Original Article

Histogenesis and Gross Morphometric Evaluation of the Human Foetal Liver: A Descriptive Observational Study

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Abstract

Background: The hepatocytes and bile duct epithelium originate from foregut endoderm as a ventral diverticulum near the anterior intestinal portal by the third week of intrauterine life. The connective tissue and sinusoidal endothelium of liver arise from the mesodermal septum transversum, while Kupffer cells derive from mesenchymal precursors. Hematopoietic stem cells initially arise from the yolk sac and later from the aorta-gonad-mesonephros (AGM) region. Endoderm–mesenchyme interactions shape the liver's architecture which is crucial for segmental resection and regeneration. Hence, a detailed study of foetal liver architecture was undertaken. The aim is to measure the morphometric parameters (length and breadth) of the human liver in aborted foetuses of all gestational age (excluding anomalies) and analyse their growth trends. To examine the sequential histological changes in the developing liver, including the appearance and maturation of vascular structures, hepatocyte cords, hemopoietic activity, connective tissue elements, and glycogen deposition. To correlate the observed developmental stages with potential implications for neonatal and adult hepatic disorders. **Material and Methods:** 42 aborted foetuses (formalin fixed) from 12 weeks to 35 weeks were taken. Liver dimensions and histological features with routine Haematoxylin and Eosin staining was done. **Results:** There is a progressive increase in length and breadth of the liver with respect to advancing gestational age from week 14 onwards till 26 weeks. But beyond that, the growth is slower. The length of liver grows faster than the breadth. Appearance of central vein, sinusoids, cords of hepatocytes and hemopoiesis noted at 12 weeks. Connective tissue elements noted from 14 weeks, with formation of incomplete lobulation. Proper portal triad established at 16-17 weeks. Kupffer cells are noted in the sinusoidal walls from 21 weeks. Glycogen vacuolation in hepatocytes noted from 26 weeks. **Conclusion:** Delayed or disrupted hemopoiesis, sinusoid formation, Kupffer cell appearance and portal triad formation could lead to potential architectural disarray in newborns and subsequently result in defects in adult life such as neonatal hemochromatosis, congenital hepatic fibrosis, extrahepatic biliary atresia, glycogen storage diseases, hepatoblastoma etc. Sometimes, these conditions are one of the causes of stillbirth or neonatal demise.

Keywords: Foetal liver, Hepatogenesis, Histogenesis, Kupffer cells, Portal triad, Hemopoiesis.

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Introduction

The largest gland of our body, the Liver is a detoxifying organ consisting of both exocrine and endocrine parts. In foetal stage, it performs the functions of glycogen storage, hemopoiesis, plasma protein synthesis and detoxification. Embryologically, the hepatocytes and epithelial lining of bile ducts take origin from foregut endoderm as a ventral diverticulum in the region of anterior intestinal portal by the third week of intra-uterine life. Whereas septum transversum, mesodermal in nature gives rise to liver connective tissue (fibroblasts, capsule) and endothelial lining of sinusoids. Kupffer cells are macrophages derived via mesenchymal precursors. The yolk sac (initial), later aortic-gonad-mesonephros (AGM) region give rise to hematopoietic stem cells during foetal life.[1–3] These interactions between endoderm and mesenchyme to form the structural architecture play a crucial role in segmental resection of liver and in liver regeneration in adult life.[4] Thus, a detailed descriptive study of the architecture of foetal liver was taken up.

Materials and Methods

After the Ethical Committee approval, aborted foetuses were collected from Obstetrics and Gynaecology department of Government Medical College, Ariyalur. The livers of 42

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aborted foetuses (formalin fixed) with the gestational age 12 weeks (CRL 8 cm) to 35 weeks (CRL 40 cm) were taken for study. Foetuses with gross anomalies were excluded from the study. For analysis purpose, the foetuses were categorised into age groups, to study the similarities, differences and progress of development between them. The dimensions of liver (length x breadth), with presence or absence of accessory lobes were noted before harvesting and preserving the specimens. Routine Haematoxylin and Eosin staining was done and observation done under microscope.

