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Morphology and Histogenesis of developing human liver

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Abstract:

Background: Hepatic tissue made from stem cells holds the promise of an unlimited source of material for transplantation. Liver is one of the organs working without a resting phase. Understanding the molecular mechanism governing liver development will also be valuable for efforts to differentiate therapeutically useful hepatic tissue from stem cells.

Aim of study: To correlate body weight, liver weight, crown-rump length with gestational ages and to study microscopic structure of liver at various gestational age groups.

Materials and method: Forty human fetuses (19 males and 21 females) of different gestational ages ranging from 12th to 36th gestational weeks were procured for the research work.

Result: High correlation between body weight and gestational age of fetus. The Crown-rump length (CRL) showed gradual increase from 12th to 36th weeks of gestation. Highly significant correlation found between liver weight and gestational age of fetus. The percentage relative weight was variable throughout the period of the gestation. Microscopy shows haemopoiesis was abundant at early stages of gestation and decrease as the age of liver advances from 12th to 36th week of gestation. Connective tissue elements increase from 12th week onwards showing thick capsule and thickened trabeculae. Central vein appears at around 16th to 17th weeks of gestation. Branches of portal vein, hepatic artery and bile ductile appear later during development at about 18th week of gestation.

Conclusion: All physical parameters showed gradual increase from 12th week to 36th week of gestation. The haemopoietic tissue was found abundant in early stage. Central vein, portal tracts appeared at around 15th to 18th weeks of gestation.

Key words: Liver, hepatic tissue, portal triad, central vein, haemopoesis

Introduction:

The liver is the largest gland of the body and consists of both exocrine and endocrine parts. The adult liver has a remarkable regenerative capacity and can completely re-grow when up to 70% of its mass is removed.[1] This ability is impaired in numerous diseases such as advanced cirrhosis and hepatitis resulting life threatening liver failure for which organ transplantation is currently the only clinical option. Hepatic tissue made from stem cells holds the promise of an unlimited source of material for transplantation. Researchers have attempted to generate hepatocytes from a variety of adult, fetal and embryonic stem cell sources.[2] These efforts,

particularly the recent successes with embryonic stem (ES) cells, have been greatly facilitated by our understanding of embryonic liver development.

Ham and Cormack[3] (1979) said that the liver is unique; there is no division of labour between those cells that produce the exocrine secretion and those that elaborate the endocrine ones. All its parenchymal cells (Hepatocytes) produce both kinds of secretions. The parenchyma of the liver must therefore be arranged so that every hepatocyte on one or more of its surfaces abuts on a passage way that connects with a duct system to carry away its exocrine secretion (bile) and abuts on a blood vessel into which it delivers its endocrine secretions**.** About 80% of the liver volume and 60% of its cell population is formed by hepatocytes (parenchymal cells). Transport of nutrients across the hepatocytes is the key regulatory step in the fetal growth and development. Recent researches indicate that hepatocytes and cholangiocytes may have been derived from a common precursor or stem cell.

Though it is known that liver is relatively large in size in prenatal period, the actual details about the weight and microscopic structure of liver at different stages of development in the prenatal period are not very much known. After knowing all the normal histological characteristics at various stages of development this study can be proposed to distinguish from certain pathological changes occurring in liver during prenatal period.

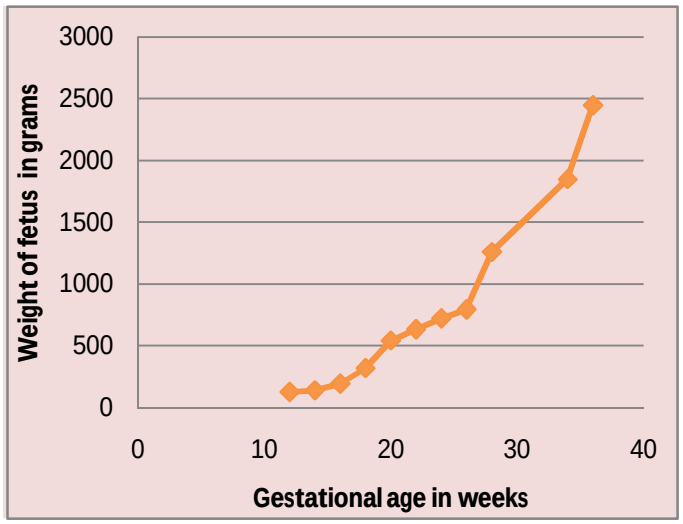
So aims and objective of the present study is to correlate body weight and liver weight at different gestational age groups, compare crown-rump length and weight of liver with gestational ages and to study microscopic structure of liver at various gestational age groups.

