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Absent gallbladder on fetal ultrasound: prenatal findings and postnatal outcome

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ABSTRACT

Objectives *Fetal gallbladder non-visualization on prenatal ultrasound in the second trimester is uncommon and in most cases the gallbladder is detected eventually. Associations of gallbladder non-visualization with cystic fibrosis, aneuploidy, agenesis of the gallbladder and biliary atresia have been reported. We present our experience and review the literature.*

Methods *During the study period from January 2004 to June 2009 we collected prospectively cases of non-visualization of the fetal gallbladder in the second trimester. In each case the fetus was evaluated by two examiners on at least two occasions, at least a week apart. Cases with no additional sonographic malformations were designated as isolated. Further evaluation included follow-up scans and a meticulous search for fetal anomalies. All patients were offered genetic consultation. Cystic fibrosis testing, amniocentesis for karyotyping and analysis of fetal digestive enzymes in the amniotic fluid were offered.*

Results *We collected 21 cases of non-visualization of the fetal gallbladder, 16 of which were isolated and five of which had additional malformations. In four of these five, the associated anomalies were severe and the pregnancies were terminated for aneuploidy (two cases of trisomy 18 and one triploidy) or for the severity of the associated anomalies. Associated anomalies included left isomerism with complex cardiac anomaly and intrauterine growth restriction with multisystem anomalies. The fifth fetus had interrupted inferior vena cava with azygos continuation without other anomalies and the child was alive and well at the age of 4 years. In 15 of the 16 isolated cases, antenatal and postnatal development were normal at the last follow-up, ranging from 4 months to 2.5 years. One case of cystic fibrosis was diagnosed prenatally and this pregnancy was terminated. There were no diagnoses of abnormal karyotype or biliary atresia among cases of isolated non-visualization of the gallbladder.*

Conclusions *When prenatal non-visualization of the fetal gallbladder is associated with other severe malformation, aneuploidy should be suspected. When it is isolated, if cystic fibrosis is ruled out, the outcome is good.*

INTRODUCTION

Prenatal non-visualization of the fetal gallbladder (PNVGB) during the second trimester is rare[1,2]. In most cases, the gallbladder is visualized on follow-up ultrasound examinations in the third trimester or postnatally[2,3]. In a minority of cases[4], agenesis of the gallbladder, a benign condition, is confirmed. PNVGB can be isolated or found in association with other abnormalities. Isolated PNVGB has been reported in association with cystic fibrosis; in 60 at-risk fetuses, it was a finding in nine of 12 affected cases, with a positive predictive value of 100%[5]. However, the association is poor if the fetus is not at increased risk for cystic fibrosis[2]. When PNVGB is non-isolated, it is associated with an increased risk for fetal chromosomal abnormalities[2,6,7]. Some authors have suggested that PNVGB may be associated with biliary atresia[1,6–10] and that analysis of fetal digestive enzymes in the amniotic fluid may support a diagnosis of biliary atresia. The aim of this study was to assess the long-term follow-up of cases diagnosed prenatally with non-visualized gallbladder and to review the literature.

PATIENTS AND METHODS

Between January 2004 and June 2009, we collected prospectively and evaluated cases of PNVGB examined at 14–22 weeks at the ultrasound units of the Departments of Obstetrics and Gynecology in Shaare Zedek Medical

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Center and Hadassah Mount Scopus. PNVGB was classified as isolated when there were no additional sonographic abnormalities. In all cases, isolated PNVGB was established by two experienced examiners based on two examinations each, performed at least 1 week apart. Following a diagnosis of PNVGB, parental DNA analysis for cystic fibrosis was offered if this had not been done previously.

Genetic consultation and amniocentesis for fetal karyotyping and analysis of digestive enzymes (gamma glutamyl transpeptidase (GGTP), aminopeptidase M and intestinal alkaline phosphatase (AP)) were offered. These analyses were performed at Biochimie Hormonologie, Hopital Robert Debre, Paris, France. Fetal DNA analysis for cystic fibrosis was performed when both parents were found to be carriers.

