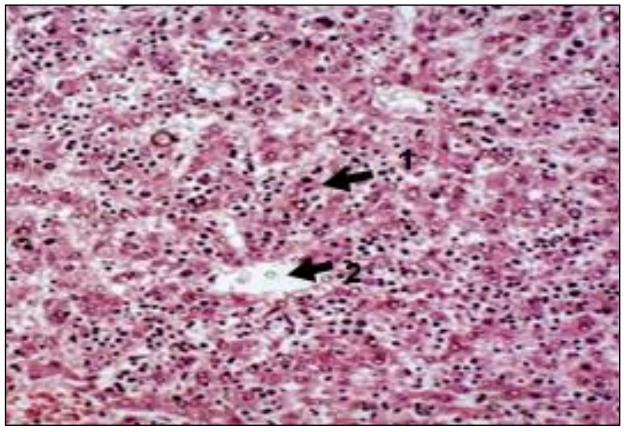

Figure 3: Photomicrography 10x;H and E; (1): Lobular pattern (2): Central vein.

Group C (21-24 weeks)

The histological structure is more or less similar to the previous stage except that Portal triad were well defined. The Hepatic lobule was very much demarcated (Figure 5).

The Haemopoisis was dominating showing haemopoietic function of liver during fetal life. The hepatocytes were arranged in a radiating fashion from the central vein.

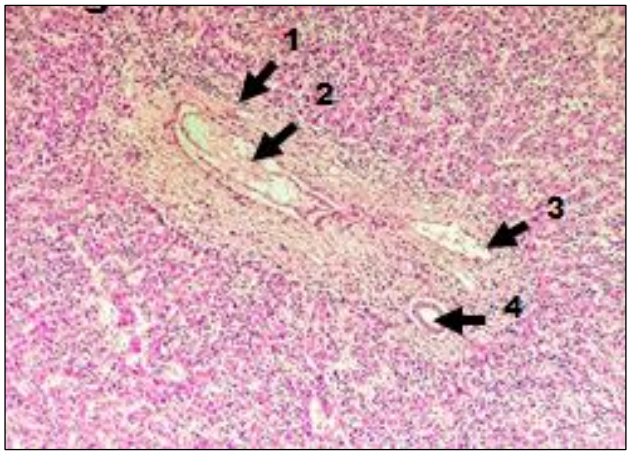

Figure 4: Photomicrography 10x; H and E; (1): connective tissue, (2): Portal vein, (3): Hepatic artery, (4): Bile duct.

The Sinusoids were clearly seen between the hepatocytes and filled with haemopoietic cells.

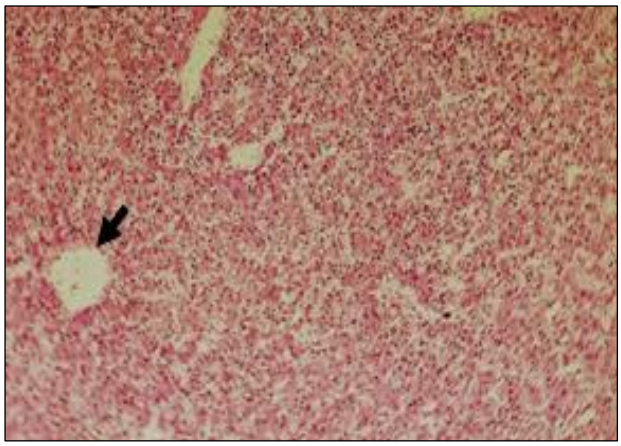

Figure 5: Photomicrography 10x;H and E; hepatocytes are arranged around central vein.

Group D (25-28 weeks)

The dominating haemopoiesis has become focal because of bone marrow haemopoiesis may have started. There are areas showing vacuoles that represent glycogen deposits. Simultaneously well-developed hepatic lobular pattern around the central vein was observed and plates of hepatocytes seen radiating from central vein (Figure 6).

Group E (29-32weeks)

All the features are well defined. The haemopoietic activity was very much reduced. Plates of hepatocytes radiating from central vein were well appreciated with clear Lobular pattern (Figure 7 and 8).

Glycogen vacuolization was seen as fine white specks indicating high glycogen activity which is a feature of developing liver towards the term.