Materials and Method:

Forty human fetuses (19 males and 21 females) of different gestational ages ranging from 12th to 36th gestational weeks were procured for the research work from the department of Obstetrics and Gynecology of tertiary care hospital with prior permission of the head of Department. Consent was taken from respective parents with approval of the Ethical Committee of our Medical College. These fetuses included the spontaneous abortus and stillborn. They were without any gross abnormality. Fetuses were obtained within 4-5 hrs of birth to avoid post-mortem changes. Gestational age, sex, Crown rump length (CRL) and body weight of the fetuses were noted in detail. Gestational age of fetus was estimated from the detailed obstetric history of each case. Crown-rump length was measured by thread and measuring tape scale. Weight of the fetuses was measured in grams on double pan balance. Liver was removed by abdominal incision and weighed immediately after removing the gall bladder completely and then was fixed in 10% formalin. Then the liver was cut into pieces and fixed in Bouin's medium for 24 hrs. Tissue processing was done and slides were stained by Haematoxylin and Eosin method.[4]

Results:

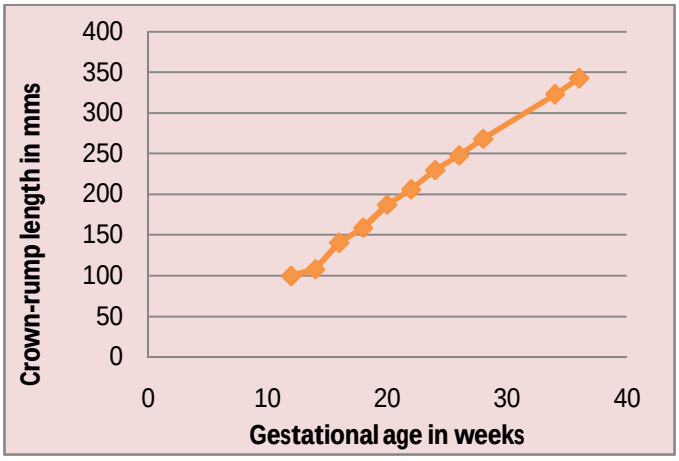
Graph 1. Correlation of body weight of fetus with gestation age.



The liver weight at 12th week of gestation was 3gms. It increased gradually up to 45gms at 28th week of gestation. Thereafter it increased at a faster rate. The weight at 36th week of gestation was 96gms. It appears that the liver weight increase

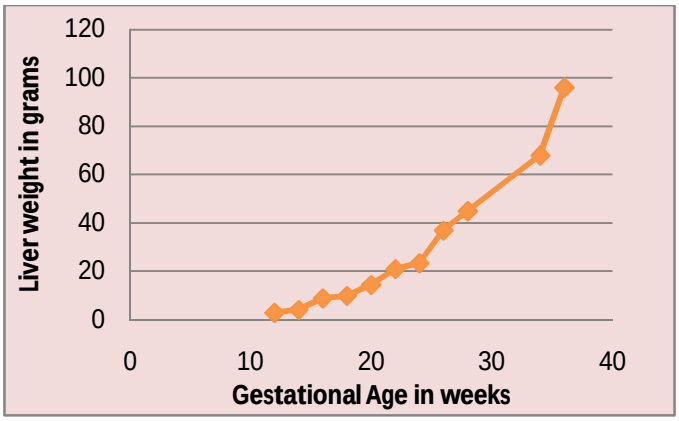
rapidly in the later part of gestation. The increase in body weight of fetus is correlated with gestational age of fetus having correlation coefficient value 0.95988 and for testing the significant correlation t test is applied. The t value is 10.25 and p value is <0.001. This shows there is high correlation between body weight and gestational age of fetus.

