Development of the liver during the fetal period

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ABSTRACT

Objective: To investigate the development of the liver in human fetuses aged between 9-40 weeks.

Methods: We studied 121 human fetuses (62 males, 59 females) with no external anomalies aged between 9-40 postmenstrual weeks during 2003-2004 in Suleyman Demirel University, Isparta, Turkey. The fetuses were divided into four groups as 1st, 2nd and 3rd trimesters and full term fetuses. We measured fetal weight, length, width, thickness, and volume of the liver. We established localization of the liver and its relation with the neighboring structures, its ligaments, and size of itself and its lobes, shapes of the liver and the localization of the porta hepatis on the visceral surface of the liver.

Results: We found significant correlations between the size, weight, volume of the liver, sizes of its lobe and gestational age ($p<0.001$). Group comparisons disclosed significant differences between groups in all parameters except between 3rd and 4th groups with respect to the heights of the liver and the caudate lobe ($p<0.05$). During the fetal period, the proportion of the distance between the porta hepatis and the right margin of the liver to the distance between the porta hepatis and the left margin of the liver did not change significantly ($p>0.05$). However, the proportion of the distance between the porta hepatis and the upper margin to the distance between the porta hepatis and the lower margin decreased significantly with gestational age ($p<0.05$). Type 3 liver (square) was the most commonly observed type of fetal liver (53%).

Conclusions: Our opinion is that the parameters obtained can be useful to diagnose pathologies of liver development and anomalies concerning several branches of medicine such as anatomy, pathologic anatomy (fetopathology), forensic medicine, medical imaging, obstetrics and pediatrics.

Saudi Med J 2005; Vol. 26 (11): 1710-1715

The liver constitutes 10% of total body weight in the intrauterine 10th week. Hemopoiesis in the liver starts in the 6th week. Hemopoietic activity gradually decreases towards the last 2 months of the pregnancy, with few hemopoietic cell islets left after birth. The liver accounts for 5% of the total body weight at birth.[1] Murao et al[2] reported, using obstetric ultrasound (US), a linear increase in the size of left and right lobes of the liver between 18-41 weeks. Similarly, in another US study by Murao et al,[3] the authors compared the liver size and other parameters used to monitor fetal growth between the 19th week and term, and found a high correlation between them and concluded that we can use liver size to assess fetal growth as well. Roberts et al[4] showed that the height of the fetal liver was 12% greater in diabetic pregnancies, aged 18 weeks and over, compared to non-diabetic pregnancies, and argued that knowing the normal range of the length of the fetal liver is beneficial to diagnose and follow-up gestational diabetes and hepatomegaly. There are also postmortem studies conducted on fetuses in the literature.[5-7] Marecki[8] evaluated the

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Received 12th June 2005. Accepted for publication in final form 10th September 2005.

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size of the liver, besides other organs, in postmortem fetuses. The liver continues to grow throughout a normal pregnancy. The fetal liver is markedly small compared to other organs in intrauterine growth retardation.[9] Previous studies found that the liver is bigger than average in isoimmunization and other fetal anemias, intrauterine infections, fetal heart failure, tumors, certain metabolic diseases and fetal macrosomias.[2,10,11] The size of the liver is a good indicator of the severity of the clinical outcome in pregnancies complicated with isoimmunization.[12] Most of the studies on fetal liver utilize obstetric ultrasound,[2-5,13,14] using mid-second trimester to term fetuses. The main reason for this is the difficulty to clearly depict fetal structures with obstetric ultrasound during the first and early second trimester pregnancies.[12] Furthermore, no data exist in previous studies on the structural characteristics of the fetal liver or the position of porta hepatis on the visceral surface of the liver. We conducted this study, spanning a wider range of age, namely, 9-40 weeks of gestation when compared with other studies, with the aim of obtaining morphometric data with anatomical dissections.

