Fetal Intrahepatic Calcification: A Case Report

Özgür Dündar, Ercüment Müngen, Levent Tütüncü, Murat Muhcu, Yusuf Ziya Yergök

[1]*Clinics of Gynecology and Obstetrics, GATA Haydarpaşa Training Hospital, İstanbul*

Abstract

Objective: Although fetal hepatic calcification detected by prenatal ultrasonography is not a rare entity, the significance of this finding and management of such cases are not well-known. The aim of this study is to present a case of prenatally diagnosed fetal intrahepatic calcification and to review the related literature.

Case: A 25-year-old, gravida 2, para 1 woman was followed in our department begining from 11 weeks of gestation. The results of routine antenatal blood and urinary analyses were within normal limits. Her obstetric and medical history was unremarkable. Maternal serum triple screening for Down syndrome performed at 16 weeks of gestation was negative. Two foci of fetal intrahepatic calcifications were detected by ultrasonography at 25 weeks of gestation. Detailed fetal ultrasonographic examination and fetal echocardiography showed no additional abnormality. Repeated serologic studies for syphilis and TORCH infections were negative. At 39 weeks of gestation an elective Cesarean section was performed because of breech presentation, and a male infant weighing 3200 g was delivered. Postnatal evaluation of the newborn by physical examination, serologic analyses for infections and cranial and abdominal ultrasonographic examinations revealed that intrahepatic calcification was an isolated benign finding.

Conclusion: Detailed fetal ultrasonography and fetal echocardiography for associated abnormalities, serologic tests for syphilis, TORCH and parvovirus B19 infections should be performed in cases in which fetal hepatic calcifications are detected on prenatal ultrasonographic examination. Fetal karyotyping should also be offered especially when additional structural anomalies are present.After fetal abnormality, aneuploidy and infection are ruled out,isolated cases have a good prognosis.

Keywords: Prenatal diagnosis, intrahepatic calcification, fetal karyotype.

Fetal intrahepatik kalsifikasyon: olgu sunumu

Amaç: Fetal intrahepatik kalsifikasyonlar, fetal karaciğerde çevredeki kemik dokulara benzer ultrasonografik ekojenite gösteren parlak alanlar olarak tanımlanır. Prenatal ultrasonografide ender rastlanan bir bulgu olmamasına karşın, klinik pratikte intrahepatik kalsifikasyonların önemi ve yönetimi ile ilgili bilgiler sınırlıdır. Prenatal dönemde saptadığımız bir intrahepatik kalsifikasyon olgusunu literatür eşliğinde sunmayı amaçladık.

Olgu: Yirmibeş yaşında G:2, P:1, A:0 olan ve 11. gebelik haftasından itibaren antenatal polikliniğinde izlenmeye başlayan hastanın rutin antenatal kan ve idrar analizleri normal sınırlardaydı ve obstetrik anamnezinde özellik yoktu. Onaltıncı gebelik haftasında yapılan üçlü tarama testi negatifti. Yirmibeşinci gebelik haftasında yapılan ultrasonografik incelemesinde fetal karaciğer parankimi içinde iki odak halinde hiperekojen alanlar (kalsifikasyonlar) saptandı. Ayrıntılı fetal anatomik ultrasonografik inceleme ve fetal ekokardiografi sonucunda ek anomali saptanmadı. TORCH ve sifiliz yönünden tekrarlanan serolojik incelemeler normal olarak bulundu. Otuzdokuzuncu gebelik haftasında fetal makadi prezentasyonun devam etmesi üzerine, elektif şartlarda sezaryan ile 3200 gr ağırlığında bir erkek bebek doğurtuldu. Doğumdan sonra yenidoğanda yapılan muayene, mikrobiyolojik serolojik çalışmalar, tüm batın ve intrakranial ultrasonografik incelemeler sonucunda hepatik kalsifikasyonların benign izole bir bulgu olduğu sonucuna varıldı.

Sonuç: Fetal intrahepatik kalsifikasyon saptanan olgular detaylı fetal ultrasonografi ve fetal ekokardiyografi ile fetal anomaliler yönünden değerlendirilmeli, TORCH, parvovirüs B19, sifiliz yönünden serolojik araştırmalar yapılmalı ve özellikle ek fetal anomali saptanan olgulara fetal karyotip tayini önerilmelidir. Tüm bu incelemeler sonucunda izole olgularda prognoz iyidir.