Graph 2. Correlation of Crown-rump length (mm) against Gestational age (weeks).



The Crown-rump length showed gradual increase from 12th to 36th weeks of gestation. The correlation between CRL and gestational age of fetus t-test is applied, having correlation value 0.99777 and t - value 44.15 so the p value obtained is < 0.001 which shows highly significant correlation between CRL and gestational age of fetus.

Graph 3. Correlation between liver weight (gms) against the gestational age (weeks).

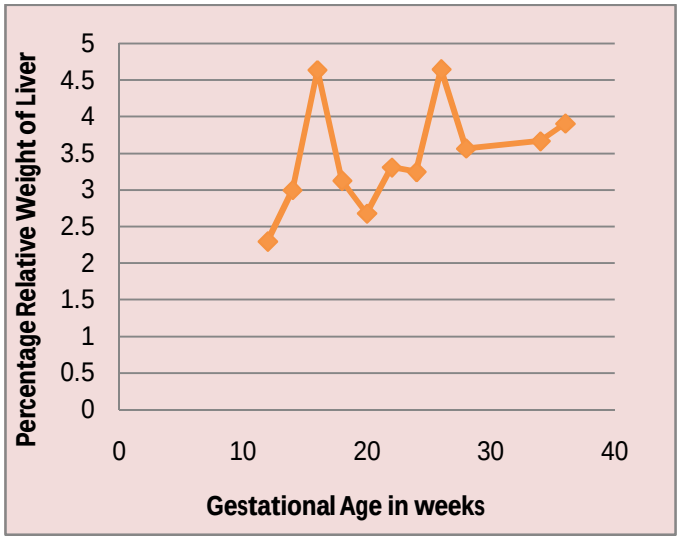


The correlation between organ weights i.e. liver weight and gestational age of fetus t-test is applied, having correlation value 0.9552 and t - value 9.6823 so the p value obtained is < 0.001 which shows highly significant correlation between liver weight and gestational age of fetus.

The relative weight of liver was calculated by the following formula:

$$\text{Relative weight of liver} = \frac{\text{Liver Weight X 100}}{\text{Body Weight}}$$

Graph 4. Showing Relative Weight of Liver against the gestational age in weeks.



The results showed that the percentage relative weight is variable throughout the period of the gestation. The lowest percentage relative liver weight is 2.3% at 12th week of gestation. It shows increase to 4.64% at 16th week and 4.65% by 26th week of gestation.

Microscopic development from 12th to 36th week Stage of Liver:

Haemopoietic tissue: Haemopoiesis was abundant at early stages of gestation. It shows decrease as the age of liver advances from 12th to 36th week of gestation.

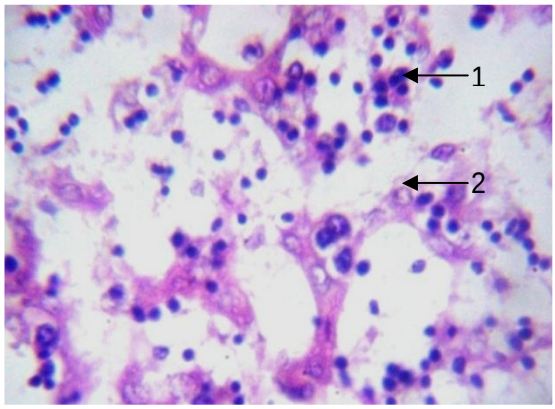
Connective tissue elements: It consists of thin capsule and diffuse connective tissue supporting the cords of hepatocytes at earlier stages. Connective tissue is also associated with blood vessels except central veins. Connective tissue elements increase

from 12th week onwards showing thick capsule and thickened trabeculae.

Central Vein: Central vein appears at around 16th to 17th weeks of gestation. Thereafter it shows increase in size.