Methods. This study was carried out on 124 fetuses (63 male and 61 female fetuses) with no external anomaly or pathology with an age range between 9-40 weeks of gestation [crown rump length (CRL): 70-420 mm]. Material was collected with the families' consent from Isparta Maternity and Children's Hospital between the years 1996 through 2002 and was preserved at the laboratory of the Department of Anatomy. Approval from the Ethics Committee of the Suleyman Demirel University School of Medicine was obtained before the study. The age of the fetuses were determined using CRL until 12th weeks and bi-parietal diameter, head circumference and foot length thereafter.[1] Fetuses aged 9-12 comprised the 1st group (1st trimester), 13-25 weeks comprised the 2nd group (2nd trimester), 26-37 weeks comprised the 3rd group (3rd trimester), and 38-40 weeks comprised the 4th group (term). Measuring tape, compass and precision ruler were used to measure the morphometric parameters in this study. In the first stage, general parameters, namely, weight, head circumference and bi-parietal diameter were measured. A transverse incision extending from the umbilicus to the mid axillary line bilaterally, and 2 vertical incisions, extending from the costal arch to the iliac crest alongside the mid axillary line bilaterally were made and the abdomen was dissected. The liver and the neighboring structures were exposed. Cases with an anomaly or malformation were not included in the study. The livers were separated into 4 groups with respect to its shape, type 1 - trapezoid, type 2 - triangular, type 3 - square, and type 4 – rectangular. The following values were measured as described: Liver height: The distance between transverse planes passing through the upper and the lowermost points of the liver. Liver width: Transverse distance between parallel vertical planes touching the margins of the liver on the left and right sides. Liver thickness: Sagittal distance between parallel vertical tangents at the anterior and posterior poles of the liver. Liver weight: The liver weight was measured using an electronic scale (Mettler Toledo Medium PB 153). Liver volume: The volume of the liver was measured by water displacement method (every measurement was repeated 3 times and the mean value was taken into account). In order to be able to compare the sizes of the liver with those of the abdomen, abdominal width, thoracic width (upper abdominal width), the distance between the xiphoid process and the pubic symphysis (anterior abdominal height) and the distance between the xiphoid process and the most posterior point of the thoracic cavity (upper abdominal depth) were also measured. The width of the right lobe: The transverse distance between the outermost point of the right lobe and the point where the umbilical vein joins the porta hepatis. The width of the left lobe: The transverse distance between the outermost point of the left lobe and the point where the umbilical vein joins the porta hepatis. The height of the caudate lobe: The vertical distance between the most superior and inferior points of this lobe. The width of the caudate lobe: The transverse distance between the outermost points on both sides of this lobe. The height of the quadrate lobe: The vertical distance between the most superior and inferior points of this lobe. The width of the quadrate lobe: The transverse distance between the outermost points on both sides of this lobe. The distances between the porta hepatis and superior-most and inferior-most points of the liver on the vertical plane and the distances on the transverse plane between the porta hepatis and the outermost points of the liver on the right and left-hand-side were measured.

The means of the parameters with respect to the gestational age, sex, and groups were computed using the SPSS statistical package. A $p<0.05$ was considered statistically significant. The values of each group were expressed as mean ± standard deviation. Non-parametric tests were used to compare groups due to the limited number of cases in some groups. After the analysis of variance with Kruskall-Wallis test, significant groups were compared pair wise with Mann-Whitney U test. The p values were adjusted for multiple comparisons using the Bonferroni correction. Pearson's correlation test was used for the relationship between the parameters and the gestational age. Student t-test was used to test all cases for sex differences in the parametric data, and the Mann-

Whitney-U test was used to assess intergroup differences. Chi-square test was used to compare percent distribution of non-parametric data among groups.