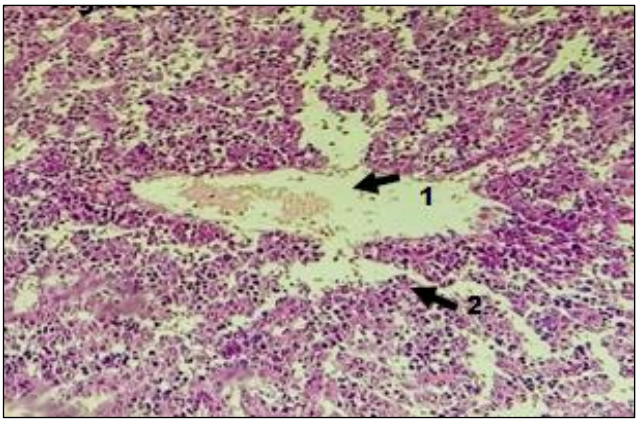

Figure 6: Photomicrography 10x; H and E; (1): Central vein (2): Hepatocytes radiating to central vein.

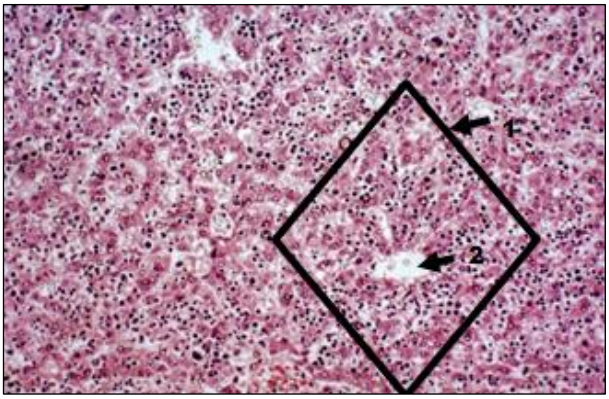

Figure 7: Photomicrography 10x; H and E ; (1): Lobular pattern (2): Central vein.

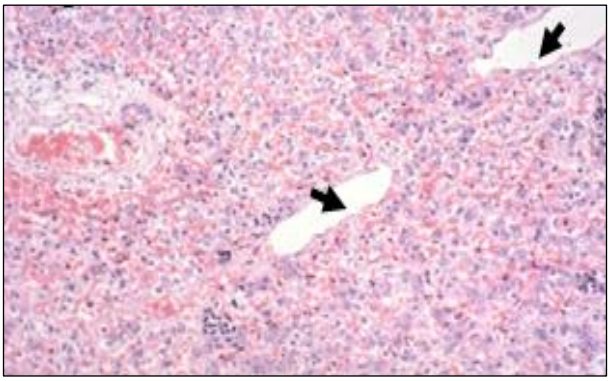

Figure 8: Photomicrography 10x; H and E; Glycogen deposits.

Group F (33-36weeks)

Clear differentiation of hepatocytes and hepatic lamellae were observed indicating well defined lobular pattern. Haemopoiesis was further reduced by absence of primitive blood cells in hepatic sinusoids. Glycogen deposits were increased enormously. The Radiating cords of the hepatocytes surrounding the central vein forming a hepatic lobule with 2-3 portal triads well recognized at periphery of the lobule (Figure 9).

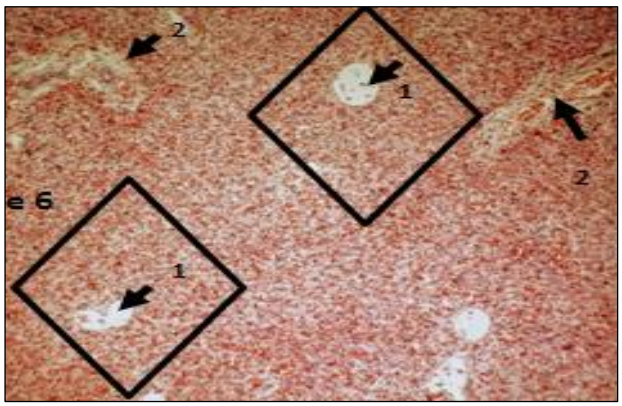

Figure 9: Photomicrography 10x;H and E; lobular pattern (1): Central vein (2): Portal triad.

DISCUSSION

Liver transplantation is an accepted treatment for patients with acute liver failure, liver based metabolic disorders and advanced cirrhosis which leads to life threatening liver failure for which organ transplantation is the only clinical option. The hepatic tissue made from stem cells holds unlimited source of transplantation. Alternatively, fetal and neonatal livers are being explored as a potential cell source.[5,6]

The structural unit of the liver is the hepatic lobule. It was first reported by Wepfer in 1664, later by Malphigi in 1666. Hepatic lobule with its central vein as a hexagonal structure was defined by Kierman. He also defined boundaries are clear by the connective tissue in only few species like pig and it is sparse in humans except around the portal triads.[7,8]

The liver as a gland with its hepatocytes is the most versatile cell in body. It is a cell with both exocrine and endocrine functions. It is the metabolic center of vertebrates and expresses various metabolic enzymes for carbohydrate metabolism and detoxification.

