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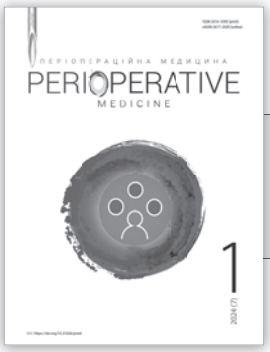

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Cholelithiasis in newborns — myth or reality?

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Abstract

Introduction: *In the past, cholelithiasis in newborns was considered extreme a rare finding, but with increasing use of ultrasound (USG) examination the abdomen is also found more and more often in them.*

Objective: *The objective of the presented work was to assess the frequency of occurrence at least as a guide cholecystolithiasis in newborns and to characterize its spontaneous development or capture it also the occurrence of complications from the biliary system in these children.*

Materials and Methods: *The author examined the cholecyst using USG over four months in 339 newborns (including the period of the COVID-19 pandemic), of which 273 children with adequate postpartum adaptation ("physiological" newborns) and 66 children with postnatal adaptation disorders who required more intensive medical care and in whom they therefore occurred to an increased extent risk factors for the development of cholelithiasis ("pathological" newborns).*

Results: *In 5 children from the first group (1.8 % of these children, of which 3 girls and 2 boys) and in 4 children from the second group (6.1 % of these children, of which 2 girls and 2 boys) was found ultrasound finding of echogenic material in the gallbladder. Among these children, 3 children went (1 from the first and 2 from the second group) o USG image of cholecystolithiasis, in 4 children (3 from the first and 1 from the second group) about the so-called USG image. "sludge-balls" and for 2 children (one from each group) o USG image "sludge". Frequency of USG image of classic cholecystolithiasis it was thus 0.36 % in "physiological" and 3.0 % in "pathological" newborns. The obvious the predominance of the USG finding of echogenic material in the gallbladder in either gender not recorded by the author. It was found in all "physiological" newborns during subsequent USG checks with the original finding of echogenic material in the gallbladder confirmed spontaneous adjustment USG findings at the age of 1 month. In three of the original 4 "pathological" newborns with the original finding of echogenic material in the gallbladder, this USG persisted image even at the age of three months and at least one of them at the age of over one of the year. They were not observed clinically in any of the monitored newborns significant complications demonstrably related to the biliary system.*

Conclusion: *USG finding of echogenic material in the cholecyst (and also cholecystolithiasis as such) therefore, it can be considered a relatively frequent finding with a good outcome in the newborn age prognosis and the very rare occurrence of complications, while the participation of risky factors in its formation is significant. Despite the good prognosis, USG follow-up should be recommended of these children in order to detect possible complications of cholelithiasis at an early stage.*

Key words: *cholelithiasis, newborn, ultrasonography, sludge, SARS-CoV-2.*

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Introduction

Cholelithiasis has been detected in the past in human fetuses, newborns and infants only relatively rarely and that is why such a finding usually occurs in generally considered exceptional. But wideusing an ultrasound (USG) examination abdomen has significantly increased in recent times detected cases of cholelithiasis in newborns. The frequency of its occurrence remains very likely still rather underestimated nowadays, since many cases of neonatal cholelithiasis it escapes diagnosis. The presented work aimed to find out at least approx frequency of occurrence of cholecystolithiasis in newborns and with subsequent USG follow-up to characterize in diagnosed patients spontaneous development of ultrasound and clinical findings, possibly capture the occurrence of complications from the side biliary system in these children.

A Set of Patients

The first group of children examined by us consisted of newborns hospitalized after childbirth in the ward physiological newborns who were without clinical difficulties ("physiological" newborns, in the next text only "F" newborns). USG examination was with them, it is usually carried out by the 5th day of the child's life. The second group consisted of hospitalized newborns after delivery in the ward for pathological newborns, and that due to their immaturity, difficulties with postpartum adaptation and the like ("pathological" newborns, in the following text only "P" newborns). In the case of this second group, it was USG examination performed only at the time when the clinical the child's condition allowed. Group "P" of newborns we are considering their clinical difficulties as also the treatment procedure that is used in them (prematurity, longer-term restricted oral food intake, parenteral nutrition, infusion therapy, antibiotic treatment of perinatal infections, administration diuretics and other drugs, etc.) considered for a group with an increased incidence of risk factors of neonatal cholelithiasis.