Anahtar Sözcükler: Prenatal tanı, intrahepatik kalsifikasyon, fetal karyotip.

Correspondence: Dr. Özgür Dündar, GATA Haydarpaşa E. H., Kadın Hastalıkları ve Doğum Kliniği, Tıbbiye Cad. 34668 Üsküdar-İstanbul
e-mail: ozgurdundar72@yahoo.com

Background

Increased echogenic areas in fetal abdomen are defined as abnormal bright areas similar to bone echogenity. Fetal liver calcification (FLC) is a case that hyperechogenic areas in fetal liver are shown by ultrasonography and having rate of 1/1307-1/1750 for incidence of appearance in prenatal ultrasonography.[1-3] It was reported that FLC may appear together with fetal infection (especially cytomegalovirus infection),[3-4] vascular illnesses of liver[5] and liver tumors.[6] Also, the relationship of FLC with chromosomal anomalies and other anomalies are reported.[7] Though FLC is relatively prevalent; causes, results and long-term prognosis of it could not precisely explained.

We hereby presented intrahepatic calcification case found in prenatal ultrasonography in our case by accompany of literature.

Case

While Mrs. E.K was a 25 years old G:2, P:1, A:0 pregnant for 11 week, her antenatal controls were started. First routine analyzes of E.K. who did not have any pathology in her CV were determined as normal. In TORCH (toxoplasmosis, rubella, cytomegalovirus, herpes simplex) research, Rubella Ig G (+) and CMV (cytomegalovirus) Ig G (+) and Ig M (-) and Ig G (-) for other viral markers were found. Risk of Trisomy 21 was found as 1:6042 in Triple test done in 16th gestational week. When the patient applied in 25th gestational week that did not come to previous controls, TORCH Ig G and Ig M were requested when 2 isolated calcification on liver were found in the ultrasonography examination (Figure 1). Rubella Ig G (+) and CMV Ig G (+) and Ig M (-) and Ig G (-) for other viral markers were found. No cordocentesis for the purpose of karyotype determination was applied due to the fact that Trisomy 21 risk was found as 1:6042 in Triple test done in 16th gestational week and intrahepatic calcification was found in 25th gestational week and also calcifications were as two isolated focuses in liver parenchyma and no additional anomaly was found in genetic sonogram which meant that intrahepatic calcification was an isolated case.

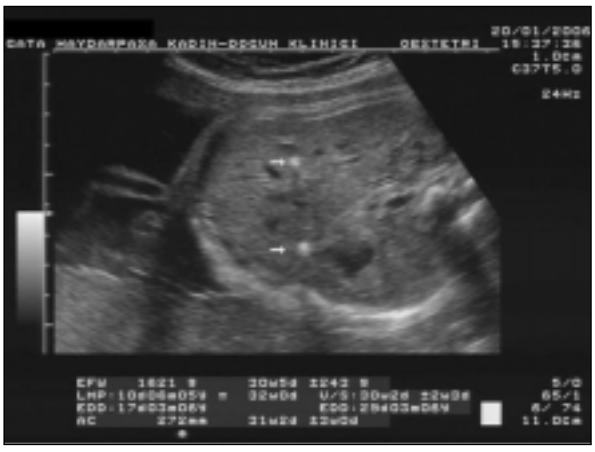

Figure 1. Intrahepatic calcification in 25th gestational week.

The patient which was invited monthly until to the 30th gestational week, once in each 2 weeks in between 30th and 36th gestational week and weekly after 36th gestational week was monitored by fetal biophysics score, NST and umbilical artery doppler studies and no fatal complication appeared. E.K. gave birth as alive and having 3200 gr male by cesarean delivery in her 39th gestational week on the determination of fetal presentation as anus and its presence up to 39th gestational week. It was thought that hepatic calcifications were a benign isolated diagnosis after examination, microbiological serologic studies and all abdomen and intracranial sonographic inspections done by clinic on newborn after birth.

