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The Natural History of Fetal Gallstones: A Case Series and Updated Literature Review

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Abstract

Introduction: The incidence of fetal gallstones is estimated at 0.45% and its clinical relevance after birth remains unknown. This study aimed to describe the natural history of fetal gallstones and their clinical sequelae after birth.

Methods: We queried a database of fetuses referred for second and third trimester sonograms performed for high-risk pregnancies, and identified cases with fetal gallstones (1996–2019). Demographics, prenatal/postnatal imaging findings, and clinical sequelae were collected. A literature review was performed according to PRISMA guidelines.

Results: We screened approximately 200,000 obstetric sonograms; 34 fetuses were found to have cholelithiasis. The median gestational age at the time of US was 35 weeks (range 22 – 38). Fifty-six percent were female and 11.8% were twin pregnancies with one affected fetus. Median maternal age was 28 years (range 17–42). Eight fetuses underwent postnatal imaging and 4 had persistent cholelithiasis. There was one case of *in utero* demise. Two patients had structural anomalies (renal and cardiac) by US. A subset of 17 patients was followed long-term (range 3–20 years), and none developed clinical sequelae from cholelithiasis.

Discussion/Conclusions: No child developed postnatal clinical sequelae related to cholelithiasis identified in utero. Fetal cholelithiasis can be managed expectantly without follow-up imaging in asymptomatic patients.

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Disclosure of interest

The authors report no conflict of interest.

Data availability statement

The data that support the findings of this study are openly available in Dryad at https://doi.org/10.7272/Q6H70D1J.

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Keywords

fetal gallstones; prenatal ultrasound; cholelithiasis

Introduction

The reported incidence of fetal gallstones, estimated at 0.45%, is much lower than the incidence of gallstones in adults [1,2]. On ultrasound, stones within the gallbladder appear as small echogenic intraluminal foci, occasionally with acoustic shadowing [2–4]. The natural history of fetal gallstones is unknown; other than two large case series [2,4], the literature consists of case reports of one to seven patients. Given the limited understanding of fetal cholelithiasis, it is difficult to counsel pregnant patients with a fetus who is incidentally noted to have gallstones. Furthermore, recommendations regarding postnatal imaging need to be better defined based on the expected outcome of this condition.[5] The purpose of this study was to present the experience from a high-volume prenatal diagnostic center over a 24-year period to determine the natural history of fetal gallstones and provide recommendations for postnatal follow-up and imaging.

Material and Methods

Case series

We queried a database of patients who were referred for second and third trimester obstetric sonograms to evaluate high-risk pregnancies between 1996–2019 at the University of California San Francisco, and identified patients with an incidental finding of fetal gallstones. The following inclusion criteria were applied: pregnant patients who 1) presented between 1996 and 2019, 2) were seen prenatally at least once at the University of California, San Francisco, and 3) underwent prenatal ultrasound (US) imaging that demonstrated fetal gallstones. Maternal demographic information (age, ethnicity, gravidity, parity) and postnatal outcomes (reported abdominal symptoms during well-child visits, hospitalizations, surgeries) were collected. The radiographic reports from prenatal and postnatal imaging studies (gestational/postnatal age at imaging, sonographic characteristics, presence or absence of cholelithiasis on earlier prenatal imaging) were reviewed. The study was approved by the University of California San Francisco's Institutional Review Board (IRB).

Literature review

According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [6], a literature review was conducted in the PubMed database using the following search terms and their combinations: "fetal", "prenatal", "gallstones", and "cholelithiasis" in April 2020. Inclusion criteria included original reports of patients with prenatally detected fetal gallstones. Exclusion criteria consisted of the following: review articles, articles that did not provide details about the patients' prenatal and/or postnatal course, and articles that we were unable to access. Two of the authors (HB, MS) independently reviewed the articles to determine those that fulfilled the inclusion criteria. The references of the included articles were then reviewed to capture additional studies that

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may not have resulted in the PubMed query. After final review, a total of 28 articles were ultimately included (Figure 1).