Statistical analysis: The morphometric data were expressed as mean +/- standard deviation (SD) and weighed mean +/- SD. Trend of liver growth and length: breadth (L:B) ratio were plotted.

Results

Morphometric analysis of foetal liver (12 weeks to 35 weeks):

A 19-week male foetus showed accessory lobe attached to the left lobe, measuring 2x2 cm in size. The size of both lobes of liver was equal in two specimens, one at 19 weeks and the other at 24 weeks of gestation.

Since the data is in the form of grouped means (average length and breadth for a given number of specimens per gestational age), a weighted mean and weighted standard deviation to reflect all 42 foetal livers was calculated. The data are given in [Table 1].

There is a progressive increase in length and breadth of the liver with respect to advancing gestational age from week 14 onwards till 26 weeks. But after that, the growth is slower (35 weeks) [Figure 1]. The length of liver increases faster in comparison to the breadth of liver, as observed from [Figure 1 & 2].

Table 1: Dimensions of liver of foetuses (12 weeks to 35 weeks)

Gestational age	Number of specimens	Liver length (cm)	Liver breadth (cm)	L:B ratio
12 weeks	2	1.9	2.75	0.69
14 weeks	2	2.5	1.5	1.67
16 weeks	8	4.6	2.4	1.92
17 weeks	5	4.3	4.3	1.00
18 weeks	9	5.2	3.5	1.49
19 weeks	5	7.3	4.1	1.78
20 weeks	3	7.7	6	1.28
21 weeks	1	8	4.5	1.78
22 weeks	1	8.5	4	2.13
24 weeks	4	8.3	4.8	1.73
26 weeks	1	9	5.5	1.64
35 weeks	1	8	4	2.00
	Mean +/- SD	6.28 +/- 2.46 cm	3.95 +/- 1.27cm	1.59 +/- 0.42
	Weighed mean +/- SD	5.72 +/- 1.93 cm	3.72 +/- 2.32 cm	

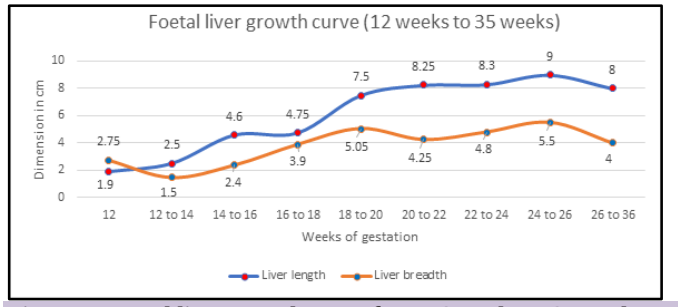

Figure 1: Foetal liver growth curve from 12 weeks to 35 weeks

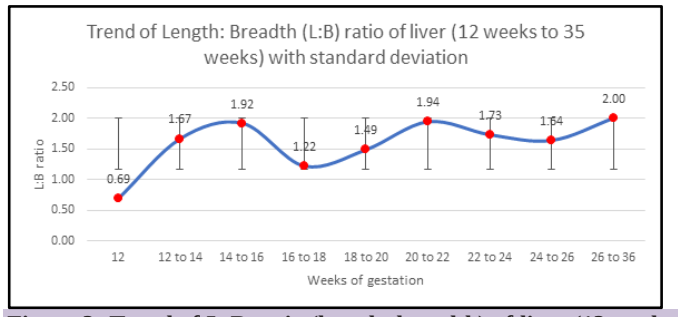

Figure 2: Trend of L:B ratio (length: breadth) of liver (12 weeks to 35 weeks) with SD

Microscopic observations of foetal liver:

Week 12: Hemopoiesis present, predominantly around the central vein [Figure 3 (A)]. Hemopoietic cells appear smaller with dark stained nuclei in comparison to the hepatocytes that are larger with pale cytoplasm and light stained nuclei. Sinusoidal space abundantly visible, with hemopoietic cells inside [Figure 3 (A)]. Portal triad starts forming, but they are not well defined. No connective tissue surrounding the portal triad structures [Figure 3 (B)]. Cords of hepatocytes visible, starting to radiate from central vein [Figure 3 (A)]. Hepatic lobular structure is not formed [Figure 3 (B)]

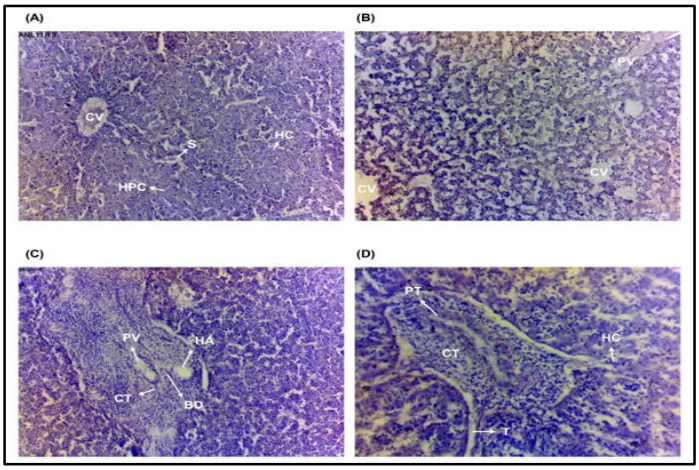

Figure 3: (A)- Features of liver at 12 weeks IUL (H&E, 10x) showing CV – central vein; HC – Hematopoietic cells; S – Sinusoidal spaces; HPC – Hepatocytes. (B)- Features of liver at 12 weeks IUL (H&E, 10x) showing PV – Portal vein; CV – central vein. (C) - Features at 16 weeks IUL (H&E, 10x) showing PV – Portal vein; HA – Hepatic artery; BD – Bile duct; CT – Connective tissue surrounding the portal triad. (D)- Features at 16 weeks IUL (H&E, 40x) showing PT – Portal triad; CT – Connective tissue surrounding portal triad; T – Incomplete trabeculae; beginning of lobulation; HC – Hematopoietic cells

Weeks 14 to 16: Hemopoiesis present. Hepatocytes arranged in cords are observed. [Figure 3 (C)]. Portal tract is now visible with connective tissue surrounding it [Figure 3 (C)]. Periportal space is visible [Figure 3 (D)]. Beginning of lobulation seen with formation of incomplete trabeculae by 16 weeks [Figure 3 (D)].

Weeks 17 to 20: Further hemopoiesis, formation of sinusoids, thickening of connective tissue around the portal triad are seen. Incomplete lobulation (although less demarcated) are seen with respect to portal triad which are surrounded by multiple central veins [Figure 4 (A)]. Radiating hepatocytes are visible.