Results. Firstly, the general parameters, namely, fetal weight, head circumference and bi-parietal diameter were measured. Means of these parameters with respect to gestational weeks and trimesters were obtained, and no significant sex difference was observed among the 124 fetuses (63 male and 61 female) in terms of general parameters (p>0.05). In all cases, the liver lay above the transverse plane passing through the umbilicus, occupying both right and left upper quadrants. The relationships between the liver and the transverse colon, stomach, right adrenal gland, right kidney, right colic flexure, inferior vena cava and diaphragm were as expected, with no abnormalities detected. However, in 11% of the cases the liver had no contact with the spleen. The hepatogastric, hepatoduodenal, falciform, coronary, triangular and hepatorenal ligaments of the liver were unremarkable in all cases; no anomalies or variations were observed. With respect to the shape, 4 types of liver were identified. The number of cases in each group and their percentages are summarized in **Table 1**. Type 2 (triangular) liver was not observed in groups 1 and 2. In group 3 and term fetuses, type 3 (square) liver was the most common. When all cases were taken into account, type 3 liver (square) was the most commonly observed type. The height, width, thickness, weight and the volume of the excised liver were measured. The means of these parameters were calculated for each gestational week and trimester (**Table 2**). The size of the liver increased with advancing gestational age and there were significant correlations between general parameters of the fetus and the liver (p<0.001). No significant sex differences were observed regarding the liver parameters (p>0.05). Group comparisons revealed a significant difference between all groups for all parameters (p<0.05) with the exception of the height of liver between 3rd trimester and term fetuses (p>0.05, **Table 2**). Then upper and lower abdominal widths, anterior abdominal height, upper and lower abdominal depths were measured in each fetus. On the visceral surface of the liver the width of the right and the left lobes, the height and width of the caudate and quadrate lobes were measured. Means and standard deviations of the means of these parameters for each gestational week and trimester were computed (**Table 3**). When the groups were compared the height of the caudate lobe in the 3rd group was not significantly different from that of the 4th group (p>0.05, **Table 3**) whereas all the remaining parameters were significantly different among each group (p<0.05). In order to determine the position of the porta hepatis on the visceral surface of the liver, the distances between the porta hepatis and the upper, lower, left and right margins of the liver were measured; means and standard deviations were computed. Throughout the fetal period, the ratio of the distance to the left margin to the distance to the right margin of the liver did not change significantly (p>0.05), while the distance to the upper margin decreased significantly compared to the distance to the lower margin nearing term (p<0.05).

Table 1 - The number of the cases and the percentage distribution of the liver types according to groups during the fetal period.

Group/ Trimester	No. of liver types (%) Type 1	Type 2	Type 3	Type 4	Total
1st trimester (9-12 week) (CRL: 70-100 mm)	2 (29)	0 (0)	4 (57)	1 (14)	7
2nd trimester (13-25 week) (CRL: 110-240 mm)	24 (36)	0 (0)	37 (56)	5 (8)	66
3rd trimester (26-37 week) (CRL: 250-350 mm)	12 (31)	2 (5)	18 (46)	7 (18)	39
Full term (38-40 week) (CRL: 360-420 mm)	1 (8)	1 (8)	7 (59)	3 (25)	12
Total (9-40 week) (CRL: 70-420 mm)	**39 (32)**	**3 (2)**	**66 (53)**	**16 (13)**	**124**

p<0.001; differences between groups χ^2=43.253
CRL - crown rump length

Discussion. The liver lies in the right hypochondrium, epigastric region and left hypochondrium in adults, but most of the liver occupies the right upper quadrant.[15-17] We did not find any publications regarding the localization of the liver and its neighboring structures during fetal life. We found the liver above the level of the transverse plane passing through umbilicus, situated in both hypochondria, as mentioned in textbooks. The liver may have contact with the spleen in adults.[1] However, no reference exists regarding the relationship between these in the fetal period. We found the spleen had a point of contact with the liver in 89% of the cases, which Moore and Persaud[1] think is because of proportionally larger liver size in the fetus.

Pathologic development of the falciform ligament can manifest itself with bowel obstruction and differential diagnosis may be difficult.[18] Therefore, it

Table 2 - The standard deviations and mean (millimeter) of the parameters of liver and abdomen according to the groups.