Materials and Methods

Using the ultrasound device Aloka SSD-1400 using a convex 7.5 MHz probe was gallbladder and its contents examined in newborns. We carried out the examination at the time of sonography screening for obstructive uropathy, that is before releasing these children from the maternity hospital home [11, 12, 16–18, 20]. During the pandemic, all rules and protocols related to the safety, prevention and treatment of SARS-CoV-2 infection were followed [10, 13–15].

A thin-walled USG finding was evaluated as negative gallbladder with its anechoic contents. In case of visualization of echogenic material in the gallbladder, this was further classified as:

USG image of classic cholecystolithiasis — compact, hyperechoic, mobile formation in the lumen cholecysts with a distal acoustic shadow (Fig. 1).

b) USG image of "sludge-balls" — a compact formation in a cholecyst of medium echogenicity without distal acoustic shadow (Fig. 2).

c) "sludge" USG image — not very compact, hypoechoic material in the gallbladder without distal acoustic shadow (Fig. 3).

Children with a positive finding of echogenic material they were in cholecyst after an agreement with their parents examined approximately 1 month apart after the first examination, if the USG persists findings were repeatedly investigated initially in approximately 1-month

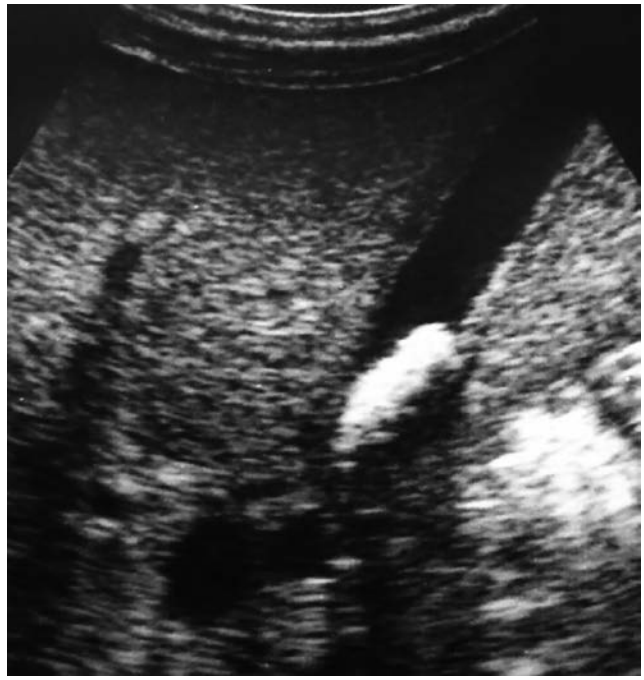

Fig. 1. USG image of classical cholecystolithiasis (compact, hyperechogenic and movable formation in the gall bladder lumen with distal acoustic shadow). Premature newborn (30th gestational week) with perinatal infection and postpartum respiratory insufficiency requiring antibiotic therapy, distension treatment, artificial lung ventilation and oxygen therapy, after phototherapy for hyperbilirubinemia and repeated transfusions for anemia