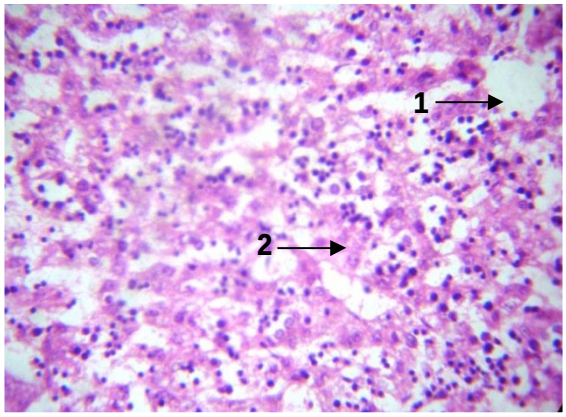
Portal tracts: These consist of the branches of portal vein, hepatic artery and bile ductule. They appear later during development at about 18th week of gestation.

Microphotograph 1. At 40X ; 12 weeks



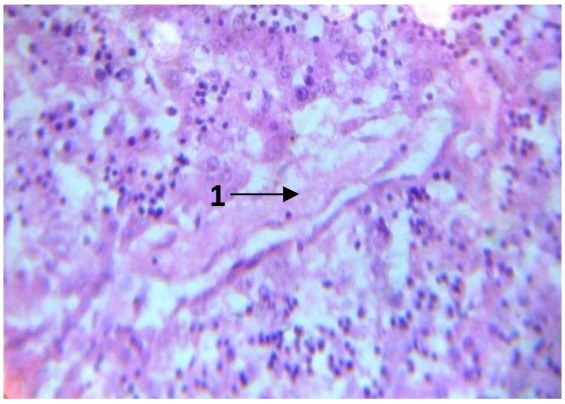
1- **Abundant haemopoietic tissue**
2- **Hepatocyte**

Microphotograph 2. At 10X ; 18 weeks



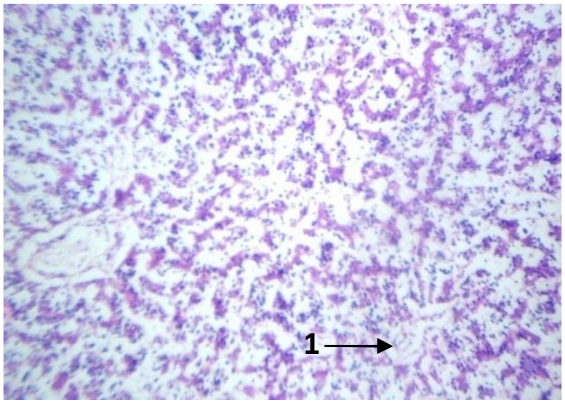
1- **Central vein**
2- **Abundant haemopoietic tissue in sinusoids**

Microphotograph 3. At 40X ; 22 weeks



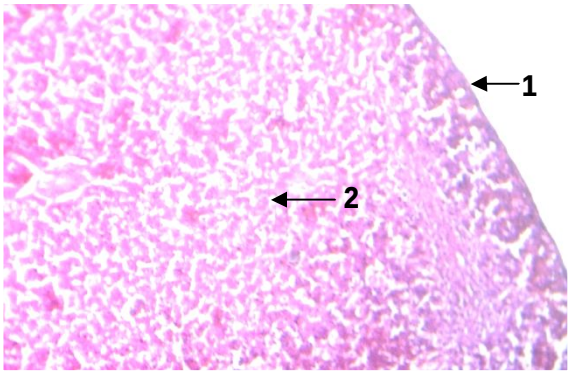
1- **Appearance of Portal triad**

Microphotograph 4. At 10X ; 28 weeks



1- **Well developed hepatic lobule around the central vein**

Microphotograph 5. At 10X ; 36 weeks



1- **Thick hepatic capsule**
2- **Cords of hepatic cells**

Discussion:

In the present study, while studying the development of liver in antenatal period, different

morphological and histological parameters of liver were considered. According to the findings of present study, body weight shows gradual increase from 12th week to 36th week of gestation. And the crown-rump length showed gradual increase as the gestational age of fetus increases. The findings are in the range of weights reported by Langman[5] (2008) and more or less comparable with reported values of Moore[6] (2008). Also liver weight of fetus shows gradual increase as gestational age of fetus increases. The reported values of Potter[7] (1961) are less than the present study. Relative weight of liver is not constant and it does not proportionate to body weight of fetus. The increase in body weight of fetus and organ weight i.e. liver is correlated with gestational age of fetus with the help of t test. The p value of correlation found < 0.001 which is similar to the finding of Albey et al[8] (2005).