In order to perform its functions efficiently, the liver possesses a highly organized and complex tissue structure composed of :

- Hepatic parenchymal cells,
- Presence of haemopoiesis,
- Organisaton of plates of hepatocytes ,
- Appearance of central veins and sinusoids,
- Formation of portal triad and classical liver lobule.
- Glycogen deposits.

Elias described the cord like arrangement of hepatocytes that branch and anastomose enclosing sinusoids between them.[9] He Suhan described the lobular formation of liver

starts between 9-12 weeks of gestation.[8] According to Zamboni et al haemopoisis in liver becomes fully established around 3rd month of intra uterine life.[10]

Potter and Craig have observed Haemopoietic activity in liver throughout the fetal period of gestation.[11]

Hamilton and Mossman stated that, haemopoisis begins very early in developing liver and reaches its peak at 6th and 7th month of fetal life and regresses up to full term.[12-14]

This study observed regarding Haemopoietic activity in fetal liver is in accordance with the all previous authors stated above. The changes in the organization of plates of hepatocytes in this study were compared with number of authors.

Balis JU et al, suggested that liver plates were formed before the development of sinusoids.[15] Potter and Craig11 reported that liver differentiates into plates of cells around 4th week of gestation. They also observed radiating cords of hepatocytes and Kupffer's cells along with central vein in the specimens from 28 weeks onwards. Hamilton and Mossman stated hepatic cords of cells are first solid but acquires lumen soon after.[12]

The current study is in accordance with Balisetal, Potter and Craig , Hamilton Boyd et al, works.

In this study the appearance of central vein and portal triad were observed around 17-20 weeks and compared with various authors in literature like Desmet VJ and Aradhyula Himabindhu et al.

Desmet VJ in his study has observed that central vein starts appearing at 16th to 17th week of gestation. Portal triad can be identified with clear cut architectural pattern around 20-21st week of gestation.[16]

Whereas Aradhyula Himabindu and Battam Narasinga Rao in their studies showed central vein with radiating hepatocytes and also portal triad around 12 weeks of gestation.[13]

The dominating haemopoisis, vacuoles representing the glycogen deposits were observed around 26 weeks of gestation in Aradhyula Himabindhu studies.[13] The hepatocytes of fetal liver at time of birth showed glycogen vacuolization of epithelial cells which is a feature of fetal liver of last weeks of gestation (Marie. et al,).[17]

The present study showed dominating haemopoisis during 21-24weeks of gestation and glycogen deposits appear later around 29-32 weeks of gestation which did not coincide with Aradhyula Himabindhu and Marie et al, studies.

Dr. HashmiIntkhab C. et at, in his studies identified clearly classical liver lobule with a clear cut architectural pattern from 20 weeks onwards and there after the size of lobule increased.[18]

Terada and Nakanuma stated that ductal plate was present around portal veins at the hepatic hilum and at 10 weeks of gestation, biliary cells budded from the plate and bile ductules were seen around portal triad.[19]

Godlewski et al, elucidated that around 60 days bile ducts developed in peri-portal connective tissue which is organized to form the portal triad.[20]

In the present study, the portal triadwith all the 3 structures (portal vein tributary, hepatic artery branch and bile ductule) were observed clearly around 17-20 weeks of gestation.

This study showed all structures of classical liver by 22nd week, the size of lobule increased thereafter. Lobular pattern of hepatocytes was demarcated around 21-24th weeks of gestation. A well-defined hepatic lobule with radiating hepatocytes around the Central vein was seen around 28-32weeksof gestation in this study.

At term 36 weeks of gestation authors found the classic lobular pattern with glycogen deposits and reduced haemopoisis.

The current study was done on 50 foetuses (34 male and 16 female) with gestational age ranging from 12-36weeks. The findings of this study were found to be within ranges of findings of other authors and also in the literature.

CONCLUSION

The present study of histogenesis of liver in human fetuses of various gestational ages is characterized by hepatocytes lobular formation , appearance of central vein , portal triad , haemopoietic function followed by glycogen deposits were with agreement with literature . Delay in histogenesis leads to histopathological and developmental abnormalities. This knowledge is important for anatomist, pathologist, pediatricians, gastroenterologists in their routine clinical procedings.

New challenges are needed to improve hepatocyte transplantation efficiency and simultaneously new approaches to decrease the impact of immune response against transplanted cells hence improving liver based metabolic disorders.

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Ethical approval: The study was approved by the Institutional Ethics Committee (Registration No. ECR/58/Inst/AP/2013/RR-16)

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