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Prenatal diagnosis and perinatal outcome in congenital diaphragmatic hernia. Single tertiary center report

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Abstract

Purpose: To evaluate the perinatal results for fetuses and neonates with left-sided congenital diaphragmatic hernia (CDH) and the role of the prenatal diagnosis in the pregnancy outcome. *Materials and Methods*: We reviewed data from fetuses and neonates with left-sided CDH, managed from January 2009 and December 2013 in the University Clinic Hospital, Craiova, Romania. The following data were analyzed: the gestational age at the time of diagnosis, fetal karyotyping, presence of associated structural malformations, ultrasound (US) data (circumference and area of right lung, lung-to-head ratio – LHR, observed/expected LHR, hepatic herniation), the type of antenatal care, the pregnancy outcome, the place of birth and the conventional autopsy data, if performed. Perinatal outcomes were obtained by reviewing hospital documents. *Results*: Twenty-one cases were identified. No fetal surgery was performed in our series. Mean gestational age at time of diagnosis was 29 weeks of amenorrhea (WA) (range, 16–37 WA). Associated structural malformations were noticed in nine (42.8%) cases, in which three fetuses had a normal karyotype and two had chromosomal abnormalities, and four fetuses were not investigated. Isolated congenital diaphragmatic hernia was confirmed in 12 (57.1%) cases. All early second trimester diagnosed cases were terminated. The overall mortality rate was 61.9%. Rates of fetal deaths, early neonatal deaths, late neonatal deaths, and survival were 28.5%, 19%, 14.2%, and 38%, respectively. The perinatal mortality rate was 19% in cases with isolated congenital diaphragmatic hernia. *Conclusions*: The overall and perinatal mortality rate in congenital diaphragmatic hernia was still high in our series. Early perinatal deaths are associated with early diagnosis and with the presence of other structural defects. The prevalence of chromosomal abnormalities in perinatal death could not be determined from these data. In isolated congenital diaphragmatic hernia, mortality is related to the presence of herniated liver and severe pulmonary hypoplasia, this being well correlated with antenatal ultrasound parameters used for the estimation of fetal lung volumes. The antenatal diagnosis allowed better counseling of the parents, description of associations and improving the neonatal care.

Keywords: ultrasound, congenital diaphragmatic hernia, neonatal mortality, prenatal diagnosis, fetal malformation.

Introduction

CDH is a developmental defect of the diaphragm that starts early in the embryological period. Herniated abdominal viscera (such as stomach, liver, small bowel, colon and spleen) shift fetal lungs, and worsens concomitant pulmonary hypoplasia. Although the lungs are shifted during fetal life, the placenta maintains respiratory function, allowing correct gas exchange. However, once the umbilical cord is clamped during birth, the hypoplastic lungs cannot perform adequate gas exchange. Newborns develop rapidly (usually in the first hours of life) symptoms of respiratory and circulatory failure [1, 2]. The most important feature is that pulmonary hypoplasia occurs bilaterally, being more severe on the affected side. Therefore, newborns are at risk for persistent pulmonary hypertension, due to underdevelopment of the pulmonary tissue and pulmonary vascular defects. Hypoxia, acidosis and mechanical ventilation lead to reflex pulmonary vasoconstriction, and subsequently to the development of vascular wall structural changes [1–3].

The incidence of CDH is about 1:2000–5000 of life births and CDH-related mortality was very high until recently (70%), yet the centers with long-term experience in the treatment of CDH patients, which provide optimal care and diagnostic procedures in the pre- and postnatal period report survival rates up to 90% [4–7].

The left-sided postero-lateral hernia (Bochdalek hernia) is the most common anatomic type, accounting about 85–90% of cases, while the anterior hernia of Morgani is rare. A bilateral defect accounts for 15–20% of cases; loss of tissue involving most of the hemidiaphragm is classified as agenesis.

An European group suggested classifying fetuses with isolated CDH on ultrasound (US) parameters, into extremely severe, severe, moderate and mild forms, based on the observed/expected lung-to-head ratio (LHR) and the presence of herniated liver in the fetal thorax [8, 9].

Particular for CDH patients is the "hidden mortality", meaning cases of intrauterine fetal deaths, deaths in delivery rooms and obstetric departments, departments of lower referential levels, lacking suitable clinical experience or possibilities to perform appropriate prenatal or postnatal diagnostic procedures. 20–40% of CDH cases

are associated with other congenital defects, some of them being lethal [10].

Based on the data gathered by the study group of the *CDH EURO Consortium*, consisting of 13 European centers, the protocols of management in American medical centers have recently been published [11–14].

Prenatal diagnosis has altered the neonatal outcome worldwide through diagnosis of other associated malformations, chromosomal abnormalities, and planning delivery in a specialized tertiary center [15]. Before the onset of prenatal sonographic diagnosis, the mortality rate was almost 100%, and CDH was considered a lethal malformation [16]. Nevertheless, in spite of the great advances in prenatal and postnatal diagnosis and management, including modern therapy, like fetal endoscopic tracheal occlusion (FETO) and extracorporeal membrane oxygenation (ECMO) [17–19], the mortality rate in neonates with isolated CDH is still high.