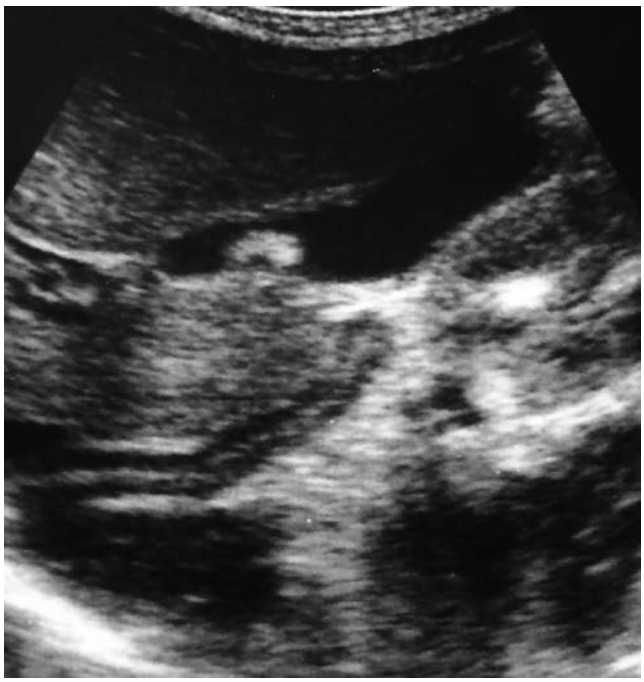

Fig. 2. USG image of "sludge-balls" (compact formation in the gall bladder lumen formation ofmedium echogenicity and without distal acoustic shadow). A physiological newborn without problems in postpartum adaptation

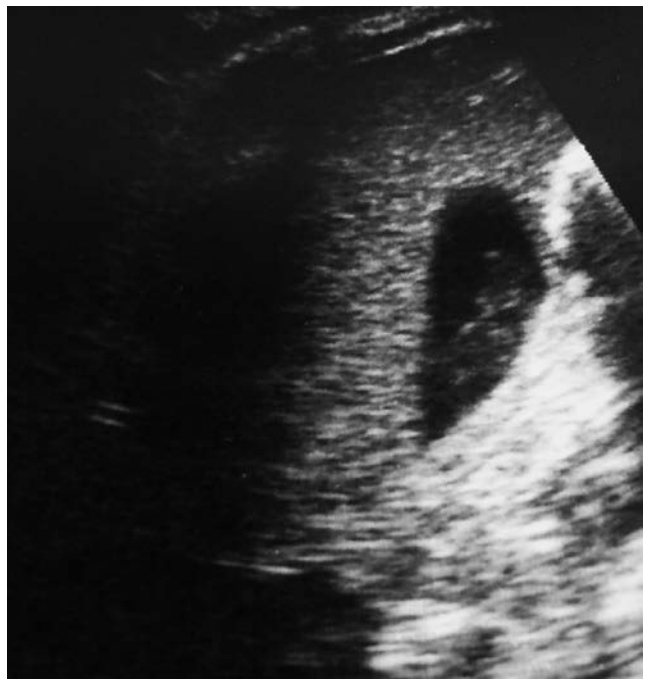

Fig. 3. USG image of "sludge" (low-compact hypoechogenicmaterial in gall bladder without distal acoustic shadow). A physiological newborn without problems in postpartum adaptation

time intervals, later in longer terms according to individual agreement with the child's parents.

Results

During four months we examined using an ultrasound examination 339 newborns (of which 273 "F" and 66 "P" newborns). Out of the examined set of children, there were 5 "F" newborns (1.8 % of these children, of which 3 girls and 2 boys) and in 4 "P" newborns (up to 6.1% of these children, of them 2 girls and 2 boys) detected by ultrasound finding of echogenic material in the gallbladder.

Among these children, 3 children (one "F" and two "P" newborns) by USG image of the classic cholecystolithiasis, in 4 children (three "F" and one "P") o USG image of the so-called "sludge-balls" and for two children (po one of "F" and "P") o USG image "sludge". Frequency occurrence of USG image of classical cholecystolithiasis was therefore 0.36 % for "physiological" and 3.0 % in "pathological" newborns.

It was present in all subsequent USG checks "F" newborns with an original finding of echogenicity material in the gallbladder confirmed spontaneous adjustment of USG findings at the age of 1 month.