Patients with isolated PNVGB were followed up by a late second- or early third-trimester ultrasound examination and by postnatal sonogram if PNVGB persisted. When an immediate postnatal scan at the hospital failed to visualize the gallbladder, an additional scan was performed at the age of approximately 1 month. When the gallbladder was not visualized in the late neonatal scan, a diagnosis of gallbladder agenesis was made. Outcome was ascertained in all survivors by telephone interview with the mother. Institutional review board approval was obtained for this study.

RESULTS

During the study period we evaluated 21 cases of PNVGB, diagnosed from 14 to 22 (mean, 16.1) weeks' gestation. Their outcomes are summarized in Figure 1. Four cases, all with no additional sonographic anomalies, were diagnosed initially by the authors, the others being referrals. Five cases were associated with additional sonographic anomalies (Table 1) and 16 cases were classified as isolated PNVGB (Table 2).

In four of five cases with associated anomalies, the anomalies were severe and the pregnancies were terminated for aneuploidy (two cases of trisomy 18 and one triploidy) or for the severity of the anomalies. Associated anomalies included left isomerism with complex cardiac anomaly and intrauterine growth restriction with multisystem anomalies. The fifth fetus had interrupted inferior vena cava with azygos continuation without other anomalies and the child was alive and well at the age of 4 years.

In 8/16 (50%) cases of isolated PNVGB, this was transient: the gallbladder was eventually seen in follow-up sonograms later in gestation (range, 24–34 weeks) or on neonatal ultrasound. In 7/16 (43%) cases the final diagnosis was gallbladder agenesis or small gallbladder and in one (7%) case the diagnosis was cystic fibrosis. In 14/16 (87.5%) cases diagnosis was made at or prior to 17 (range, 14–17) weeks, as most patients in Israel choose to have early scans. In 8/13 (61%) survivors with an early diagnosis, PNVGB was transient and the gallbladder was eventually visible in the third trimester or postnatally. Both cases that were diagnosed initially after 17 weeks had agenesis of the gallbladder. In 5/16 (31%) cases we tested for digestive enzymes and all values were normal in all cases. In 11/16 (69%) cases chromosomal analysis was performed and was normal in all cases.

In all 16 cases with isolated PNVGB, the mother was evaluated for cystic fibrosis mutation carrier status. Fifteen of them were negative. In the case with cystic fibrosis, the couple, who had two healthy children, was evaluated for a cystic fibrosis mutation screening panel once PNVGB was confirmed. Digestive enzyme analysis was not performed. The father was found to carry an X1282W mutation, and the mother to carry a ΔF508 mutation in the cystic fibrosis transmembrane (CFTR) conductance regulator gene. Diagnosis of cystic fibrosis was established by genetic testing on amniocentesis, and the pregnancy was terminated.

All 15 surviving children were examined by a neonatologist and had no abnormalities on physical examination. None of them had biliary atresia or clinically apparent aneuploidy. They were healthy and

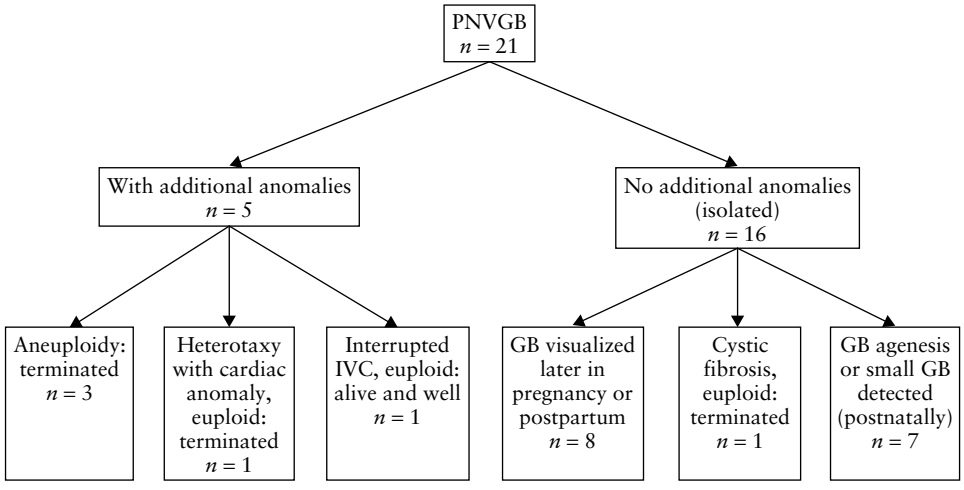

Figure 1 Summary of outcome of 21 cases of prenatal non-visualization of the fetal gall bladder (PNVGB). GB, gallbladder; IVC, inferior vena cava.