Discussion

FLC is relatively a prevalent diagnosis and all fetuses found calcification should be monitored closely in terms of malformation, viral infection and chromosomal anomaly. If no pathology is found during this observation, neonatal result is generally good. If a hyperechogenic area is found in liver at ultrasonographic examination, intrauterine infection, ischemic infarcts, portal and hepatic venous thromboemboly, tumors, mud and stone of gall bladder should be remembered. While most information of FLC were being achieved from cases8 with spontaneous abortus, autopsy of infants or ill newborns,[9] early diagnosis by fetal sonography is possible as a result of using real-time ultrasonographies with high resolution and increase of knowledge and experience of doctors.1 Prenatal diagnosis of FLC was done first in the middle of 1980s.[10,11]

Carroll and Maxwell assemble the FLC into three groups as to its localization as peritoneal, parenchymal and vascular.[12] Calcified lesions in peritoneal liver calcification are on liver surface and

they appear due to peritonitis growing as a result of ruptured hydrometrocolpos or meconium peritonitis growing as a result of intestine rupture. This relationship was reported by other authorities.[13,14,15] Parenchymal liver calcification appears as a result of intrauterine infection (cytomegalovirus, herpes simplex, rubella, varicella zoster, echovirus, parvovirus B19) and primary (hemangioma, haemangioendothelioma, hamartoma, teratoma, hepatoblastoma) or metastatic (neuroblastoma) tumors.[3,4,10] First, intrauterine infection is remembered in parenchymal liver calcification and while nodular calcified areas are found in ultrasonography at infections, complex mass image including increased echogenic areas in tumors is monitored.[3,4] Vascular lesions causing FLC is examined in three categories. These are calcified portal or hepatic venous clots and focuses related to ischemic liver growing as a result of thromboemboly. Fetal ultrasonography can not differentiate between calcified portal venous thrombus and calcified venous thrombus and parenchymal calcifications. Simchen et al did not see any difference between reasons and results of parenchymal and calcifications on liver surface.[7] Most frequent reason in vascular lesions is vascular failure. While Blanc et al first[21] defining FLC due to vascular failure in the case, Friedman et al later reported calcified portal venous in totally 6 newborns that 3 of them were observed as having multiple fetal anomaly.[9] Hawass et al, in cases with spontaneous abortus, defined FLC in 33 cases by anatomic dissection and histopathologic studies in radiographies done by contrast materials[8] and they reported calcification related to hepatic venous thrombus in 18 of cases, calcification related to portal venous thrombus in 12 of cases, parenchymal calcification in 2 of cases and mixed type calcification in one case. While Hawass emphasizing that FLC and fetal anomalies are related in a high rate (85%), he stated that 33% of mothers have oral contraceptive usage and that there is an inverse ratio between gravida and FLC.[8]

A few pathogenic mechanisms are put forth for calcified thrombus seen in livers of newborns. While fetal liver embolization is caused by thrombosis in placental venous in some cases, big parietal venous thrombus was found in placenta of some newborns with portal venous thrombus.[13] In another theory, it is said that fetal venous thrombus is formed of intravascular fibrin formation growing as a result of maternal or oscillation of fetal thromboplastin. Because, calcified fibrin thrombosis which was formed when fetus was alive were found in autopsies of death-born infants.[9,13] In another theory explaining calcified thrombus formation, it is mentioned that an anemia appears due to placental damage secondarily occurring to vascular thrombus and organ infarcts appear as a result of it.[11,13] But clinical data support the last theory less.[1] Ultrasonographic diagnoses showed that subcapsularis calcifications first appear due to vascular lesion,[11] diffuse calcifications arise from ischemic infarcts.

It is reported in first studies that relationship between FLC and fetal anomaly is too much.[8,9,11] Blanc et al13 reported heavy fetal anomaly in 43% of 21 cases, Hawass et al[8] reported heavy fetal anomaly in 85% of 33 cases, Friedman et al[9] reported heavy fetal anomaly in 50% of 6 cases. Incidence of FLC and multiple fetal anomalies is seen too much due to the fact that data are achieved from abortus materials and autopsies of newborns born ill or dead. Avni et al reported calcification dispersed over liver surface in 4 cases and parenchymal calcification in 2 cases within 6 cases having liver cyst together with increased liver echogenity.[17] Avni reported that calcification in liver was isolated in 3 of 6 cases and results were good; trisomy 18 was found in two of three cases and one case was resulted as abortus. After this study, it was emphasized that intrauterine diagnosis would be hard if it was liver cyst and a certain diagnosis would be diagnosed by a successful surgery. Bronshtein et al[1] found FLC 14 of 24600 pregnants (1/1750) in between 14th and 26th gestational week they reported that multiple fetal anomaly accompanied to FLC in 21% of these cases. It is reported that chromosomal anomalies are seen much in FLC cases growing due to vascular lesions in articles reporting that relationship of FLC and multiple fetal anomaly is seen highly.[8,9] While Blanc et al[13] was reporting trisomy 18 in 2 cases in their series, Bronshtein et al[1] reported trisomy 18 in 2 cases in their series including 14 cases.