Results

Case series

During the 24-year period queried, thirty-four fetuses referred for second or third trimester obstetric sonograms due to high-risk pregnancies were incidentally noted to have cholelithiasis (Table 1). All 34 fetuses in our series had gallstones on prenatal imaging. Four patients (11.8%) had a single gallstone; sonogram reports from the remaining 30 patients did not quantify the number of gallstones present. Seven patients (20.6%) were noted to have sludge and two patients (5.4%) were found to have acoustic shadowing in the gallbladder in addition to gallstones.

The median gestational age at the time of sonogram showing fetal cholelithiasis was 34.7 weeks (range 22 – 38); only two were diagnosed with gallstones prior to 31 weeks. Pregnant patients underwent US imaging for a variety of indications, including evaluation for size unequal to dates, oligohydramnios, intrauterine growth restriction, and suspected fetal anomalies. Nineteen of the 34 patients had a prior obstetric sonogram in our system (typically a second trimester anatomy scan done at 18–20 weeks' gestation), which did not reveal fetal cholelithiasis. Fifty-six percent were female fetuses. Four (11.8%) were twin pregnancies and in all of these cases, only one of the twin pair had cholelithiasis. One fetus had growth restriction and suffered in utero demise at 27 weeks' gestation. The notable findings for this fetus included echogenic bowel on prenatal US and an elevated maternal serum alpha-fetoprotein (AFP). All 33 other fetuses survived to birth. Postnatally, one patient had nephrotic syndrome requiring renal transplantation; another was diagnosed with Trisomy 21 as well as aortic coarctation and ventricular septal defect (VSD) requiring repair; one patient was found to have Noonan syndrome; and one patient had a VSD and hypoplastic aortic arch requiring repair.

The median maternal age was 28 years (range 17–42) and maternal ethnicities were as follows: 32.4% (n=11), Hispanic or Latina; 20.6% (n=7), White; 17.6% (n=6), Black or African American; 11.8% (n=4), Asian; 2.9% (n=1), Native Hawaiian or other Pacific Islander; 2.9% (n=1), Black or African American and White; and 11.8% (n=4), not specified. Median gravidity was 2 (range 1–7) and parity was 1 (range 0–5). Five women had cholelithiasis themselves, seen on imaging prior to the index pregnancy and two had previously undergone cholecystectomy. One woman underwent cholecystectomy during pregnancy after gallstones were identified; the second was noted to have gallstones (detected while undergoing obstetric US) and underwent cholecystectomy after delivery.

Eight fetuses (23.5%) underwent postnatal imaging (US or CT) at an age ranging from 1 day to 18 years old, either to follow up the finding of fetal cholelithiasis or for other indications. Four of the eight patients were reported to have persistent gallbladder findings on postnatal imaging: described as "sludge" in 2 patients (at 1 and 2 days old), "gallstone" in 1 patient (at 18 months old), and 1 patient whose sonogram at 3 months of age showed a "3 mm

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hyperechoic structure near the gallbladder neck" that was later found (at 12 months) to have a "gallbladder fold at the previous region of echogenicity."

A subset of 17 patients (50%) was followed long-term with well-child visits; no patient developed clinical sequelae from cholelithiasis. One patient, currently 13 years old, developed intermittent chronic abdominal pain over the past year but has not undergone imaging and it is unknown whether the symptoms are related to cholelithiasis.

Literature review

Twenty-eight articles published from 1983 to 2020 were included, reporting on a total of 98 fetuses (Table 2). Studies were authored by researchers from North America, South America, Europe, Oceania, India, and Japan. There are nineteen case reports of 1–2 patients and two large case series. Brown et al. described 26 fetuses with cholelithiasis over a 7-year period [4] and more recently Sepulveda et al. presented 19 fetuses diagnosed with cholelithiasis over a 3-year period [2]. All but four fetuses were noted to have cholelithiasis during third trimester sonograms (range 19 – 42 weeks' gestation). Of the 22 studies that included imaging both during and after the neonatal period, 20 described patients with cholelithiasis on neonatal sonograms that resolved on follow-up exams (ranging from 3 weeks to 10 months of age). The articles reviewed did not report any clinical sequelae from cholelithiasis.