On the other hand, in three of the original 4 "P" newborns the USG image of cholecystolithiasis persisted even at the age of three months. Least this finding was present in one of them even at the age of more than one year. In one child with a persistent finding cholecystolithiasis was detected during control USG examinations repeatedly observed virtually complete lack of cholecyst filling despite the fact that the child was fasting 5–6 hours before the examination. Possible the clinical significance of this finding will be determined further USG monitoring of the child.

Another "P" child was approximately 2 months old short-term hospitalized due to non-specific abdominal colic, but without confirming their connection with the presence of cholecystolithiasis. Overall, however, it can be concluded that none among the monitored newborns, they were not until at the age of 3 months no clinically significant observed complications from the biliary system.

Discussion

We were led to the implementation of the presented work repeatedly findings of asymptomatic cholecystolithiasis detected during USG examination in children in the first years of life. We tried to find out the frequency of occurrence in it cholecystolithiasis in newborns and also to characterize spontaneous development of

this finding as well as clinical status of such children and possibly in them detect the occurrence of complications from the biliary side system.

We succeeded within four months to examine a relatively extensive set of patients and although its range is compared to some of the older ones published works of other authors smaller, despite our work brings interesting results.

Unlike other authors who have published articles in Slovak and Czech professional literature with the topic of cholecystolithiasis in childhood (e.g. Volf and colleagues [36] or Zeman with the collective of authors [38]), we focused exclusively for newborn age. Physiology of creation and bile excretion in the prenatal and neonatal period period is not examined in detail, but it can be assumed that he has cholelithiasis in this period, as well as in other periods childhood, its specifics in terms of its etiology, pathogenesis, prognosis and therapy.

Cholelithiasis was detected in the past in newborns, infants and younger children only relatively rarely, usually symptomatic choledocholithiasis. Only exceptionally was she diagnosed cholecystolithiasis, which is often asymptomatic and therefore did not give reason for investigation of the child. For example, in a work published in In 1993, its authors describe a group of 40 younger children than one year with a diagnosis of cholelithiasis, with which met during the previous 17 years of practice. Only 6 of them were randomly detected, asymptomatic cholecystolithiasis (while with conservative treatment was observed spontaneously in two of them disappearance of cholelithiasis) and in 34 children it went about choledocholithiasis with initial manifestations such as cholestatic icterus (21 children), acholic stool (8 children), sepsis (4 children) and abdominal pain (1 child) [9]. On the other hand, around this time an article also appeared in the professional literature, in which 14 previously published were summarized cases of incidentally detected neonatal cholelithiasis, of which 12 newborns were asymptomatic and to the spontaneous adjustment of the finding to 6 months of life occurred in 8 of them. In children with the persistence of this finding even after 6 months of life was not necessary except for long-term follow-up no special treatment. The authors of the article therefore conclude, that accidentally detect cholelithiasis in newborns can be considered a benign condition with approximately 50 % probability of its adjustment during the first 6 months of life [28].

Wide use of ultrasound examination in the recent period, the number of those caught has significantly increased cases of cholelithiasis in newborns. Maybe however, assume that its incidence remains very likely even earlier today underestimated, since the USG examination of the abdomen so far it does not belong to newborn screening examinations and so many cases of neonatal cholelithiasis it escapes diagnosis. Cholecystolithiasis (in the sense of finding hyperechoic material in the gallbladder) is sometimes found already in fetuses during prenatal ultrasound examination. Typically, such a finding appears up to in the later stages of pregnancy (usually in the 3rd trimester pregnancy), is probably somewhat more common in boys and usually occurs later spontaneous retreat. When contracted gallbladder can sometimes imitate hepatic, or peritoneal calcification [24]. There are several available case studies on this topic [33, 35]. However, it is interesting in particular, a summary of data on 26 human fetuses, in whom it was detected during prenatal USG examination the presence of echogenic material in the gallbladder, between 28 and 42 weeks of gestation weeks at the time of diagnosis (average age 36.2 weeks). This echogenic material in the gallbladder was associated with acoustic shadow in 8 cases (30%), with comet artifact in 9 cases (35%) and no distal artifact was also present in 9 cases (35%). She was not with any of these children detected hemolytic anemia or any other known predisposing factor and neither clinical signs diseases of the biliary system. In 9 patients among 17 children who were followed up postnatally, there was a spontaneous disappearance of this echogenic material in the gallbladder. In 3 children, however, this one the finding persisted at least until the age of 4.5 years [8]. C holecystolithiasis in fetuses and some cases Cholelithiasis in the newborn age therefore represent the same phenomenon, differing only in term his diagnosis. They are probably important in its creation yet unspecified maternal predisposing factors factors that influence the postpartum period ends, which leads to the spontaneous disappearance of concretions. Another part of cases of cholelithiasis in newborns may be related to natural postpartum adaptations processes and changes such as temporarily limited oral food intake or physiological jaundice of newborns. And finally another part of neonatal cases cholelithiasis is associated with the occurrence of risk factors factors. Its clear distinction from the previous ones there are no groups of neonatal cholelithiasis often possible, especially in the absence of a reliable USG examinations that would precede the operation risk factor. Therefore, it is necessary to judge carefully some references about a possible

