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Fetal "gallstones" are still an unsolved mystery. Case series.

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Abstract

Background. Echogenic content in the fetal gallbladder is rather an incidental finding during third-trimester ultrasonography. The etiology, clinical course, and prognosis of this condition are still unclear. We highlight the demographic, clinical and ultrasound characteristics of our patients with echogenic content in the fetal gallbladder. **Methods.** This is a retrospective single-center study conducted at the University of Medicine and Pharmacy Cluj-Napoca, Romania, between March 2022 and April 2023. All pregnant patients who were admitted to the hospital and had echogenic content in the fetal gallbladder detected by ultrasound were identified. The clinical and ultrasonography parameters were obtained from the databases of the ultrasound units and the medical records of the patients. **Results.** Four patients were found to have echogenic content in the fetal gallbladder. The mean maternal age at diagnosis was 27.5 years (range 25–31). All patients had singleton pregnancies. The mean gestational age at diagnosis was 36.5 weeks (range 35–40). In all cases, the predominant aspect of echogenic content on ultrasound was multiple hyperechogenic foci; additionally, in one case, sludge was also observed. The mean maximal length of the hyperechogenic foci was 3.375 mm (range 1.6–5.4). All fetuses were delivered at full term, either vaginally or by cesarean section. The mean weight at birth was 3082.5 g (range 2800–3450). In all four cases, the EC disappeared spontaneously at birth. Neither of the four newborns displayed digestive symptoms or complications during the follow-up. **Conclusion.** The EC is still a medical mystery since little is known about its etiology and long-term outcome. Many cases are likely to be undetected until after birth; therefore, fetal gallbladder examination should be included in the US routine. The condition appears to be benign, and usually, it improves naturally after birth. Consecutively, asymptomatic newborns with EC can be managed through a wait-and-see approach.

Key-words: fetal gallstones; fetal cholelithiasis; fetal biliary echogenic content; fetal echogenicities; fetal gallbladder

Introduction

Echogenic content (EC) in the fetal gallbladder is rather an incidental finding during the third-trimester ultrasonography. It may appear in the gallbladder lumen as hyperechogenic foci, or diffuse echogenic material (sludge). EC can create acoustic artifacts such as distal shadowing, comet tail, and twinkling on occasion [1-3].

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In 1928, A.H. Potter cited two cases of prenatal cholelithiasis diagnosed at the time of autopsy as the first description of this condition to appear in the medical literature [4]. Fetal autopsies were the only diagnostic possibility before the arrival of ultrasound (US). The first case of EC described by US in a patient with preeclampsia was reported by Beretsky and Lankin in 1983 [2]. Forty years later, there is still a lack of prospective cohort research; as a result, crucial characteristics of EC, such as etiopathogenesis, natural course, and outcome, are still unclear. We recently conducted a systematic review from which we can draw certain conclusions regarding the evolution and outcome of fetuses with EC [5]. Nonetheless, we must acknowledge that the etiopathogenesis of this condition remains an enigma.

In this study, we highlight the demographic, clinical and ultrasound characteristics of our patients with EC.

Material and methods

This is a retrospective single-center study conducted at the University of Medicine and Pharmacy Cluj-Napoca and the 1st Department of Obstetrics and Gynecology at the Emergency County Hospital Cluj-Napoca, Romania, between March 2022 and April 2023. All pregnant patients admitted to the hospital who had EC detected by US were identified. The clinical and US parameters were retrospectively obtained from the databases of the US units and the medical records of the patients. The patients were scanned using a Voluson S8 ultrasound machine with abdominal convex array volume probe RAB6-RS (GE Healthcare, Zipf, Austria). The US aspect of EC (sludge or hyperechogenic foci) was observed, and the acoustic artefact was described (distal shadowing, comet tail or twinkling). In addition, obstetrical and neonatal outcome as well as data regarding follow-up during and after pregnancy were recorded. The only published algorithm for the assessment and follow-up of newborns with EC [5] was applied. For this study, informed consent was obtained from the patients, according to the World Medical Association Declaration of Helsinki, revised in 2000, Edinburgh.

Results

Four patients were found to present EC. The mean maternal age at diagnosis was 27.5 years (range 25-31). All patients had singleton pregnancies. The mean gestational age at diagnosis was 36.5 weeks (range 35-40). The mean of the patients' BMI was 26.6 (range 25.4-28.5).

Fig 1. Case No. 1. At 38 gestational weeks, multiple hyperechogenic foci with comet tail artefacts were discovered in the fetal gallbladder.