Discussion

Fetal cholelithiasis is a rare incidental finding with an unknown natural history. The objective of this study was to investigate the clinical sequelae of fetal cholelithiasis at a high-volume fetal treatment and prenatal diagnostic center. Of the thirty-four patients identified in our series with fetal cholelithiasis, eight patients underwent postnatal imaging, of whom three had persistent cholelithiasis. None of the patients developed any clinical sequelae attributable to their cholelithiasis.

The composition of fetal gallstones has not been studied, which limits our understanding of the process by which gallstones form in utero. Adults most commonly have cholesterol or mixed gallstones while children are more likely to have pigmented stones, secondary to hemolytic diseases, long-term TPN dependence, ileal disease, and congenital biliary disease [7,8]. The composition of fetal gallstones and how it compares to adult and pediatric gallstones is poorly understood. The fetal gallbladder can be seen as early as 12 weeks and is visualized on >90% of obstetric sonograms done between 16 to 34 weeks' gestation [9]. A postmortem study of fetal bile collected between 16 and 19 weeks' gestation revealed that more than 80% of the bile acids were conjugated with taurine, while 5–10% were unconjugated bile acids and bile acids conjugated with glycine [10]. This is different from adult bile, in which the ratio of taurine/glycine conjugates is approximately 1:3. The fetal total bile acid concentrations were 100-fold less compared to adult bile [10]. The combination of different bile acid conjugate composition and concentration may contribute to the rapid dissolution of gallstones postnatally.

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The risk factors predisposing to fetal cholelithiasis are unclear. Maternal history of gallstones, hemolysis, and transplacental distribution of Ceftriaxone have been proposed as possible precipitants. A maternal history of gallstones was seen in 7 cases in the literature review [4,11,12] and 4 cases in our series - this is not higher than the reported incidence of 7–15% in the general adult population [13–15]. Hemolysis is a known risk factor for the development of gallstones in the pediatric population, due to diseases such as sickle cell or spherocytosis [16], yet none of the mothers or fetuses in our series had a known history of hemolytic disease. Others have suggested that transplacental distribution of Ceftriaxone, known to increase precipitation of insoluble calcium salts [17,18], or increased maternal estrogen and progestin levels (such as twin pregnancies) [4,11,19] could play a role in the development of fetal cholelithiasis[20]. Our series included 4 sets of twins (3 monochorionic-diamniotic, 1 dichorionic-diamniotic) yet in all cases only one of the pair had cholelithiasis, which suggests that a genetic predisposition is unlikely. Furthermore, three fetuses had congenital anomalies and two fetuses had a genetic syndrome (Trisomy 21, Noonan). Additional investigations into fetal cholelithiasis are needed to elucidate potential risk factors.

In our case series and literature review, fetal cholelithiasis was typically detected during third trimester imaging but not seen on the routine anatomy scan (done at 18–20 weeks) and resolved shortly after birth. In the most recent large series of 19 fetuses, all cholelithiasis resolved on postnatal imaging [2]. Similar to our series, the largest case series to date of 26 fetuses found that 53% of patients who underwent postnatal imaging had resolution of their gallstones within 6 months [4]. The exact mechanism by which cholelithiasis resolves between the third trimester of pregnancy and the neonatal period is unknown. The bile flow appears to increase and change in composition postnatally, which may contribute to postnatal resolution [10]. Sepulveda et al. postulated that once feeding is established after birth, there are increased amounts of cholecystokinin which cause gallbladder contraction and allow the sludge or stones to pass into the duodenum [2]. We speculate that the unique bile composition combined with changes in bile flow could play a part in the dissolution of the majority of fetal gallstones.