Recent research has focused on prenatal predictors of neonatal outcome in isolated CDH, such as lung/head ratio [20, 21] and fetal lung volume [22–25], to differentiate cases with a worse prognosis, in which fetal therapy or termination of pregnancy may be indicated, from those with better prognosis, requiring only specialized postnatal care [17–19].

In spite of the worldwide-published experience, there are extremely few data about perinatal results in cases of CDH in Romania. Therefore, we reviewed all cases of left-sided CDH in a tertiary center, focusing on the gestational age (GA) at the time of diagnosis, the frequency of associated structural malformations and chromosomal abnormalities, liver herniation, the type of antenatal care, the place of birth, the final outcome and the mortality rate, and the conventional autopsy data, if performed. Our purpose was to report the perinatal results for this population: fetuses and neonates with left-sided CDH. In addition, we aimed to find out if the prenatal diagnosis does alter the pregnancy outcome.

Materials and Methods

We reviewed the prenatal database from January 2009 and December 2013 in the University Clinic Hospital, Craiova, Romania and identified 21 cases of left-sided CDH.

Prenatal characteristics were retrospectively analyzed from the ultrasonography database in the Prenatal Diagnosis Unit (PDU). In cases scanned in the PDU, the fetal anatomy was assessed, as recommended in recent guidelines [26]. Two-dimensional fetal ultrasound and three-dimensional US was carried out in all cases, by means of 3D static thoracic volumes acquisition (Voluson 730 Expert and E8 US machines, GE Medical Systems, Kretztechnik, Zipf, Austria). In selected cases, post-processing of the acquired volumes was performed, in order to assess the fetal lung volumes.

The US diagnostic criterion was the presence of abdominal viscera at the thoracic level (Figure 1, 2D images). We collected additional data if the GA was more than 20 WA: the liver position (diagnosed by Doppler color mapping), the amniotic fluid index, the lung-to-head ratio (LHR), obtained by the described technique [21, 27]. Also, by the PDU protocol, the right lung circumference (measured by manual tracing) and area were calculated. Finally, the observed/expected LHR (o/e LHR) was assessed [8] (Figure 2, protocol). As said, in several cases, the lung volumes was retrospectively measured off-line, using he VOCAL (Virtual Organ Computer-aided AnaLysis) technique. A 3D volume of the fetal thorax was obtained by transabdominal sonography (RAB 4–8L probe). The sweep angle was selected in order to include the whole thorax, depending on the gestational age (GA). A sequence of six sections of the fetal thorax was obtained, each after a 30^0 rotation from the previous one. The contour of the fetal lung was drawn manually in each of the six different planes to obtain the 3D volume measurement (Figure 3, volumes).