Bronshtein et al1 reported FLC incidence as 1/1750. They did detailed sonographic examination and bacterial, virological and serological examinations applied amniocentesis for 14 fetuses. One or two focal focuses in 12 fetuses, 4 dispersed focuses in 1 fetus and diffuse calcification together with peritoneal and intestinal calcification in 1 fetus are reported in this study. Trisomy 18 in 2 fetuses and heavy fetal anomaly accompanied by hydronephrosis and dwarfism of three fetuses and

these fetuses are done miscarrying. Bronshtein found no toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus or syphilis serologically in any case in the study, and in amnios fluid cultures, they found no cytomegalovirus in examination of urine of newborn. They reported that 10 of 14 cases were normal at delivery and 9 of 10 born fetuses were healthy and normal in controls 4 months and 4.5 years later.

Stein et al reported that intrahepatic calcification was found in 33 fetuses in between 16th 38th gestational weeks and 4 of them died in their works they retrospectively studied intrahepatic calcification found in between 16th and 40th gestational weeks.[18] No examination is done for cystic fibrosis and chromosomal anomalies. Parenchymal in 29 cases and surface calcification in 4 cases were found within 33 cases in which intrahepatic calcification was found. No relationship could found between the type of calcifications and anomalies and their results. Only ultrasonographic intrahepatic calcification was found in one fetus and cytomegalovirus infection was positive in that case and it was seen that calcification focuses in liver increased in next controls. While normal postnatal results were gained from 24 of 25 fetuses (96%), cytomegalovirus infection was found in one fetus. It is reported that additional anomaly was found in 8 fetuses and while 5 of these fetuses were alive, only 2 fetuses born as healthy.

Joseph ve ark.[23] tanımladıkları olgu sunumunda, orta ve büyük damarların internal elastik laminasında kalsiyum depolanması ile karakterize nadir bir otosomal resesif hastalık olan idiopatik infantil arterial kalsinozisi (İİAK) bildirmişlerdir. Onsekiz haftalık monozigotik ikiz gebelik olgusunda ultrasonografide fetuslardan birinde karaciğerde kalsifikasyon görerek ayrıntılı incelemenin yapıldığını raporlamaktadırlar. Bu hastalık tablosunda yaşamın ilk yıllarında koroner arterlerde oklüzyona bağlı myokardial iskemi sonucu ölüm görülmektedir. Hastalığın prenatal tanısı aort ve pulmoner arter kalsifikasyonu, hipertrofik kardiyomyopati ve nonimmün hidrops ile sınırlıdır. Bundan önceki yayınlarda İİAK tanıları üçüncü trimesterde konurken, bu yayında erken dönem ikinci trimesterde de tanı konabileceği vurgulanmaktadır.[24]

Achiron et al found no chromosomal anomaly in all fetuses and in their works including totally 5 cases which have parenchymal calcification in 3 cases and mixed type calcification (parenchymal and superficial) in 2 cases they reported that 4 fetuses with isolated calcification born as healthy and that they terminated gestation due to the fact that 1 fetus included fetal anomalies addition to calcifications.[19] Koopman and Wladimiroff reported incidence as 1/1037 in their works including totally 7 cases that 5 of them are isolated FLC and 2 of them are mixed type FLC and they told that fetuses with isolated calcification born health and other 2 fetuses had additional anomalies and trisomy 18 was found in one of these fetuses and gestation having trisomy 18 was ended and other fetus was ended after finding it in utero.[2] In this work, appearance frequency of anomaly together with calcification is reported as 20-50% in fetuses though isolated calcification and good neonatal result. There publications showing that trisomy 18 and 13 together with FLC.[1,2,17] Satge et al reported that they found liver calcification in autopsy by ending gestation in trisomy 9 case that they diagnosed by cordocentesis.[20] Jay et al reported amniocentesis and partial mosaic trisomy 8 in fetus on 16th gestation week which has cardiac and skeleton anomaly together with FLC.21 There are also publications showing relationship of FLC and skeleton anomaly.[10] Also, trisomy[21,18,14,13] and monosomy X together with FLC are reported in newborn and dead born infants.[9,13]