Table 1. Significant risk factors for the development of neonatal cholelithiasis.

prematurity
dehydration
prolonged starvation
hemolysis
total parenteral nutrition
administration of diuretics (furosemide)
biliary tract abnormalities
sepsis, perinatal infection
short bowel syndrome, malabsorption
cystic fibrosis
pseudohypoaldosteronism

neonatal association cholelithiasis with various diseases or syndromes.

On the other hand, however, the role of risk factors it is definitely not to be underestimated what it testifies to also a significantly higher incidence of cholelithiasis in "P" newborns compared to "F" newborns, which we observed in our ensemble.

In general, as risk factors for the development Cholelithiasis in the newborn age is mentioned in particular hemolysis, total parenteral nutrition, administration diuretic (furosemide) and prolonged fasting (tab. 1). For example, Almond and associates describe the cases of two newborns with the early onset of cholelithiasis, in which it was used extracorporeal membrane oxygenation (ECMO) and believe that just the above risk factors that are usually associated with the use of ECMO, may predispose to the development early cholelithiasis [4]. Randall with associates sonographically determined the incidence of cholelithiasis in 42 infants given furosemide and found that cholelithiasis occurred in these children significantly more often than in children who receive treatment they did not receive furosemide [30].

Other risk factors are prematurity, biliary tract anomalies, general infections in newborns (sepsis), bronchopulmonary dysplasia. In the later period, it is also necessary to take into account take the possibility of diagnosis of cystic fibrosis, diseases small intestine (intestinal malabsorption, syndrome short intestine, etc.), excessive nutrition and others.

Several authors describe a possible pathogenetic connection between pseudohypoaldosteronism and cholelithiasis at an early age and possibly already in during the fetal period, which probably arises as result of dehydration and electrolyte imbalance [23]. Diagnosis of pseudohypoaldosteronism at the same time may be overlooked, especially if there are salt losses only transitory. In these patients, therefore, apparently recommend regular USG checks with the aim of early detection of cholelithiasis [2]. Early biliary pseudolithiasis has been repeatedly described, which may occur during treatment by ceftriaxone (3rd generation cephalosporin), which induces reversible precipitation in the cholecyst. Vo they generally appear in the case of ceftriaxone treatment USG signs of pseudolithiasis and possibly also clinical symptoms after 9–11 days of treatment. This pseudolithiasis is usually asymptomatic and relatively it quickly improves spontaneously after the end of treatment [7, 19, 21, 26]. However, ceftriaxone-induced pseudolithiasis may not always be a clinically insignificant finding. For example, the case of a 6-year-old is described of a boy with treatment-induced cholelithiasis ceftriaxone caused acute jaundice [32].