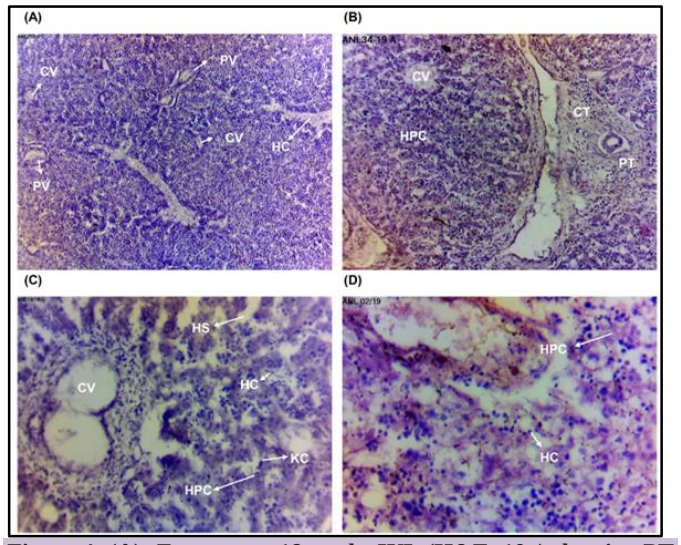

Figure 4: (A)- Features at 19 weeks IUL (H&E, 10x) showing PT – Portal triad; CV – Central vein; HS – Hepatic sinusoids; HC – Hematopoietic cells, abundant and found within sinusoids; Less demarcated hepatic lobules. (B) - Features at 21 weeks IUL (H&E, 10x) showing PT – Portal triad; CT – Connective tissue surrounding the portal triad; CV – Central vein; HPC – Radiating hepatocytes; Well demarcated hepatic lobule. (C) - Features at 24 weeks IUL (H&E, 40x) showing CV – Central vein; KC – Kupffer cells; HC – Hemopoietic cells; HS – Hepatic sinusoids; HPC – Hepatocytes with vesicular nuclei. (D) - Features at 26 weeks IUL (H&E, 40x) showing HPC – Hepatocytes showing vacuolation; HC – Hemopoietic cells

Weeks 21 to 24: Hemopoiesis is still predominant with hemopoietic cells seen in well-defined sinusoids. Radiating hepatocytes are clearly seen. Portal triad is well demarcated with surrounding connective tissue [Figure 4 (B)]. Hepatic lobulation is more clearly seen, but hepatocytes communicating with adjacent lobules indicate immaturity of liver [Figure 4 (B)]. Binucleated hepatocytes are seen. The nuclei appear vesicular. [Figure 4 (C)]. By 22 weeks, Kupffer cells are identified in the walls of sinusoids. They are characterised by large cells with irregular, elongated, dark stained nuclei. [Figure 5 (C)].

Week 26: Glycogen storage begins, evident by vacuolation of hepatocytes. [Table/Fig-5 (D)]. Fibroblasts in connective tissue surrounding the portal triad is clearer. The remaining findings correlate with previous weeks, but hemopoiesis begins to fall.

Week 35: Marked reduction in hemopoiesis. Cytoarchitecture seen is similar to new-born liver.

Discussion

In a morphometric study done by Aggarwal et al,[5] length of liver was 3.15 +/- 0.9 cm and breadth was 4.79 +/- 0.87 cm. The present study shows length of 6.28 +/- 2.46 cm and breadth of 3.95 +/- 1.27cm. The similarity in increasing dimensions of liver with foetal age was noted.

The microanatomy of liver studied at different gestational ages are categorised into the following parameters for discussion.

- Connective tissue and capsule
- Presence of hemopoiesis
- Change in organisation of hepatocytes and glycogen vacuolation
- Liver lobulation
- Appearance of central veins
- Appearance of sinusoids
- Formation of portal triad
- Appearance of Kupffer cells

Connective tissue and capsule: Presence of connective tissue surrounding the portal triad starts from 14 weeks in the present study. Ansari et al,[6] noted this from 12 weeks, along with thickened capsule. Whereas, Hashmi et al,[7] noted connective tissue element from 12 weeks, but capsule was noted to be initially thin, then progressively became thicker.

Presence of hemopoiesis: Evidence of hemopoiesis in the present study starts from 12 weeks onwards, peaking by 20-24 weeks. With 26 weeks and above, there is gradual decrease in hemopoiesis. The 35 weeks liver showed marked reduction. These findings correlate with the study done by Ansari et al,[6] and Zamboni.[8] But a study by Linda et al,[9] noted earlier hemopoiesis from 7-8 weeks, regressing by 32 weeks. Hemopoiesis starting by 10th week was noted by Islam.[10] Haldar et al,[4] noted hemopoiesis at 15 weeks but completely ceased at 35 weeks.

Change in organisation of hepatocytes and glycogen vacuolation:

Similar to the current study, Islam,[10] noted cords of hepatocytes at 12 weeks, anastomosing pattern beginning by 14th week. Radiating nature of hepatocytes as plates are seen clearly from 20 weeks onwards in this study.