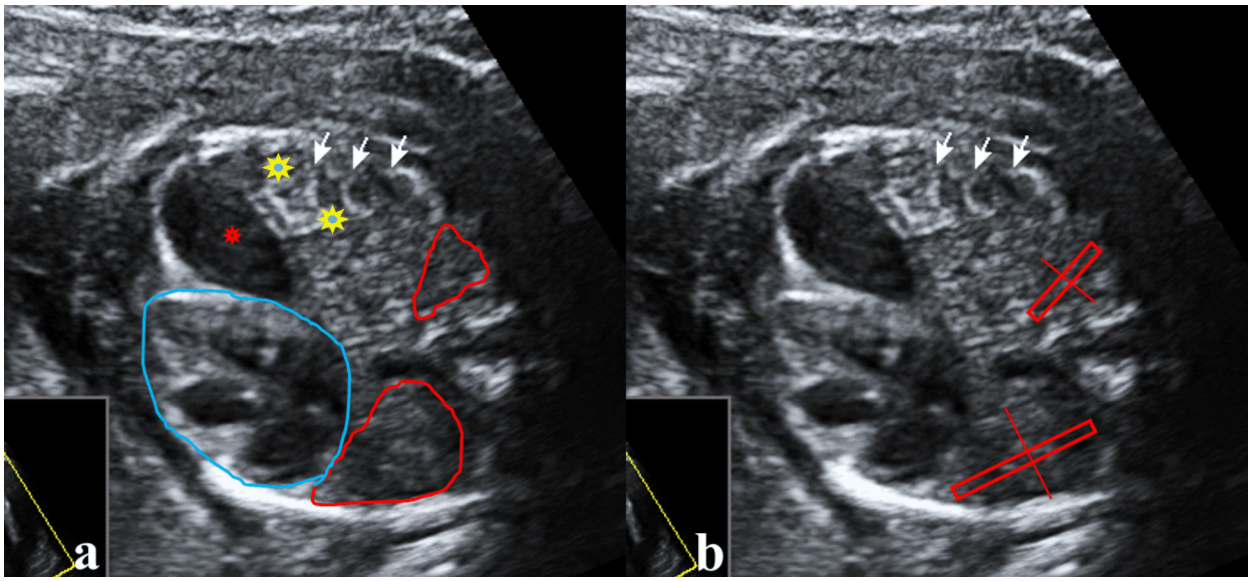

Figure 1 – ***Two-dimensional US images in the cross-sectional plane of the thorax (used for examination of the four-chamber view of the heart): (a) The presence of the intrathoracic stomach image (red star), the presence of small bowel loops images (yellow stars) (the intestinal walls have increased echogenicity – white arrows); also, cardiac area represented (blue tracing line) and both lungs areas (red tracing lines); (b) Measurements of the lungs area; represented: the longest diameter of each lung (red empty rectangle), crossed-over by its longest perpendicular diameter (red line).***

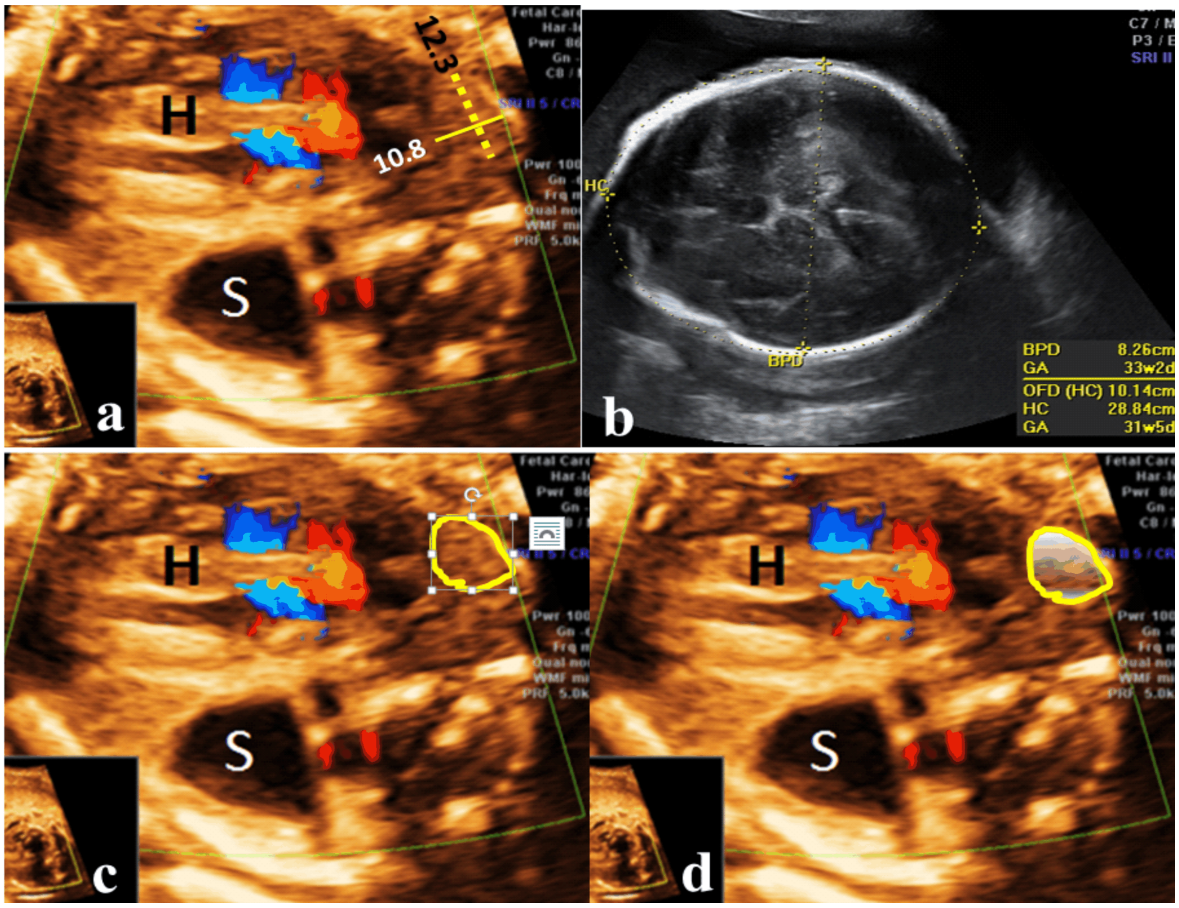

Figure 2 – ***The Prenatal Diagnostic Unit protocol to assess the neonatal prognosis function of the fetal lung volume. Two-dimensional ultrasound images: (a) The measurement of the right lung area in the cross-sectional plane of the thorax (used for examination of the four-chamber view of the heart); we used the multiplication of the longest diameter of the lung (yellow dotted line) by its longest perpendicular diameter (yellow line); (b) Fetal head: axial section at the level of the thalami and cavum septum pellucidum (recommended for head circumference measurement); (c) Manual tracing of the limits of the lungs; (d) Obtaining the lung surface. In this case (Case No. 20), the figures were: 132.84/ 288.4=0.46 LHR (normal values at 33 WA = 3.15); o/e LHR=0.46/3.15×100=14.6%; Lung circumference = 37.1 mm; Lung surface = 100 mm^2 (normal values at 33 WA = 915 mm^2); The fetal death occurred in the first hours of life, before surgery.***