Although fetal gallstones have been described in several case series, the clinical ramifications are unclear when there is an absence of symptoms in the mother (such as preterm labor), fetus, or neonate. There have been case reports citing complications such as cholecystitis [21], choledocholithiasis [21,22], and biliary perforation [23–25], but these reports are biased in their inclusion of symptomatic patients. For asymptomatic patients, there are no standard guidelines for follow-up, which has resulted in a paucity of long-term outcome data. While this limits our ability to perform high quality observational studies of this condition, given the lack of any clinical sequelae from fetal cholelithiasis in our series and the high chance of gallstone resolution shortly after birth, we do not believe that follow-up imaging is warranted in asymptomatic patients. Further studies will be needed, however, to determine whether there is a subset of fetuses with cholelithiasis whose imaging characteristics (e.g. size of gallstone, presence of acoustic shadowing) portend a higher chance for developing postnatal sequelae of gallstone disease and would therefore warrant further monitoring.

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This study has several limitations. As a tertiary care center, we routinely see patients who undergo prenatal imaging evaluation and receive the remainder of their obstetric and postnatal care at their local hospital. This contributed to the small proportion of patients with documented postnatal follow-up and imaging. The patient population may also be biased since our center is a referral practice for complicated, high-risk pregnancies. Nevertheless, to our knowledge, this is the largest published series of patients with fetal cholelithiasis. We anticipate that as the technology of prenatal imaging continues to improve, more fetuses may be incidentally noted to have cholelithiasis. Sharing this experience is thus important for obstetric imagers/sonologists who identify fetal cholelithiasis and maternal-fetal medicine providers who counsel patients on the meaning and consequence these ultrasound findings. In conclusion, the natural history for fetal gallstones appears to be resolution. Based on our series, we do not recommend postnatal imaging in asymptomatic patients.

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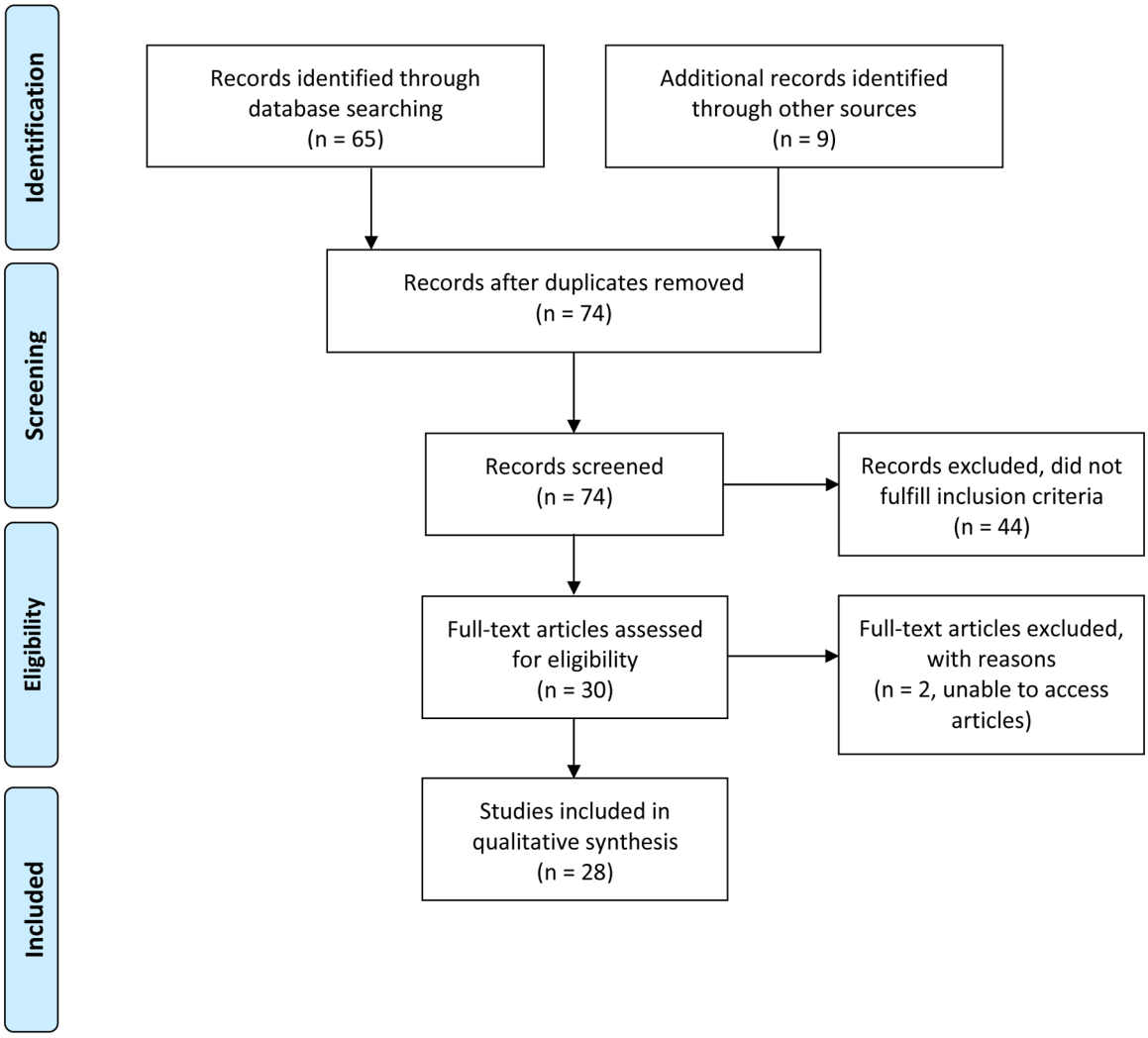