Potter[7] (1961) reported that the liver differentiates into masses and plates of cells at 4th week. The mesenchyme of septum transversum forms capsule and connective tissue elements. Endodermal cells transform into hepatic parenchyma, while vascular channels from the hepatic sinusoids.

Hamilton and Mossman[9] (1975) state that, hepatic rudiment appears at 18th day. Pars hepatica enters the septum transversum. These solid cords (hepatic cords) anastomose with each other and isolate into small clusters of mesenchymal cells which will form the blood vessels and haemocytoblasts.

Enzan et al[10] (1997) observed at 5 weeks of gestation in humans, the hepatic cords grow into the mesenchymal tissue of the septum transversum, and the primitive sinusoid like structure is simultaneously observed between the liver cell cords.

In the present study, it was seen that the connective tissue elements consists of a thin capsule and reticular fibers supporting hepatic cords, but later on it is associated only with blood vessels except central vein. Connective tissue element increase from 12th weeks onwards showing thickened capsule and more thickened trabeculae.

According to Potter[7] (1961), within the mesenchyme of septum transversum, capillary plexus are formed and the endodermal cells invest the branches of these plexuses. These endodermal cells are now transformed as a single layer of plates of hepatic parenchyma, while vascular channels in between will form hepatic sinusoids. Further growth takes place by simultaneous formation of new sinusoids and plates. Around these hepatic cells bile canaliculus is formed which flows to the periphery of the lobule and opens into the bile ductules. These bile ductules along with the branches of hepatic artery and portal vein together form the portal triad.

Balis, Chan and Conen[11] (1964) suggested that liver plates were formed before the development of sinusoids. Peripheral bile tubules were the earliest organised structures formed by association of hepatocytes and cholangiolar cells. They established an interrelationship between these tubules, bile canaliculi, sinusoids, and periportal venous channels**.** Hamilton and Mossman[9] (1975) stated that hepatic cords at first are solid but soon acquires lumen and form bile canaliculi. Mesoderm of septum transversum will form the connective tissue around the branches of portal vein forming portal triad.

Terada and Nakanuma[12] (1993) stated that at 7 weeks of gestation, the ductal plate was present in the periportal immature hepatocytes around the portal veins at the hepatic hilum. At 10 weeks of gestation, biliary cells began to bud from the ductal plate into the mesenchyme and formed double-layered cords and tubules. The double-layered cords had transformed completely into tubules by 30 weeks gestation. The tubules then gradually increased in number.

Enzan et al[10] (1997) observed that at 8 weeks of gestation in humans, the basic structure of the sinusoids has developed. Embryonic hepatic sinusoids are usually lined by a continuous endothelium without basement membranes, and an incompletely fenestrated sinusoid appears at the mid gestational stage**.**

Godlewski et al[13] (1997) elucidated that from 42-58 day, biliary ductules developed in periportal connective tissue producing ductal plates that received biliary capillaries.

In the present study, it was seen that at 16th to 17th week central veins appear initially. Sinusoidal walls lined by endothelial cells are also identified first at this stage. Portal tract can be identified first at 18th week liver, but the clear-cut architectural pattern becomes evident only at 20th to 21st week of gestation. All the structures of classical liver can be identified clearly at 22nd week. The size of lobule increases thereafter.

Hamilton and Mossman[9] (1978) states that, haemopoiesis begins very early in developing liver and reaches its peak at 6th to 7th month of fetal life and then regresses up to full term. Moore and Persaud[6] (2008) mentioned that haemopoiesis begins during the sixth week, giving the liver a bright reddish appearance. Present study is in accord with all the previous workers stated above. Haemopoiesis was seen prominently in all the stages studied but gradual decrease in haemopoiesis was found from 24th to 30th weeks of gestation, and after 32nd weeks, scanty foci of haemopoietic tissues were seen.

Conclusion:

From the above study it can be concluded that all physical parameters including body weight, crown-rump length, liver weight and relative liver weight showed gradual increase from 12th week to 36th week of gestation. The haemopoietic tissue was found abundant in early stage but it regressed to cease at late stages of gestation. Central vein, portal tracts appeared at around 15th to 18th weeks of gestation.

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