Ch et al,[11] noted glycogen deposits by 25 weeks, Himabindu et al,[12] by 26 weeks, Ansari et al,[6] by 28 weeks and Marie,[13] by term. The present study shows glycogen vacuolation by 26 weeks, similar to Himabindu et al.

Liver lobulation: Hepatic lobule formation was identifiable by Bates et al,[14] at 6 weeks, by He Suyan,[15] at 9-12 weeks. Lobular pattern starts to be defined at 21-24 weeks in a study by Ch et al,[11] at 22 weeks by Mohan et al,[16] and Hashmi et al.[7] The classic lobule measurement from 22 weeks onwards

was done by Ansari et al.[6] Whereas in this study, lobulation begins at 14th week. Classic lobule is not well defined till 35 weeks.

Appearance of central veins: Mohan et al,[16] noted the appearance of central vein at 12-18 weeks; Hashmi et al,[7] and Zorn,[17] noted the same at 16-17 weeks; and Ch et al,[11] at 17 – 20 weeks; The current study reflects Mohan's by showing central vein formation at 12 weeks. Surrounding connective tissue elements occur from 14 weeks forward.

Appearance of sinusoids: Appearance of sinusoids at 5-6 weeks was noted by Naik et al,[18] at 12-18 weeks by Mohan et al,[16] at 17 weeks by Macchiarelli et al,[19] at 24 weeks by Sree et al.[20] Macchiarelli et al,[19] also noted that prior to 17 weeks, there are capillaries, which transform into sinusoids by 17 weeks. In the present study, at 12 weeks, sinusoids are plenty in the specimens, similar to Naik et al. Sinusoids show hemopoietic cells inside them.

Formation of portal triad: Islam,[10] and Vijayan et al,[21] noted fully formed portal triad by 16th week; Ch et al,[11] by 17 weeks; Hashmi et al,[7] by 18 weeks. While Haldar et al,[4] and Sree et al,[20] noted the portal vein with central vein and sinusoids surrounded by periportal connective tissue by 24 weeks.

This study shows ill-defined portal vein at 12 weeks. By 16th week, portal vein is clearly seen, with minimal connective tissue surrounding it, similar to Islam and Vijayan et al. The portal triad structures are clearly seen from 17th week onwards along with proper periportal connective tissue.

Appearance of Kupffer cells: Appearance of Kupffer cells along the walls of sinusoids was noted by Sree et al,[20] at 20 weeks, Ansari et al,[6] at 22 weeks, by Islam,[10] at 26 weeks, by Haldar et al,[4] at 36 weeks of gestation. This study shows Kupffer cells by 21-22 weeks of gestational age, similar to Ansari et al.

Delayed or disrupted hemopoiesis, sinusoid formation, Kupffer cell appearance and portal triad formation could lead to potential architectural disarray in newborns and subsequently result in defects in adult life. Neonatal hemochromatosis due to feto-maternal alloimmune disease results in destroyed hepatocytes, while portal triad remains mostly unaffected.[22] Congenital hepatic fibrosis results due to defective interaction between ductal plate and mesenchymal cells causing 'cyst-like' lesions.[23] Hepatoblastoma is tied to tumorous growth of hepatic stem cells which provide the epithelial components of liver tissue.[24] Thus, these conditions are one of the contributing reasons for stillbirth or neonatal demise.

Conclusion

There is a progressive increase in length and breadth of the liver with respect to advancing gestational age from week 14 onwards till 26 weeks. But beyond that, the growth is slower. The length of liver grows faster than the breadth.

The foetal liver shows a clear pattern of morphological and histological maturation with advancing gestational age. Early structural elements such as central vein, sinusoids, hemopoiesis and hepatocyte cords appear by 12 weeks, followed by gradual development of connective tissue (14 weeks), portal triads (16-17 weeks), and Kupffer cells (21 weeks). Glycogen accumulation begins by 26 weeks. These findings highlight the coordinated timeline of liver development, essential for understanding hepatic function and pathology in the perinatal period.

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Conflicts of interest

There are no conflicts of interest.

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