Group Trimester	N	Liver parameters Height	Width	Thickness	Volume	Weight	Density	Liver parameters Height	Width	Depth
1st trimester (9-12 week) (CRL: 70-100 mm)	7	13 ± 2	19 ± 3	11 ± 1	1.8 ± 0.6	1.8 ± 0.7	0.95 ± 0.8	13.14 ± 1.57	19.57 ± 2.87	11.14 ± 1.21
2nd trimester (13-25 week) (CRL: 110-240 mm)	66	25 ± 8	39 ± 12	18 ± 5	14.8 ± 12.5	15.6 ± 12.8	1.06 ± 0.7	25.58 ± 8.43	39.36 ± 11.61	18.33 ± 5.53
3rd trimester (26-37 week) (CRL: 250-350 mm)	39	41 ± 7	67 ± 11	26 ± 5	45.7 ± 21	47.3 ± 21.4	1.04 ± 0.3	41.26 ± 7.28	67.07 ± 10.99	26.52 ± 5.27
Full term (38-40 week) (CRL: 360-420 mm)	12	47 ± 8	82 ± 9	31 ± 8	71.8 ± 19.9	74 ± 20.3	1.03 ± 0.3	46.54 ± 8.26	82.09 ± 8.53	31.81 ± 8.51
Total (9-40 week) (CRL: 70-420 mm)	**124**	**32 ± 12**	**51 ± 20**	**22 ± 8**	**29.5 ± 25.9**	**30.7 ± 26.6**	**1.05 ± 0.7**	**31.69 ± 12.23**	**50.81 ± 20.42**	**21.71 ± 7.77**

$p<0.05$; differences between groups (except for liver height between 3rd trimester and full term groups, weight and volume between 1st trimester and 2nd trimester groups). CRL - crown rump length

Table 3 - Mean (millimeter) and standard deviations of the parameters of the lobes of liver and according to the groups.

Group Trimester	Right lobe width	Left lobe width	Caudate lobe height	Caudate lobe width	Quadrate lobe height	Quadrate lobe width
1st trimester (9-12 week) (CRL: 70-100 mm)	11 ± 2	9 ± 2	5 ± 1	4 ± 1	8 ± 1	4 ± 1
2nd trimester (13-25 week) (CRL: 110-240 mm)	22 ± 6	18 ± 6	10 ± 3	7 ± 2	14 ± 4	8 ± 3
3rd trimester (26-37 week) (CRL: 250-350 mm)	36 ± 10	31 ± 5	16 ± 3	11 ± 2	23 ± 6	13 ± 4
Full term (38-40 week) (CRL: 360-420 mm)	45 ± 7	38 ± 5	18 ± 4	13 ± 3	29 ± 5	17 ± 5
Total (9-40 week) (CRL: 70-420 mm)	**28 ± 12**	**24 ± 10**	**13 ± 5**	**9 ± 3**	**18 ± 7**	**10 ± 5**

$p<0.05$; differences between groups (except for caudate lobe height between 3rd trimester and full term groups). CRL - crown rump length is important to be aware of variations of the liver and its ligaments.[19] We did not find any anomalies or variations in the peritoneal attachments of the liver among our cases. We classified the fetuses into 4 groups according to the shape of the liver. We did not encounter type 2 (triangular) livers in the 1st and 2nd groups. Type 3 (square) liver was the most common in all cases. The number of type 1 (trapezoid) livers decreased in favor of type 4 (rectangular) in term fetuses. Nearer term, the shape of the liver began to resemble adult shape. We know that liver variations, pathologies and anomalies observed in adulthood may be associated with the intrauterine period.[15] Knowing the developmental variations of the fetal liver will help researchers to better identify liver pathologies and variations in adulthood.

Previous studies studying the length parameters of the fetal liver were performed on fetuses older than 2nd trimester using mostly obstetric ultrasound.[2-5,13,14] In these studies, they usually only measured the height of the liver. In the present study, however, we measured, in addition to the height, the width and the thickness between 9 and 40 weeks of gestation. We observed that these parameters show a linear increase with gestational age. We calculated the ratios of the width to the height and thickness of the liver, and found that the increase in these ratios was not the same. The rate of increase in the width and the height of the liver exceeded that of the thickness with advancing gestational age. Comparing the upper abdominal height, width and depth with the liver parameters revealed that the liver grew at the same rate as the abdomen in the transverse and vertical directions, while in the sagittal axis the liver growth rate fell short of the abdominal growth rate. When we compared our findings on liver height with the data acquired in studies performed using obstetric US,[3,5] we found that our findings were in agreement between the 20th week and term. However, US studies do not give information before the 20th week. Since the data for the 20th-40th week period is in agreement, the data pertaining to 9th-20th weeks would be useful as well in evaluating the fetal liver in that period. Roberts et al[4] assessed the fetal liver height in fetuses with gestational diabetic mothers with US and found the fetal liver higher than normal. In another study by Roberts et al,[20] the fetal height was below average in 18% of small-for-gestational age (SGA) fetuses. Similarly, Kuno et al[21] reported that the liver height was 30% lower than average in SGA fetuses. These studies highlight the importance of knowing the normal range of the fetal liver size.