Fig. 1.
PRISMA flow diagram

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Table 1:

Patient series, divided into those with a known postnatal course (above double line), and those without a known postnatal course.

Year	GA at imaging	Sonographic findings	Fetus gender	Maternal age	Maternal gallstones	Postnatal imaging	Postnatal course
2000	33.4	Echogenic material in fetal GB raising possibility of fetal gallstones	F	19	?	CT at 18yo: no gallstones	Followed regularly, no issues
2003	21.7	Large calcified gallstone in GB	M	28	yes	no	Followed regularly, no issues
2003	37.1	Fetal gallstones within fetal GB	F	30	yes	no	Followed regularly, no issues
2004	37.3	Fetal gallstone	F	19	no	no	Followed regularly, no issues
2006	33.7	Gallstones within fetal GB	F	19	yes	no	Chronic intermittent abdominal pain, awaiting imaging
2007	36.1	Tiny echogenic foci in right upper abdomen suggestive of fetal gallstones	F	24	?	no	Followed regularly, no issues
2007	35	Fetal cholelithiasis	F	34	?	no	Followed until 4yo, no issues
2007	36	Fetal gallstones	M	28	no	US at 18mo: gallstone	Underwent gastrostomy tube in context of renal transplantation. Followed regularly, no issues
2008	37	Echogenic foci in fetal GB consistent with probable sludge versus small gallstones	M	35	?	no	Followed regularly, no issues
2009	34.1	Punctate bright echo within fetal GB with comet tail artifact possibly representing tiny gallstone	M	34	?	CT at 9yo: unremarkable gallbladder	Followed regularly, no issues
2009	?	Punctate brightly echogenic foci within GB which may represent gallstones or biliary sand	M	24	yes	no	IUGR with echogenic bowel, IUFD
2013	34	Fetal gallstones	F	24	?	no	Followed regularly, no issues
2013	?	Fetal cholelithiasis	F	?	?	US at 3mo: 3mm hyperechoic structure near gallbladder neck. US at 12mo: gallbladder fold at previous region of echogenicity.	Followed regularly, no issues
2014	33.6	Fetal gallstones	M	17	yes (prior cholecystectomy)	no	Followed for 1year