Simchen et al[7] reported isolated liver calcification in 21 patients (35%) and abnormal fetal diagnoses together with liver calcification in 40 patients (65%) of 61 patients that they found FLC in between 15th and 40th gestational weeks. Central nervous system anomalies in 13 pregnants, cardiac anomalies in 12 pregnants, cystic hygroma in 12 pregnants, skeleton anomalies in 11 pregnants and hydrops fetalis in 9 pregnants in 40 pregnants found fetal anomaly. Intracardiac echogenic focus (11 patients) and hyperechogenic intestine (10 patients) are frequently found in these cases as minor dysmorphic diagnosis. Intrauterine retardation was observed in 12 of cases with FLC. Surface calcification was found in 9 patients and parenchymal calcification was found in 52 patients of 61 patients with FLC and single focus in 25 patients and multiple focus in 36 patients are reported. No relationship between Localization and number of FLC and infection, aneuploid or other anomalies. Amniocentesis was applied to 34 patients in this study and karyotype anomaly was reported in 18% of cases by finding abnormal karyotype in 11 patients. Trisomy 13 was found in 4 patients having karyotype anomaly, trisomy 2 was found in 2

patients, monosomy x (45,X) was found in 1 patient and other chromosomal anomalies such as 4p-, 22q+ or 8p+ were found in other 3 patients. While heavy intrauterine retardation, oligohydroamnios, cerebral ventriculomegaly, hydrops fetalis and hyperechogenic intestine were observed together with cytomegalovirus infection in one fetus, multiple liver calcification together with parvovirus B19 infection was reported in one fetus. The writer emphasizes that even there is no other fetal anomaly together with FLC, chromosomal anomaly may exist. Simchen tells that there is no publication showing relationship of parvovirus B19 with FLC without additional fetal anomalies by showing relationship of parvovirus B19 with FLC.

Joseph et al[23] reported idiopathic infantile arterial calcinosis (IIAC) which is a rare autosomal recessive illness characterized by calcium storage at internal elastic lamina of middle and big veins. They reported that they did a detailed examination by observing a liver calcification in ultrasonography at eight week monozygotic twin gestation case. Death is observed as a result of myocardial ischemia related to occlusion in coroner arteries in the first hears of life in that illness. Prenatal diagnosis and aorta and pulmonary artery calcification of the illness is limited with hypertrophic cardiomyopathy and non-immune hydrops. While IIAC diagnoses are done in third trimester, it is emphasized in this publication that it might be diagnosed in early second trimester.[24]

Conclusion

Cases having FLC should be evaluated by detailed fetal ultrasonography and fetal echocardiography in terms of fetal anomalies and serological researches should be done in terms of TORCH, parvovirus B19 and syphilis and chromosomal anomalies should be excluded. Fetal karyotype determination should be done certainly in cases having additional ultrasonographic diagnosis. Prognosis is good in isolated cases after these examinations.