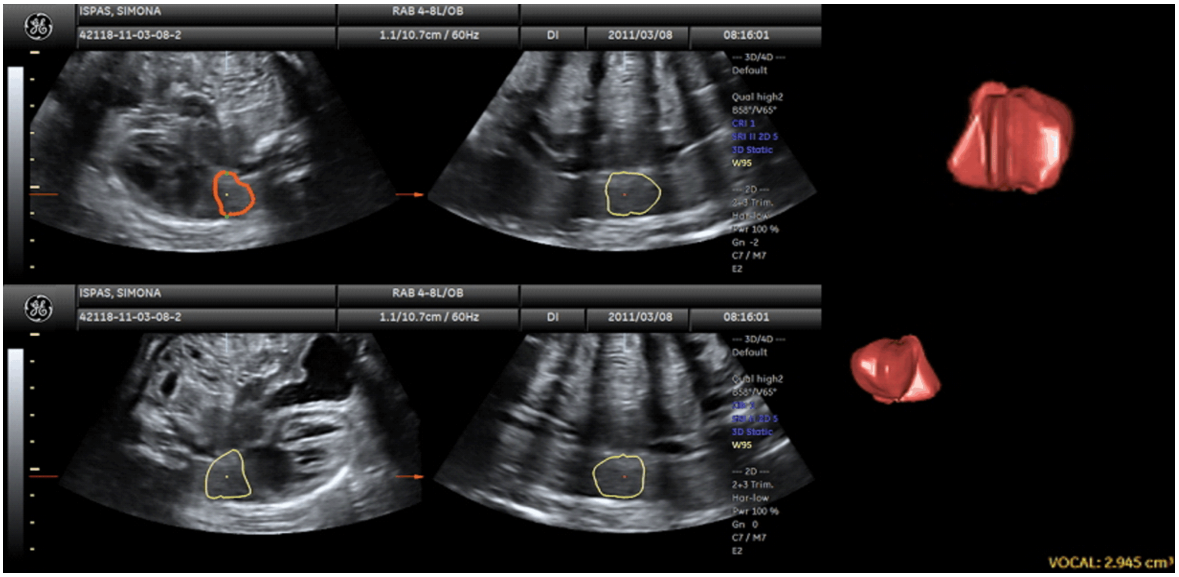

Figure 3 – ***The off-line measurement, using he VOCAL (Virtual Organ Computer-aided AnaLysis) technique. The 3D volume of the fetal thorax was obtained by transabdominal sonography (RAB 4–8L probe). The sweep angle was selected in order to include the whole thorax (in this case 65^0). A sequence of six sections of the fetal thorax was obtained, each after a 30^0 rotation from the previous one. The contour of the fetal lung was drawn manually in each of the six different planes to obtain the 3D volume measurement. Images from Case No. 15, 37 WA, fetal right lung volume estimated 2.945 cm^3, neonatal death day 4.***

Invasive testing was offered in prenatally diagnosed cases. If amniocentesis performed, conventional G banding karyotype was obtained. Cell cultures were initiated, a long-term culture using two different media. After about 9–11 days, cells were blocked in metaphase with Colcemid, then hypotonia was induced and cells were fixed. Chromosome preparations were G banded and examined by microscope (AxioImager, Carl Zeiss). 25–30 metaphases/case were analyzed directly and five metaphases were, at least, karyotyped [28, 29]. Postnatal echocardiography was performed in cases with birth outcome.

If medical termination of pregnancy (TOP) was performed, autopsies were performed by trained perinatal pathologists and followed accepted protocols [30, 31]. Information for the pathologist was provided and included the obstetrical and medical history, invasive testing, imaging, and family history. Direct communication with the pathologist was present. The autopsy photographic files were obtained with a Sony DSLR A200 camera (10.2 megapixels), and with a digital microscope Leica IC80HD camera (three megapixels) (Figure 4, autopsy; Figure 5, liver-down; Figure 6, liver-up).

Perinatal outcome was reviewed by consulting prenatal, neonatal, and pediatric surgery databases. Cases were classified according to perinatal outcome including fetal death, early neonatal death (from birth to seven days of life), and late neonatal death (after seven days of life up to 28 days), and discharged.

The data entered the final analysis were: the GA at the diagnosis and birth/abortum, presence of associated structural malformations, fetal karyotyping, liver herniation, polyhydramnios presence, LHR, circumference and area of the right lung, o/e LHR, the fetal/neonatal weight, the type of antenatal care, the type of hospital where delivery was performed, the mode of delivery, the timing of surgery if performed, the hospitalization stay, the final outcome and the conventional autopsy data.