Table 1 Characteristics of five cases of non-isolated prenatal non-visualization of the fetal gall bladder

Case	*GA (weeks)*	*Additional US findings*	*Enzymes*	*Karyotype*	*Parental DNA analysis for CFTR mutations*	*Outcome*	*Follow-up*
1	15	Severe IUGR, hydrocephaly	NP	69,XXY	NP	TOP	NA
2	15	VSD, clenched hands, micrognathia	NP	Trisomy 18	NP	TOP	NA
3	16	Omphalocele, clubfoot, clenched hands	NP	Trisomy 18	NP	TOP	NA
4	15	Left isomerism, complex cardiac anomaly, abdominal heterotaxy	NP	Normal	Normal	TOP	NA
5	17	Interrupted IVC with azygous continuation	Normal	Normal	Normal	Small GB detected postnatally	A&W at 4 years

A&W, alive and well; CFTR, cystic fibrosis transmembrane conductance regulator gene; DNA, deoxyribonucleic acid; GA, gestational age at diagnosis; GB, gallbladder; IUGR, intrauterine growth restriction; IVC, inferior vena cava; NA, not applicable; NP, not performed; TOP, termination of pregnancy; US, ultrasound; VSD, ventricular septal defect.

Table 2 Characteristics of 16 cases of isolated prenatal non-visualization of the fetal gall bladder (PNVGB)

Case	*GA (weeks)*	*Time GB visualized*	*Enzymes*	*Karyotype*	*Final diagnosis*	*Outcome*	*Follow-up*
1	15	Not	NP	Normal	Cystic fibrosis	TOP	—
2	15	26 weeks	All normal	Normal	Transient PNVGB	Normal	6 months
3	15	32 weeks	NP	NP	Transient PNVGB	Normal	2.5 years
4	15	2 days postpartum	NP	Normal	Transient PNVGB	Normal	1 year
5	15	28 weeks	NP	NP	Transient PNVGB	Normal	6 months
6	22	Not	NP	NP	GB agenesis	Normal	1.5 years
7	16	2 days postpartum	All normal	Normal	Transient PNVGB	Normal	2 years
8*	17	2 days postpartum	NP	NP	Small GB	Normal	2 years
9*	14	Not	NP	Normal	GB agenesis	Normal	2.5 years
10	14	Not	NP	Normal	GB agenesis	Normal	6 months
11	14	34 weeks	NP	Normal	Transient PNVGB	Normal	6 months
12	16	Not	All normal	Normal	GB agenesis	Normal	6 months
13	22	Not	NP	Normal	GB agenesis	Normal	6 months
14	17	24 weeks	All normal	NP	Transient PNVGB	Normal	2.5 years
15	15	Not	All normal	Normal	GB agenesis	Normal	4 months
16	16	30 weeks	NP	Normal	Transient PNVGB	Normal	4 months

*Singleton siblings born to the same mother. GA, gestational age at diagnosis; GB, gallbladder; NP, not performed; TOP, termination of pregnancy.

well-developed at 4 months to 2.5 years of age, as ascertained by telephone interview with the mother.

At parental request, fetal autopsies were not performed in any of the terminated cases.

DISCUSSION

The gallbladder is a fluid-filled structure and can be visualized without difficulty on fetal ultrasound during the second and third trimesters of pregnancy. Normal reference values for its dimensions from 13 weeks to term have been published[11]. Isolated PNVGB in almost all cases results in a normal, healthy child[2,3,7]. In most cases, the gallbladder will be imaged later in pregnancy or in the neonatal period. In some cases, agenesis of the gallbladder is confirmed postnatally[1,2] – a benign condition with an incidence of 1 : 6300[4]. In rare cases, an association with cystic fibrosis is found[5].