Previous studies with obstetric US,[5,6] provide the range of fetal liver weight broken down for gestational weeks. However, there is available no data as to how the weight of the liver, in addition to other parameters varied before the 20th week. In this study, we acquired data on the biological variation in the weight of the fetal liver between 9-40th weeks. Our findings on liver weight are in line with previous investigations.[5,6] Previous studies report that the liver comprises 10% of the body weight at the 10th week and 2% at birth.[1,15] Our measurements show that the liver comprises 6-7% of the body weight in the 1st and 2nd trimesters and this ratio drops down to 3-4% nearer term. These ratios are in contrast to the reference books, and we believe this is due to the fetuses in this study being fixed in formalin.

Kuno and colleagues[21] measured liver volume in SGA fetuses, and reported that the volume decreases significantly from the mid 3rd trimester onwards. They suggest that liver volume is a good measure and emphasize the need to know the normal range of liver volume. Similar to the findings of Kuno et al,[21] we, in a larger series spanning 31 gestational weeks from 9-40 weeks, found a high correlation between liver volume and gestational age (p<0.001, r=0.86). The density of the fetal liver, calculated by dividing the weight to volume did not show any change throughout the gestation, and we observed no difference among groups (p<0.05). This shows that the weight and the volume of the liver increase at a similar rate.

A literature search did not reveal any publications regarding the structures on the visceral surface of the liver. We detected a linear increase in the width of the left and the right lobes with respect to gestational age in the present study. The fact that the ratio between right and left lobe sizes does not show a significant change (p>0.05) throughout the gestation implies that both lobes grow at a similar rate. Moreover, we demonstrated a high positive correlation between the sizes of the caudate and quadrate lobes and gestational age. Comparisons of these parameters among groups revealed a non-significant difference in the height of the caudate lobe between the 3rd and 4th groups (p>0.05), while the widths of the caudate and quadrate lobes as well as the height of the quadrate lobe demonstrated a significant increase (p<0.05).

To date, there are no studies on the localization of the porta hepatis on the visceral surface of the liver. Therefore, to determine the localization of the porta hepatis on the visceral surface of the liver we measured the distances between the center of the porta hepatis and the margins of the liver and examined how these measurements varied throughout pregnancy. We took the proportions of these measurements, namely, the distance to the right margin/distance to the left margin, and the distance to the upper margin/distance to the lower margin. Right/left ratio did not show a significant change during the fetal period (p>0.05), while upper/lower ratio decreased with gestation.

Comparing the upper/lower ratio among groups showed a significant change between groups, with the exception of between 3rd and 4th groups (p<0.05). This suggests that the porta hepatis moves towards the upper margin of the liver with advancing gestational age. If we consider the porta hepatis a stable, fixed-positioned structure, then it is possible to say that the section of the liver beneath the porta hepatis grows more rapidly than the section above the porta hepatis.

Many studies suggest that fetal liver size measurements are valuable tools in detecting intrauterine growth retardation, gestational diabetes, intrauterine infections, isoimmunization, fetal heart failure, neoplasms, certain metabolic diseases and fetal macrosomias and their follow-up.[2,9-12] We require knowledge of the pathologies and anomalies of the fetal liver for their diagnoses and treatments, and this necessitates a thorough knowledge of the anatomy. Anatomical dissections yield more precise and reliable information than radiological methods. We carried out the present study on a larger sample size compared to studies in the literature, and performed more detailed measurements. Therefore, our findings are a useful guide for ultrasound investigations of the liver. Furthermore, the data is helpful for the evaluation of fetal autopsy materials in forensic medicine and fetal pathology departments.

In conclusion, the data acquired in this study will facilitate the diagnosis of anomalies, pathologies and variations of the fetal liver and may contribute to future studies in obstetrics, perinatology, forensic medicine, and fetal pathology.

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