Cholelithiasis occurs in children with Down syndrome probably more common than generally believed. For example, Aughton and associates describe the cases of three affected boys Down's syndrome, which she was at the age of one day, 12 weeks, or 4 months detected cholelithiasis, while all were on the cholelithiasis side asymptomatic [6]. Predominantly within case studies, they were assumed also multiple associations between cholelithiasis in early age and some syndromes, or diseases, for example, cholecystolithiasis described in a 1-month-old of a child with Klinefelter syndrome [3], the case of a congenitally affected newborn hyperinsulinism, in which after administration octreotide developed cholelithiasis associated with jaundice [29], or the case of a 2-month-old boy with VACTER syndrome in which cholelithiasis was diagnosed as the cause of persistent and progressive obstructive icterus connected with the finding of acholic stool [5]. We did not evaluate the "P" newborns we monitored specifically the presence of each of the above listed risk factors, but we satisfied only with a global "riskiness" rating dividing our file into "P" and "F" newborns, which is fully sufficient for the purposes of our work. Regarding the occurrence of neonatal cholelithiasis, there are several published works to determine its frequency in healthy newborns. In a study with probably the most numerous yet a group of

examined newborns performed her authors ultrasound screening in 6000 newborns and diagnosed cholecystolithiasis (stones) only in two children (aged 1 and 2 days) and in three other children they found numerous floating hyperechoic reflexes in the lumen of the gallbladder (positive they found the finding in a total of approximately 0.08 % of those examined children). In one of the aforementioned newborns this finding also persisted with cholecystolithiasis at the age of 6 months, in the other children the USG findings spontaneously adjusted to this age [25]. We found out in our file in comparison with the aforementioned work a significantly higher frequency cholelithiasis in newborns (we note that in the first group of physiological newborns without known risk factors for cholelithiasis and without clinical difficulties it was approx 0.36 % of examined children). The classification used by us The USG findings correspond to the commonly accepted ones criteria, it is even stricter in this in the sense that it requires the presence of an acoustic shadow to confirm the diagnosis of a concretion, as many as possible the authors do not consider it necessary. Used ultrasonic we also consider the instrument and probe frequency as fully sufficient for a precise evaluation USG findings. One of the reasons for the mentioned differences could be a smaller number examined by us of children compared to the aforementioned work. Impossible exclude even the influence of a possible (t. no. only hypothetical) seasonal variability of the occurrence of this USG finding in newborns as we are our tracking conducted only during four months of the year. The published results are closer to our results in another work in which the authors investigated using USG examination of the prevalence of cholelithiasis in 3500 newborns, while the examination was carried out during the first 4 days of life as part of the newborn screening.

Among those examined of children found sludge or cholelithiasis in 19 newborns (0.5%). None of these children had grades cholestasis. Subsequently, they followed 11 such children, whereas in 4 of them the finding of cholelithiasis persisted even at the age of 18 months [37]. The results in this regard are very interesting another study that estimated the incidence of fetal cholelithiasis at 0.39%, while the authors found none predisposing factor from the side of the fetus or the mother [1]. These data are practically identical to ours results in physiological newborns (examined during the first days after birth). Despite the fact that in most children with cholelithiasis detected in the newborn age will occur spontaneously the disappearance of these concretions, was described several case reports of children with symptomatic cholelithiasis, possibly with the occurrence of complications associated with this diagnosis. For example, the case of an infant with cholelithiasis is described, which developed a deficit on its basis of vitamin K with symptoms of profuse bleeding [27], or a case study of a newborn sonographically detected cholecystolithiasis and intrahepatic dilation of the bile ducts, indicating antenatal obstruction of the ductus choledochus, in which was performed laparoscopically at the age of 16 days operation. Intraoperative cholangiography confirmed wedged concretion in the infundibule of a cholecyst and histological examination subsequently confirmed the signs chronic cholecystitis [22]. In connection with cholecystolithiasis, although in early childhood as extremely rare finding, also discover the perforation of the cholecyst. Described is the case of a 3.5-month-old child, born premature at the age of 26 gestational weeks which received parenteral during the first 9 days of life nutrition. She was at the forefront of his clinical symptoms abdominal distension and failure to thrive. USG examination found the presence of ascites and complex cystic mass in the region of the porta hepatis. At the subsequent one cholecyst perforation was confirmed at laparotomy and cholecystolithiasis [31]. Considering the possibility of spontaneous adjustment is in case of USG findings of cholelithiasis in asymptomatic patients conservative procedure is indicated for infants — in general, only USG follow-up is sufficient. Surgical solution, possibly interventional radiological performance (ERCP) are considered only in symptomatic children, or in children with cholelithiasis arising on the basis of lithogenic diseases [34]. Deciding on surgical versus therefore, conservative treatment depends on several factors factors such as the severity of clinical symptoms, laboratory changes and ultrasound image, age and the general condition of the child, etc.

