Table 1 Literature review of series of non-visualized fetal gallbladder (NVGB) on prenatal ultrasound examination and final diagnoses

		Final diagnosis					
Reference	*NVGB**	*Aneu.*	*BA*	*CF*	*Other severe*	*GA*	*Healthy*
Blazer (2002)[1]	34	5	0	2	7	5	15
Ochshorn (2007)[2]	19	1	0	1	1	2	14
Shen (2011)[3]	21	3	0	1	1	0	16
Dugueperoux (2012)[4]	24	0	0	5	0	9	10
Dreux (2012)[5]	102	1	8	10	6	22	55

Data are given as *n*. Only the first author of each study is given. *Isolated or non-isolated NVGB. Aneu., aneuploidy; BA, biliary atresia; CF, cystic fibrosis; GA, gallbladder agenesis.

Role of fetal blood sampling in cases of non-visualization of fetal gallbladder

The fetal gallbladder is visualized from 14 weeks of gestation as an anechoic structure located below the liver in the right anterosuperior quadrant of the abdomen. Non-visualization of the gallbladder occurs in only 0.1% of pregnancies[1] and has been reported in association with a range of abnormalities, from benign gallbladder agenesis or empty gallbladder, to aneuploidies, cystic fibrosis (CF) and biliary atresia (BA), all of which carry a poor prognosis (Table 1)[1–5]. Based on two cases, we examined the potential utility of fetal blood sampling when the gallbladder could not be visualized by prenatal imaging.

Case 1 was a 37-year-old primigravida in whom ultrasound examination at 12 + 3 weeks' gestation had revealed a fetal nuchal translucency thickness of 5.2 mm. Karyotype determined following chorionic villus sampling was 46,XX. Subsequent ultrasound examinations at 18 + 1 and 21 + 2 weeks' gestation showed an atrioventricular septal defect and hyperechogenic fetal bowel, and the gallbladder could not be visualized. Amniocentesis was performed at 21 + 2 weeks, which confirmed normal karyotype, did not detect *CFTR* gene mutation and showed gamma-glutamyl transpeptidase (GGTP) level to be low ($< 1^{st}$ percentile[4,5]). At 24 weeks, ultrasound examination showed an interruption of the inferior vena cava, persistence of the azygos vein and left superior vena cava, and polysplenia. In this context of left heterotaxy syndrome, BA was suspected. The patient agreed to fetal blood sampling for a GGTP assay, which found GGTP to be > 10 multiples of the median (1628 IU/L) and thus a diagnosis of BA was deemed highly likely. According to local law, the patient elected to terminate the pregnancy owing to the poor prognosis associated with BA. Autopsy and histological hepatic examination confirmed BA and left heterotaxy syndrome.

In Case 2, routine ultrasound examination in a 27-year-old woman at 12 + 5 weeks' gestation showed an anechoic structure (14 × 12 × 14 mm) in the right flank of the fetus. Subsequent ultrasound examinations at 15 and 19 weeks' gestation confirmed the presence of a multiseptate intrahepatic cyst. By 23 weeks, the cyst had been replaced by a smaller hyperechogenic structure and the gallbladder could not be visualized, as was the case at repeat ultrasound examination at 33 weeks. Screening for CF was negative and, following parental consent, fetal blood sampling was performed which showed the GGTP level to be normal (55 IU/L). At 39 weeks, a 2680-g female neonate was delivered with normal clinical and biochemical findings. The gallbladder, bile duct and common hepatic duct were all detected on postnatal ultrasound examination.

Non-visualization of the fetal gallbladder has been associated with both benign (gallbladder agenesis) and severe (aneuploidy, BA or CF) abnormalities. Management of such cases includes karyotyping and screening for a CF mutation. Low amniotic fluid GGTP is suggestive of BA, but only before 22 weeks' gestation. After this, it is impossible to distinguish between a physiological decrease in GGTP levels and a morbid process[4,5]. As postpartum serum levels of GGTP are increased in cases with BA due to an impaired excretion of bile, we hypothesized that GGTP would also be increased in fetal blood. Blood levels of GGTP were abnormally high (1628 IU/L) in Case 1 (BA) and within the normal range (55 IU/L) in Case 2 (normal) when compared to that of 32 controls (median, 130 (range, 44–337) IU/L). In conclusion, in view of the severity of the disease, suspicion of BA might warrant the risks associated with amniocentesis before 22 weeks and that of fetal blood sampling after 22 weeks to allow for appropriate management of the pregnancy.

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