The demographic data noted were: the maternal age, the gestation and parity range.

Results

The flow diagram of our population is shown in Figure 7. From the 21 cases of left-sided CDH, 11 were diagnosed before the pregnancy ended, six in the second trimester (ST), and five in the third trimester (TT) and the mean GA at diagnosis was 29 weeks (range, 16–37 weeks). Ten cases were diagnosed postnatally.

Our results in regards to the prenatal US characteristics and measurements, the maternal demographic data and the pregnancy outcome are summarized in Table 1.

Among the TT antenatally diagnosed cases, we noticed three fetuses with LHR<1.4 and one fetus with LHR>1.4.

Six cases were terminated in the ST and 15 cases have resulted in term or preterm births, in the TT.

Associated structural malformations were noticed in nine (42.8%) cases, in which two fetuses had a normal karyotype and two had chromosomal abnormalities (trisomy 18 – one case and trisomy 13 – one case), and five fetuses were not investigated (Table 1).

Five cases had also heart malformations in association with congenital diaphragmatic hernia (large interventricular defect, common arterial trunk, atrioventricular defect and two cases of interatrial defect, respectively).

The overall perinatal mortality rate was 61.9%. Rates of fetal deaths, early neonatal deaths, late neonatal deaths, and survival were 28.5%, 19%, 14.2%, and 38%, respectively. The perinatal mortality rate was 19% in cases with isolated congenital diaphragmatic hernia.

Four of six second-trimester diagnosed fetuses were terminated due to severe malformations associated. Also, a term birth neonate died at 10 hours after birth, before surgery. This newborn had association of common arterial trunk and bilateral anophthalmia (Figure 4, autopsy).

Between the two cases with associated structural malformation and normal karyotyping, one was terminated in the ST and one also died before the 7th day of life, due to postoperative complications.

Fourteen (66.6%) neonates underwent surgical repair after satisfactory ventilatory condition and preoperative stabilization between one and 33 days of life. Isolated congenital diaphragmatic hernia was antenatally diagnosed and confirmed by surgery in 10 (71.4%) cases. In this group, three neonates died postoperatively. All had the LHR under 1.4. Herniated liver was confirmed in six cases. All neonates with a herniated liver died before the 28th day of life. Among all surgically repaired cases, eight infants with CDH survived more than 28 days after surgical repair (survival rate 57.1%) (Table 1). The majority (10 out of 14, 71.4%) of surgically repaired cases were diagnosed postnatally. Most of these babies (12 out of 14, 85.7%) had no prenatal care and no prenatal US examinations before the hospitalization for delivery. Eight out of 14 babies (57.1%) were delivered in rural areas and secondary centers (Table 1).

Many cases were primigravida (52.4% cases) or primipara (42.8%) patients, and most mothers (90.4%) belong to 20–30 years group (Table 1).

Nine cases had normal KT, there were two trisomic fetuses and in the rest of 10 cases, the KT was unavailable, either because parents declined the invasive maneuver, or due to high costs of the procedure.

From the 13 fetuses and neonates that died, autopsy was performed in five cases. No postabortion autopsy was declined, all but one postpartum autopsies were declined.

Discussion

In nowadays-healthcare system in our country, CDH remains probably an unsolved clinical problem, in terms of prenatal diagnosis and postsurgical results, associated with a high perinatal mortality and morbidity. It has been advocated that fetal surgery may salvage the most severely affected fetuses. At the time of writing, these techniques are preserved for few high quality equipped fetal centers in Europe.

The prenatal ultrasound diagnosis of CDH is based on either direct signs, such as bowel loops, stomach and/or liver parts displaced into the thoracic cavity, or indirect signs, such as an abnormal position of the heart with mediastinal shift. Our results confirm that today most cases of CDH can be prenatally diagnosed during ultrasound screening, as all cases in our series that presented in the Prenatal Diagnostic Unit were. The US examination not only ruled out associated anomalies but also gave an individual prognosis for isolated cases, through the multi-disciplinary counseling process. The modern techniques described were used in searching for an accurate prognosis.