Conclusion

Finding echogenic material in a cholecyst (and also cholecystolithiasis as such) maybe in the newborn age to be considered relatively common a finding with a good prognosis and very rare occurrence complications. Nevertheless, it should be recommended USG follow-up of these children in order to detect possible complications of cholelithiasis.

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Жовчнокам'яна хвороба у новонароджених — міф чи реальність?

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Резюме

Вступ: *Раніше холелітіаз у новонароджених вважався дуже рідкісною знахідкою, але при все більшому використанні ультразвукового дослідження (УЗД) він діагностується все частіше.*

Мета: *Метою представленої роботи було хоча б орієнтовно оцінити частоту появи холецистолітіазу у новонароджених і охарактеризувати його спонтанний подальший розвиток або зафіксувати виникнення ускладнень з боку жовчовивідної системи у таких пацієнтів.*

Методи: *Автор досліджував жовчний міхур за допомогою УЗД протягом чотирьох місяців (включаючи період пандемії COVID-19) у 339 новонароджених, з них 273 дитини з адекватною післяпологовою адаптацією («фізіологічні» новонароджені) та 66 дітей з порушеннями постнатальної адаптації, які потребували більш інтенсивної медичної допомоги та мали підвищений ризик розвитку жовчнокам'яної хвороби («патологічні» новонароджені).*

Результати: *У 5 дітей першої групи (1,8 % цих дітей, з них три дівчинки і два хлопчики) та у 4 дітей II групи (6,1 % цих дітей, з них дві дівчинки і два хлопчики) було виявлено ехогенний матеріал у жовчному міхурі. Серед цих дітей троє (одна з першої та двоє з другої групи) на УЗД мали ознаки холецистолітіазу, у 4 дітей (3 з першої та 1 з другої групи) USG-зображення «сладж-кульок» та у 2 дітей (по одному з кожної групи) було виявлено «сладж». Частота УЗД-ознак класичного холецистолітіазу становила 0,36 % у «фізіологічних» і 3,0 % у «патологічних» новонароджених. Очевидне переважання на УЗД ехогенного матеріалу в жовчному міхурі в обох статей не зафіксовано автором. Під час наступних контрольних УЗД-перевірок відзначалось зникнення ехогенного матеріалу в жовчному міхурі у віці 1 місяця. У трьох із чотирьох «патологічних» новонароджених з виявленим ехогенним матеріалом у жовчному міхурі УЗД-ознаки зберігалися навіть у віці трьох місяців, а у одного з пацієнтів навіть у віці старше 1 року. Скарг та ускладнень, пов'язаних з жовчовивідною системою, не було у жодного з пацієнтів.*

Висновок: *УЗД-виявлення ехогенного матеріалу в в жовчному міхурі (а також холецистолітіаз як такий) можна вважати відносно частою знахідкою у віці новонародженості з хорошим прогнозом і дуже рідкісним виникненням ускладнень. При цьому участь ризикових факторів у його формуванні є істотною. Незважаючи на сприятливий прогноз, слід рекомендувати подальше УЗД-спостереження цих дітей з метою раннього виявлення можливих ускладнень жовчнокам'яної хвороби.*

Ключові слова: *жовчнокам'яна хвороба, новонароджений, УЗД, сладж, SARS-CoV-2.*