References

1. Bronshtein M, Blazer S. Prenatal diagnosis of liver calcifications. *Obstet Gynecol* 1995; 86: 739-43.
2. Koopman E, Wladimiroff JW. Fetal intrahepatic hyperechogenic foci: prenatal ultrasound diagnosis and outcome. *Prenatal Diagn* 1998; 18: 339-42.
3. Drose JA, Dennis MA, Thickman D. Infection in utero: US findings in 19 cases. *Radiology* 1991; 178: 369-74.
4. Yamashita Y, Iwanaga R, Goto A, Kaneko S, Yamashita F, Waseda N, et al. Congenital cytomegalovirus infection associated with fetal ascites and intrahepatic calcifications. *Acta Paediatr Scand* 1989; 78: 965-7.
5. Nguyen DL, Leonard JC. Ischemic hepatic necrosis: a cause of fetal liver calcification. *Am J Roentgenol* 1986; 147: 596-7.
6. Rypens F, Avni EF, Abehsera MM, Donner C, Vermeylen DE, Struyven JL. Areas of increased echogenicity in the fetal abdomen: diagnosis and significance. *Radiographics* 1995; 15: 1329-44.
7. Hawass ND, El Badawi MG, Fatani JA, Al-Meshari A, Makanjoula D, Edress YB. Foetal hepatic calcification. *Pediatr Radiol* 1990; 20: 528-35.
8. Friedman AP, Haller JO, Boyer B, Cooper B. Calcified portal vein tromboemboli in infants: radiology and ultrasonography. *Radiology* 1981; 140: 381-2.
9. Lince DM, Pretorius DH, Manco-Johnson ML, Manchester D, Clewell WH. The clinical significance of increased echogenicity in the fetal abdomen. *Am J Roentgenol* 1985; 145: 683-6.
10. Nguyen DL, Leonard JC. Ischemic hepatic necrosis; a cause of fetal liver calcification. AJR 1986; 147: 596-7.
11. Carroll SG, Maxwell DJ. The significance of echogenic areas in the fetal abdomen. *Ultrasound Obstet Gynecol* 1996; 7: 293-8.
12. Foster MA, Nyberg DA, Mahony BS, Mack LA, Marks WM, Raabe RD. Meconium peritonitis: prenatal sonographic findings and their clinical significance. *Radiology* 1987; 165: 661-5.
13. Zerbini M, Gentilomi GA, Gallinella G, Morandi R, Calvi S, Guerra B, et al. Intra-uterine parvovirus B19 infection and meconium peritonitis. *Prenat Diagn* 1998; 18: 599-606.
14. Muller F, Dommergues M, Aubry MC, Simon-Bouy B, Gautier E, Oury JF, et al. Hyperechogenic fetal bowel: an ultrasonographic marker for adverse fetal and neonatal outcome. *Am J Obstet Gynecol* 1995; 173: 508-13.
15. Avni EF, Rypens F, Donner C, Cuvelliez P, Rodesch F. Hepatic cysts and hyperechogenicities: perinatal assessment and unifying theory on their origin. *Pediatr Radiol* 1994; 24: 569-72.
16. Stein B, Bromley B, Michlewitz H, Miller WA, Benacerraf BR. Fetal liver calcifications: sonographic appearance and postnatal outcome. *Radiology* 1995; 197: 489-92.
17. Achiron R, Seidman DS, Afek A, Malinger G, Lipitz S, Mashiach S, et al. Prenatal ultrasonographic diagnosis of fetal hepatic hyperechogenicities: clinical significance and implications for management. *Ultrasound Obstet Gynecol* 1996; 7: 251-5.
18. Stage D, Gasser B, Geneix A, Malet P, Stoll C. Hepatic calcifications in a Fetus with trisomy 9 that underwent cordocentesis. *Prenat Diagn* 1994; 14: 303-6.
19. Jay A, Kilby D, Roberts E, Brackley K, Platt C, McHugo J, Davison EV. Prenatal diagnosis of mosaicism for partial trisomy 8: a case report including fetal pathology. *Prenat Diagn* 1999; 19: 976-9.
20. Lince DM, Pretorius DH, Manco-Johnson ML, Manchester D, Clewell WH. The clinical significance of increased echogenicity in the fetal abdomen. *Am J Roentgenol* 1985; 145: 683-6.
21. Wax JR, Blackstone J, Pinette MG, Cartin A. Hepatic vascular calcification: An early second trimester sonographic feature of idiopathic infantile arterial calcinosis. *Am J Obstet Gynecol* 2001; 185: 1267-8.
22. Simchen MJ, Toi A, Bona M, Alkazaleh F, Ryan G, Chitayat D. Fetal hepatic calcifications: Prenatal diagnosis and outcome. *Am J Obstet Gynecol* 2002; 187: 1617-22.
23. Blanc WA, Berdon WE, Baker DH, Wigger HJ. Calcified portal vein thromboemboli in newborn and stillborn infants. *Radiology* 1967; 88: 287-92.
24. Juul S, Ledbetter D, Wight TN, Woodrum D. New insights into idiopathic infantile arterial calcinosis. *Am J Dis Child* 1990; 144: 229-33.