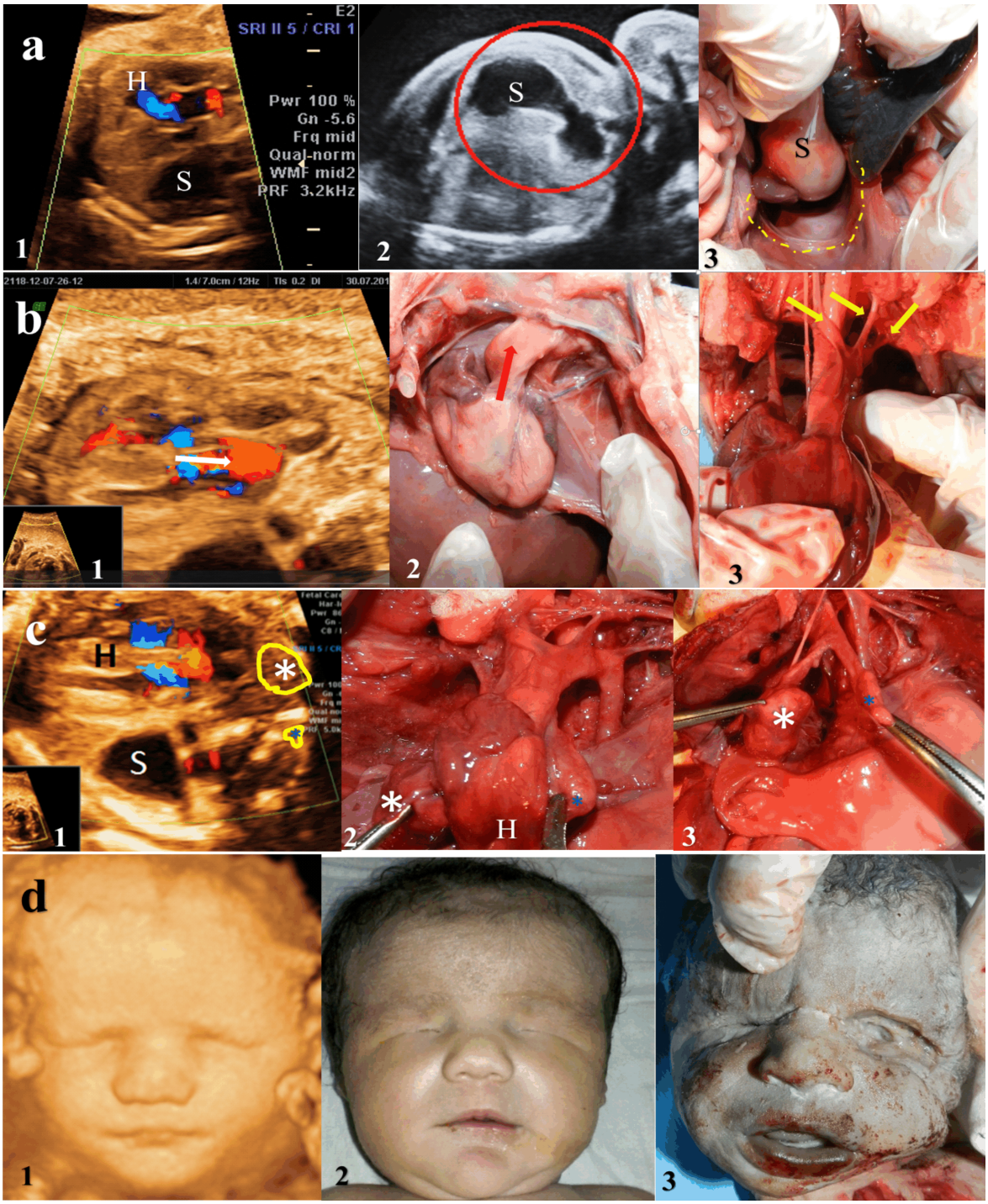

Figure 4 – ***Autopsy of a third trimester fetus (Case No. 20) that confirmed the major digestive, cardiac and facial abnormalities suspected by US: (a) Large diaphragmatic defect; (b) Common arterial trunk; (c) Pulmonary hypoplasia; (d) Anophthalmia; (a1) 2D US transversal section of the thorax, showing the intrathoracic stomach image (S) and the severe mediastinal shift, with the dextrorotation of the heart (H); (a2) 2D US oblique thoracic section, showing the herniation of an enlarged stomach (S) into the thorax; (a3) Conventional postmortem autopsy, showing the large diaphragmatic defect (yellow dotted tracing) and the large stomach entering the thorax (S); (b1) 2D US transversal section of the thorax, with color Doppler applied, showing the four-chamber view transversal plane: a large vessel, single outflow tract, overriding the interventricular septum, arising from the heart, with a cranial direction (white arrow); (b2) Conventional postmortem autopsy, confirming the large vessel as being the common arterial trunk (red arrow); (b3) Head and neck vessels arising from the common arterial trunk (yellow arrows); (c1) 2D US transversal section of the thorax, showing the reduced lungs area (yellow tracing lines). Right lung – white big star, left lung – blue small star; (c2) Conventional postmortem autopsy, confirming the hypoplastic lungs, because of massive herniation of the stomach into the thorax. Presence of a rudiment of left lung. Heart – H, right lung – white big star, left lung – blue small star; (c3) Detail from postmortem autopsy, the hypoplastic lungs seen after the heart had been lifted superior; (d1) 3D US, surface rendering of the fetal face, to underline the facial dimorphism and the bilateral absence of the orbits and eyeballs; (d2) Postpartum aspect of the fetal face; (d3) Postmortem autopsy, absence of the orbits and eyeballs, failure to demonstrate them by dissecting the eyelid.***