In all cases, the predominant feature of EC on US was multiple hyperechogenic foci; additionally, in case No. 3, sludge was also observed. The mean maximal length of the hyperechogenic foci was 3.375 mm (range 1.6-5.4). All fetuses were delivered at full term, vaginally or by cesarean section. The mean weight at birth was 3082.5 g (range 2800-3450).

One of our patients was diagnosed with COVID-19 at 12 weeks of gestation, representing the third reported case of an association between COVID-19 during pregnancy and echogenic content in the fetal gallbladder.

In all four cases, the EC disappeared spontaneously at birth. Neither of the four newborns displayed digestive symptoms or complications during the follow-up.

Maternal, US, obstetrical, and neonatal parameters are included in Table I.

Figures 1-4 and movies 1-4 depict US images that are representative of the cases included in this study.

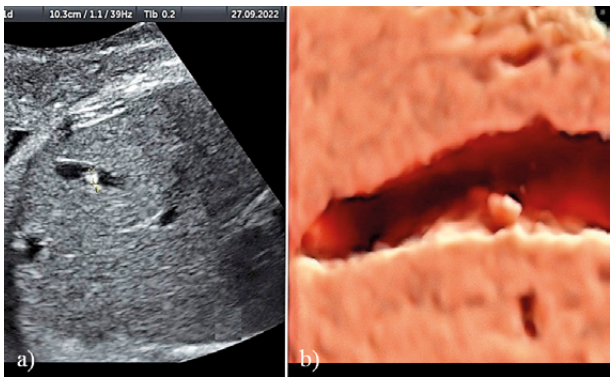

Fig 2. Case No. 2. a) At 40 weeks of gestation, biliary hyperechogenic focus measuring 3.7 mm in diameter was found. There are no acoustic artefacts to be observed; b) 3D rendered image of hyperechogenic focus in the fetal gallbladder lumen.

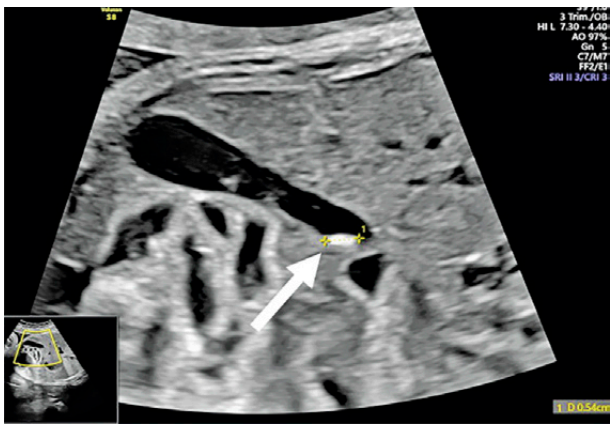

Fig 3. Case No. 3. Echogenic content within the fetal gallbladder was found at 36 gestational weeks. It consists of sludge and a hyperechogenic focus (arrow) that does not have acoustic artefacts and is located near the neck of the gallbladder.

Table I. Demographic, ultrasound, and maternal-fetal characteristics of the cases studied.

Case	1	2	3	4
maternal parameters				
age at diagnosis (years)	31	25	28	26
parity	nullipara	nullipara	multipara	multipara
type of pregnancy	singleton	singleton	singleton	singleton
medical history	- cholecystectomy - mild COVID-19 at 12 GW - a miscarriage at 5 GW	- a miscarriage at 5 GW	- cholecystectomy - a miscarriage at 7 GW	- premature birth at 34 GW
actual conditions	- hypertriglyceridemia - hypercholesterolemia - healthy carrier of hepatitis B virus	- hereditary prothrombin thrombophilia - carrier of group B Streptococcus	- cholestasis of pregnancy - hypothyroidy	- late IUGR
family history	- father with diabetes mellitus type 2	- mother with diabetes mellitus type 2	negative	negative
BMI (kg/m2)	26.4	26.1	28.5	25.4
US aspect of EC				
sludge	no	no	yes	no
number of foci	multiple	multiple	multiple	multiple
maximal length (mm)	2.8	3.7	5.4	1.6
distal shadowing	no	no	no	no
comet tail	yes	no	no	yes
twinkling	not assessed	not assessed	no	no
obstetrical outcome				
GA at diagnosis (weeks)	35	40	36	35
GA at delivery (weeks)	39	40	37	38
mode of delivery	CS on request	CS on request	iterative CS	vaginal
maternal outcome	postpartum depression	no complications	no complications	no complications
neonatal outcome				
gender of the newborn	female	male	female	female
weight of the newborn (g)	3080	3000	3450	3000
Apgar score at 5 minutes	10	10	9	10
US at 2 days	resolution	resolution	resolution	resolution
follow-up of the baby	asymptomatic at 1 year	asymptomatic at 6 months	asymptomatic at 4 months	asymptomatic at 1 month