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Year	GA at imaging	Sonographic findings	Fetus gender	Maternal age	Maternal gallstones	Postnatal imaging	Postnatal course
2015	32.1	Fetal gallstones	M	34	no	no	Followed regularly, no issues
2017	35.9	Echogenic shadowing content within expected location of GB consistent with gallstones	F	30	?	US at DOL1: minimal amounts of biliary sludge	VSD and hypoplastic aortic arch repaired. Followed regularly, no issues
2017	34.3	Fetal gallstones	M	33	?	US at DOL2: gallbladder sludge	Noonan syndrome, required fundoplication for GERD, otherwise no issues
2019	34.6	Fetal gallstones	M	35	?	US at 3mo: no gallstones	Followed regularly, no issues
1996	37.9	Echogenic material is noted within fetal GB consistent with gallstones or sludge	F	32	?	no	-
1998	37.1	Fetal gallstones	M	35	no	no	-
2002	34.7	Fetal gallstones and sludge	?	25	no	no	-
2003	35.6	Fetal gallstones	?	24	?	no	-
2003	38.3	Echogenic material within fetal GB suggesting gallstones	M	28	?	no	-
2003	37	Tiny gallstones within GB	?	37	?	no	-
2004	28.6	Sludge or stones are present in the fetal GB	F	33	?	no	-
2007	33.3	Gallstones in GB of twin B only	M	18	?	no	-
2007	31.4	Gallstones and GB sludge	?	27	?	no	-
2008	34.6	Echogenic foci within GB consistent with sludge with possible gallstones in twin A	M	39	yes (prior cholecystectomy)	no	-
2008	31.4	Gallstones within GB lumen of twin B	?	22	?	no	-
2011	36.7	Echogenic shadowing in the region of the fetal GB, suggesting incidental fetal gallstones	F	18	?	no	-
2013	37	Multiple fetal gallstones	F	36	no	no	-
2018	33	Tiny echogenic foci within GB of twin A	?	39	?	no	-
2019	37.3	Fetal gallstones	F	42	?	no	Postnatally diagnosed with trisomy 21, VSD, ASD. Not followed after.
2019	35.3	Echogenic intraluminal material possibly	?	27	?	no	-

Year	GA at imaging	Sonographic findings	Fetus gender	Maternal age	Maternal gallstones	Postnatal imaging	Postnatal course
		representing tiny gallstones					

Abbreviations include GA, gestational age; GB, gallbladder; VSD, ventricular septal defect; ASD, atrial septal defect; IUFD, intrauterine fetal demise; US, ultrasound; DOL, day of life.

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Table 2:

Literature review

Year	Author	N	GA at detection	Prenatal imaging	Postnatal Diagnostics	Outcome
1983	Beretsky [3]	1	36	Well-defined echogenic focus within GB with shadowing	US at birth: gallstones	US at 1mo: no stones
1985	Heijne [26]	1	34	Multiple stones in GB	Neonatal US: multiple stones	US at 6mo: no stones
1988	Klingensmith [27]	1	37	Multiple echogenic, shadowing structures in GB	US at 3d: stones	US at 6wk: no stones
1989	Schirmer [21]	1	7th month	Multiple stones	US at 1d: multiple stones	Asymptomatic at 2yo, no imaging
1990	Abbitt [28]	1	33.4	Echogenic foci within GB	US at 1d: stones	US at 10mo: no stones
1992	Devonald [29]	7	37–41	Single vs multiple foci of echogenic foci within GB	Neonatal US in 6 patients: 3 without stones, 3 with calculi or echogenicity	1 patient with US at 18mo: calculi, 1 patient with US at 1mo: no stones; 1 patient with US at 1 wk: no stones
1992	Brown [4]	26	28–42	Echogenic foci in GB	17/26 with postnatal imaging, 9/17 no stones	17/26 with postnatal imaging, 9/17 no stones
1993	Suchet [30]	1	36	Nonshadowing echogenic mass which moved with gravity in GB	US at 2d: multiple intramural echodensities that had comet-tail artifacts on dependent and nondependent walls of GB	US at 9d: normal GB without echodensities or comet-tail artifacts. 6mo: asymptomatic patient
1994	Clarke [31]	1	19	Single gallstone	Neonatal US: single gallstone	US at 2mo: no stone
1996	Petrikovsky [32]	5	28–36	Fetal gallstones or sludge in GB neck	4 with postnatal imaging (1 with multiple stones, 3 normal GB)	1 patient with US at 3mo: no stones
1996	Stringer [33]	3	32–35	Multiple echogenic foci in GB, multiple mobile echogenic foci with shadowing	Patient 1: US at 1wk: single mobile echogenic focus in GB Patient 2: none Patient 3: none	Patient 1: US at 4wk: no stones (confirmed on multiple repeat US) Patient 2: US at 6wk: no stones (confirmed on US at 4y) Patient 3: US at 7wk: several gallstones
1996	Sepulveda [19]	1	36	Sludge in GB	Neonatal US: sludge in GB	No follow-up
1997	Kiserud [34]	6	33–38	Echogenic material/foci/ sludge within GB	US at 1–28d; two abnormal, 4 normal	Patient 1: US at ?: sludge Patient 2: US at 8mo: calculi Patient 3: US at ?: echogenic foci Patient 4: US at 5wk: no stones nl scan
1997	Nishi [35]	1	34	Nonshadowing opacity filling entire GB	US at 3d: echogenic foci	None
1998	Suma [36]	2	34, 37	Large shadowing echogenic mass within GB, GB completely filled with multiple small echogenic foci	US at 4d, 3d: both confirming stones	US at 8 weeks: no stones US at 7 weeks: no stones
1998	Hertzberg [37]	2	37, 37	Echogenic foci in GB, circumscribed group of echogenic foci with shadowing	US at 1d: stones	US at 8wk: no stones