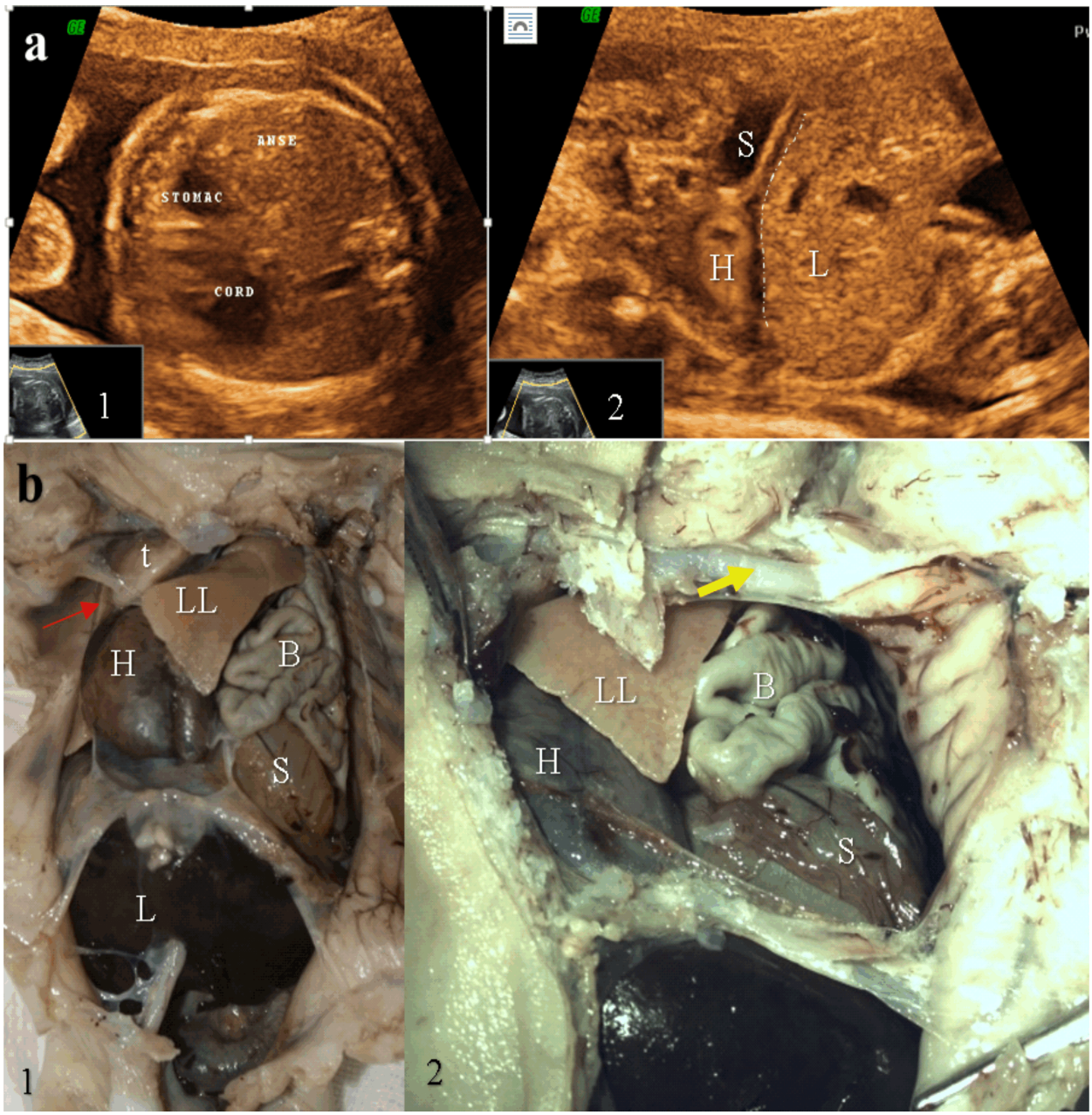

Figure 5 – ***(a) Antenatal US features (Case No. 3); (b) Postmortem conventional autopsy (same case); (a1) 2D US transversal section of the thorax, showing the intrathoracic stomach image, heterogeneous intrathoracic mass, containing small bowel loops, and the mediastinal shift, with the dextroposition of the heart; (a2) 2D US longitudinal section of the abdomen and thorax, showing the presence of the stomach (S) and heart (H) above the diaphragm, and the presence of the liver (L) distal to the diaphragm, intraabdominal, and a relatively normal diaphragm US image (white dotted line). Prenatally, a grade 2 of stomach herniation was suspected (less than half of the stomach herniated into the right chest); (b1) Global view of the abdominal cavity and ribcage, after the removal of the anterior walls. Of note, the intrathoracic small bowel loops (B) and stomach (S), on the left side of the thorax. The left lung (LL) displaced anteriorly and to the right of the fetus. The entire liver mass (L) placed intraabdominal. t – Thymus. The RL, extremely reduced volume, difficult to visualize (red arrow); (b2) Detail from the conventional autopsy: small bowel loops (B), stomach (S), the left lung (LL), liver (L). Of note that the stomach and the bowel loops occupies the entire left hemithorax, exceeding the left lung peak (clavicle – yellow arrow), and that grade 2 herniation of the stomach was confirmed.***