GW: gestational weeks; IUGR: intrauterine growth restriction; GA: gestational age; CS: cesarean section

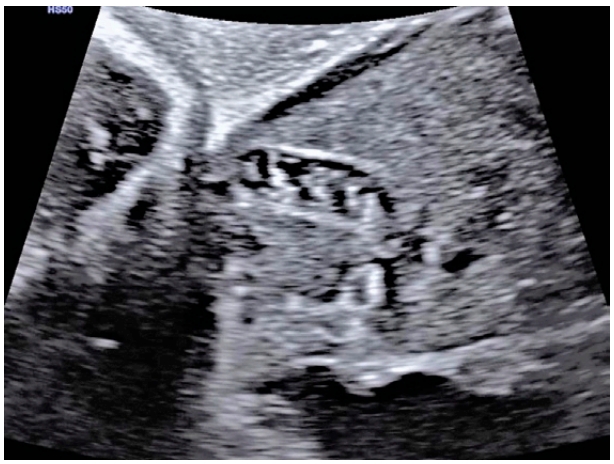

Fig 4. Case No. 4. Multiple hyperechogenic foci with comet tail artefact were observed in the fetal gallbladder at 35 gestational weeks.

Discussion

In this study, we describe the demographic, clinical, and US features of four cases of EC diagnosed in our unit over a period of 13 months.

The incidence of EC is reported to be 0.48% [5]. The small number of cases found in literature might not reflect the disease's actual low incidence, but rather a lack of paying attention to the fetal gallbladder during obstetrical US [6] or, in the case of retrospective studies, a deficiency of US images [1]. Although technology has advanced, about 70% of cases of EC are still discovered after birth [4], making it highly likely that the reported number of cases in fetuses is significantly underestimated [7,8]. The exact incidence of EC is therefore unknown, and it can only be determined in a large prospective study of nonselected patients who underwent meticulous evaluation of the fetal gallbladder [7].

EC is typically detected during the third trimester of pregnancy, as was the case with our patients. Likewise, in the group of 523 fetuses examined after 28 weeks in the study by Kiserud et al, six cases of EC were identified, equating to an incidence of 1.15%, which is twice as high as reported in other studies. However, none of the 1.133 fetuses in this study evaluated by US before 28 weeks displayed EC [9].

The fetuses included in our study were the result of singleton pregnancies. Although twin pregnancies have been reported to be impacted by EC, typically only one twin is at concern [1,3,10-13]. There are two case reports of twin pregnancies in which both fetuses were affected [14,15].

In the present study, three of the fetuses were female, consistent with research indicating that the incidence of EC is three times higher in female than in male fetuses [4]. Recent research suggests a slight male preponderance among EC cases [1]; however, there are other studies that contradict the male prevalence [3,6,14].

The birth weight of the newborns in our study was normal; they were neither growth restricted nor large for gestational age. These results are in line with the study of Cancho et al, who found an overall mean birth weight of 3.285 g (95% CI: 2,805-3,765) [16].

In case No. 1 we report an association between Covid-19 during pregnancy and fetal EC. To the best of our knowledge, only two cases of Covid-19 during pregnancy that resulted in fetal EC have previously been reported [17,18]. It was not possible to demonstrate a causal connection between the two conditions.

The patient in the case No. 1 has a medical history of metabolic syndrome with hypertriglyceridemia, hypercholesterolemia, and cholecystectomy for gallstones; in the meantime, she is a healthy hepatitis B virus carrier. The patient in the case No. 3 had undergone a cholecystectomy. Currently, she was hospitalized with cholestasis of pregnancy. The fetus in the case No. 4 was affected by late intra-uterine growth restriction. In the first two patients' family histories, we found that each had a parent with type 2 diabetes mellitus. Multiple maternal risk factors, including cholestasis during pregnancy or a biliary disorders (gallstones, cholecystitis) accompanied by dyslipidemia, have been proposed [12]. Some authors provided a comprehensive list of maternal conditions potentially associated with EC [19,20]. To date, however, a causal relationship of various maternal diseases with fetal EC was unable to be confirmed.

Among fetuses with EC, Kiserud et al identified multiple related malformations or disorders [9]. On the other hand, some authors believe that EC is a benign, isolated condition [16,21,22].