It has also been suggested that isolated PNVGB in the second trimester may be associated with biliary atresia[1,2,6–8,10]. Typically, in children with biliary atresia the gallbladder is not seen or is very small on ultrasound[12]. As biliary atresia is a serious condition, frequently resulting in severe morbidity, liver transplantation or death, a prenatal diagnosis warrants consideration of terminating the pregnancy. The incidence of PNVGB has been reported to be 1 : 875[2] and that of biliary atresia has been reported as 0.7 per 10 000 live births[13]. Early diagnosis and surgical treatment improve the prognosis[14,15]. There are two types of biliary atresia: the fetal-embryonic form, characterized by early cholestasis that appears in the first 2 weeks of postnatal life, which accounts for 10–25% of all cases. In this form, the bile ducts are discontinuous at birth and affected neonates have associated heterotaxy syndrome, including situs inversus, polysplenia, malrotation of the gut, intestinal atresia and cardiac anomalies,

among others. In these cases, biliary atresia may be suspected prenatally as part of the heterotaxy syndrome or when a cystic structure is identified in the right upper quadrant, with or without PNVGB[16–24]. The perinatal acquired form of biliary atresia, with late onset of jaundice and acholic stool, accounts for the remaining 75–90% of cases. The etiology of these cases is unknown but may be related to viral infection by reovirus or rotavirus[25,26].

Despite the suggested association between isolated PNVGB and biliary atresia[1,2,6–8,10], we found only two case reports describing an association between them[6,8]. In the first case, the pregnancy was terminated at approximately 18 weeks and the diagnosis was made on autopsy. In the second case, the child was reported to have biliary atresia with an unusual postnatal course, associated with ileal necrosis and peritonitis. In this case, a small gallbladder was imaged postpartum. In five published case series of PNVGB, including the present study, a total of 168 cases of PNVGB were described[1–3,7], none of which was associated with biliary atresia. The paucity of reports linking biliary atresia to PNVGB is not surprising, since most cases of biliary atresia are of the perinatal or acquired form, in which the disease process has a late manifestation, possibly later than when the scans are performed in the second trimester. Considering the pathogenesis of the acquired perinatal form, prenatal diagnosis is not to be expected. In view of our data and those of others, any association between PNVGB and biliary atresia is most likely a chance occurrence.

Since digestive enzyme analysis was performed in only five of our isolated cases, all with normal outcome, we cannot draw conclusions on its significance. In four cases in the literature, an association has been described between pathologically low levels of digestive enzymes in amniotic fluid before 24 weeks and biliary atresia[8,16,27]. Enzyme types and levels as well as sonographic findings varied among cases. The sporadic reports, the unknown sensitivity and specificity and the significant variation in the type of enzyme abnormalities involved all cast doubt on the validity of amniotic fluid digestive enzyme abnormality as a predictor of biliary atresia.

Overall, therefore, there have been two published cases linking PNVGB and biliary atresia and four cases with potentially discriminating low values of various amniotic fluid enzyme activities associated with biliary atresia. In only one of these[8], biliary atresia was associated with both PNVGB and low enzyme levels. We believe this is insufficient evidence to support amniotic fluid enzyme testing when PNVGB is diagnosed.

Regarding the association between isolated PNVGB and aneuploidy, almost all cases with isolated PNVGB have not been found to be associated with chromosomal abnormalities. A search of the literature showed only two cases with this combination: a case with karyotype 47,XXX[7], which was an incidental finding, and a case with trisomy 21[3]. Almost all cases with PNVGB and aneuploidy[2,28] have additional detectable fetal abnormalities. Our experience concurs with the published information. Thus, it is likely that isolated PNVGB and aneuploidy is a chance association.

Considering the data presented and this review of the literature, when isolated PNVGB is diagnosed, parental testing for CFTR mutations should be considered. If the result is negative the parents should be reassured that the outcome is likely to be good and no further testing is required. There is a need for further research comparing prenatal ultrasound findings and analysis of fetal digestive enzymes in the amniotic fluid in cases which are diagnosed postnatally with biliary atresia.

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