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Year	Author	N	GA at detection	Prenatal imaging	Postnatal Diagnostics	Outcome
1999	Agnifili [38]	3	38	Three echogenic foci that did not change position with gravity, two echogenic foci free-moving with gravity, diffuse echogenic material in GB	None	No imaging, clinically asymptomatic.
2005	Muniuluri [39]	2	34	Small echogenic focus in GB, small gallstones in GB	1 patient: US at birth: 2 stones	Both patients: US at 8wk: no stones
2006	LaRiviere [40]	1	36	Echogenic structure thought to be GB filled with sludge or possible small stones	None	None
2006	Sheiner [41]	4	29–32	GB filled with gallstones	US at 3–4 wk: no stones	None
2010	Tam [11]	2	35, 35	Multiple gallstones (twin A), evidence of sludge (twin B)	Twin A neonatal US: multiple mobile gallstones	Twin A: US at 5wk: no stones Twin B: US at 3mo: no stones
2010	Holloway [12]	1	36	11mm hyperechoic mass suggestive of calculus in fetal GB	None	US at 2mo: large mobile calcified calculus within GB
2013	Triunfo [42]	1	35	Large nonshadowing multiple small echogenic foci within GB	US at 2d: minimal cholelithiasis	US at 2mo: no stones
2014	Suhag [43]	1	32	Multiple echogenic structures within the GB with normal hepatobiliary anatomy	US at 3d: two stones	US at 4wk: persistent stones US at 8wk: no stones
2014	Troyano-Luque [17]	2	26, >30	Distended GB with echogenic content of lumpy consistency	Patient 1: neonatal US: persistent cholelithiasis Patient 2: neonatal US: persistent cholelithiasis	Patient 1: US at 2.5y: symptomatic cholelithiasis Patient 2: US at 7mo: no stones
2017	Hurni [20]	2	33.4	Hyperechogenic intra-cystic cholelithiasis	US at birth: gallstones in twin A, no stones in twin B	US at 6mo: no stones
2018	Kesrouani [5]	3	21–29	Area of hyperechogenicity at the site of the GB	None	1 patient: US at 3 mo: persistent hyperechogenicity
2020	Sepulveda [2]	19	32.4–38.2	Echogenic material in GB	Neonatal US in 12 patients: 9 with stones, 3 no stones	US at 3wk-10mo in 12 patients: no stones

Abbreviations include GA, gestational age; US, ultrasound; GB, gallbladder.