EC in our cases appeared as hyperechogenic foci in the gallbladder lumen. In the cases No. 1 and No. 4, EC did not exhibit distal shadowing but instead comet tail artifact. In cases No. 2 and No. 3, neither distal shadowing nor a comet tail was present. The absence of pericholecystic fluid, dilatation of the bile ducts, or thickened gallbladder in all cases allowed for a differential diagnosis with cholesterolosis and adenomyomatosis. Only the cases No. 3 and No. 4 were investigated with color Doppler but the twinkling artifact, which was only discussed by Annac et al [1], was not detected. Neither genetic analysis nor other imaging techniques, such as magnetic resonance imaging, were deemed necessary in any of the cited references, nor were they performed in any of our cases.

As in the first reported case, informing the mother of a clinical diagnosis based solely on US images could induce an elevated level of anxiety. We are discussing a condition that, in the vast majority of cases, does not produce symptoms, for which follow-up of asymptomatic individuals is not recommended and treatment is not necessary [1,11,12]. Moreover, in the overwhelming majority of cases, the EC entirely disappears shortly after birth [5]. Given the potential for psychological difficulties when announcing a fetal disease, parents must be given this reassuring information [23].

The differential diagnosis of EC includes calcified hepatic masses (hepatoma), gallbladder tumors (hemangioendothelioma, adenoma), intestinal calcifications, and meconial peritonitis. The sonographer must be aware of these conditions since it might be challenging to differentiate between them in certain situations, such as when the gallbladder is constricted [15,21,24].

All of our patients delivered at full term, as was the case in all of the cited references. We believe that there is no reason to deliver fetuses prematurely because of EC if obstetric circumstances do not necessitate a premature birth; furthermore, intrauterine complications linked with this condition are quite uncommon.

EC spontaneously disappeared at birth in all fetuses in our study. The detected EC lacked distal shadowing, suggesting that they were not solid "gallstones." This is the most intriguing aspect of this condition, as it is difficult to accept that the EC are genuine "gallstones" that suddenly disappear without producing any digestive symptoms in newborns. The babies were followed-up for varying periods of time, and neither manifested digestive symptoms or complications. However, the spontaneous resolution of EC during the first year of life appears to be its natural course [12,15]. Relevant to the unfavorable evolution are the early gestational age at diagnosis, related familial or maternal conditions, and US appearance of the EC. The development of EC after 30 weeks of gestation in the absence of risk factors was associated with a favorable clinical course [4], as observed in our reported patients.

There are currently no recommendations addressing the optimal treatment for neonates with asymptomatic EC. Therefore, based on a systematic review of the literature, we have proposed an algorithm for the evaluation and follow-up of babies with EC, which has been applied in our cases [5].

The retrospective type of this study, as well as the small number of patients that were followed up for a short length of time, limits its scope. This makes it impossible to draw a valid conclusion about the EC's clinical implications. Prospective studies and a longer follow-up period are required to clarify the etiology, maternal and fetal risk factors, genetic involvement, natural history, and outcome of newborns with EC. Deeper comprehension might serve to prevent the development of this condition [25].

Conclusion

The EC is still a medical mystery since little is known about its etiology and long-term outcome. In the case of EC, the US description cannot ensure a genuine disease diagnosis. Informing parents of a clinical diagnosis based solely on ultrasound scans may cause major psychological issues. Many cases are likely to be undetected until after birth; therefore, fetal gallbladder examination should be included in the US routine. The condition appears to be benign, and usually, it improves naturally after birth. Therefore, asymptomatic newborns with EC can be managed through a wait-and-see approach. The babies should be monitored for spontaneous resolution after appropriately reassuring the parents; no medical or surgical intervention is advised if the patients are asymptomatic.

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Movie 1.1 Case No. 1. At 38 gestational weeks, multiple hyperechogenic foci with comet tail artefacts were discovered in the fetal gallbladder.

Movie 1.2 Case No. 2. At 40 weeks of gestation, a biliary hyperechogenic focus measuring 3.7 mm in diameter was found. There are no acoustic artefacts to be observed.

Movie 1.3 Case No. 3. Echogenic content within the fetal gallbladder was found at 36 gestational weeks. It consists of sludge and a hyperechogenic focus (arrow) that do not have acoustic artefacts and are located near the neck of the gallbladder.

Movie 1.4 Case No. 4. Multiple hyperechogenic foci with comet tail artefact were observed in the fetal gallbladder at 35 gestational weeks.