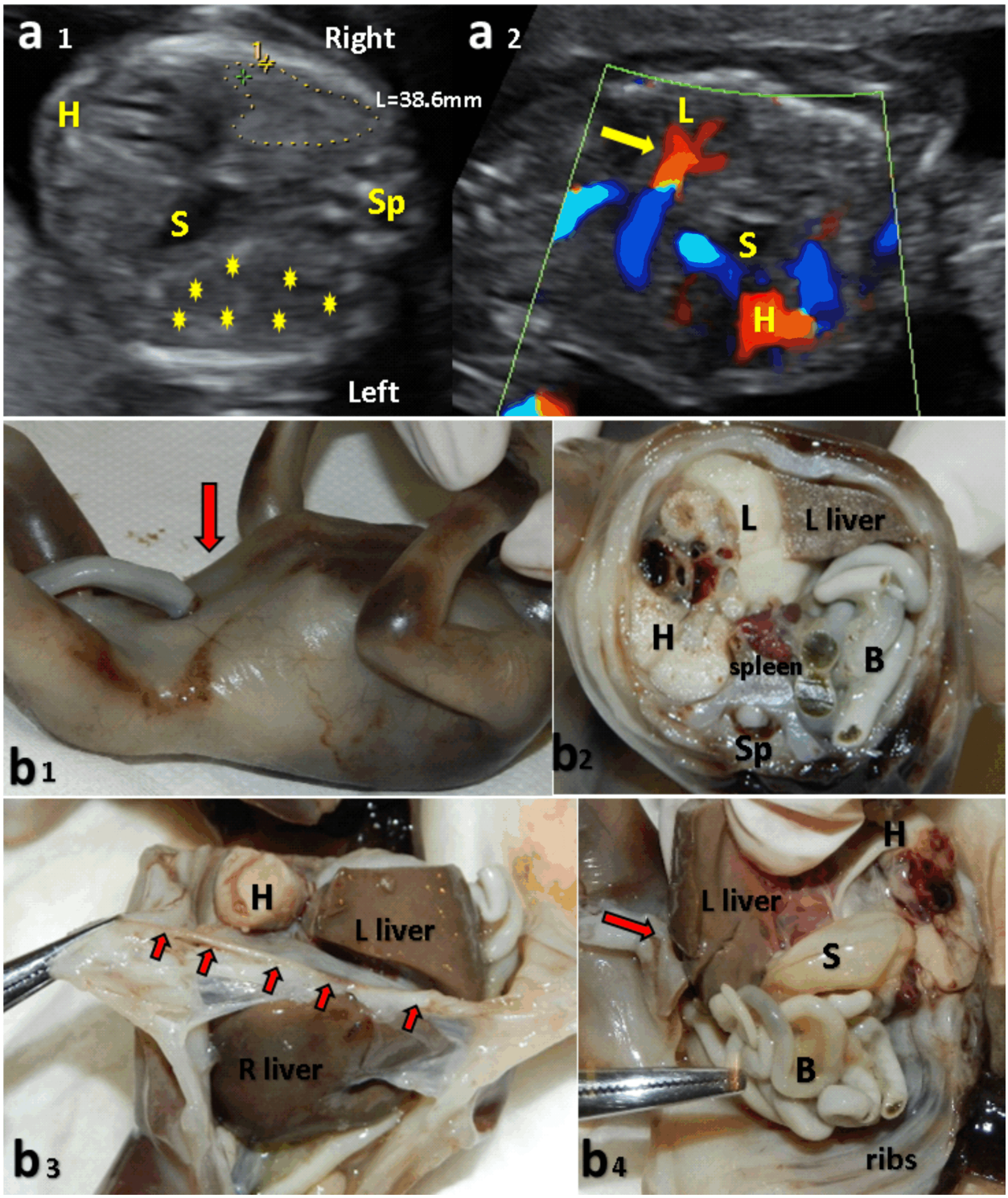

Figure 6 – *(a) Antenatal US features (Case No. 21); (b) Postmortem conventional autopsy (same case); (a1) 2D US transversal section of the thorax, showing the intrathoracic stomach image (S), heterogeneous intrathoracic mass (yellow stars), containing small bowel loops, and the mediastinal shift, with the dextroposition of the heart (H). Also, seen the left lung area measurement. Sp – Spine; (a2) 2D US oblique longitudinal section of the abdomen and thorax, showing the presence of the stomach (S) and the liver (L), highlighted by the color Doppler map applied (yellow arrow) above the diaphragm, next to the heart (H); (b1) Global view of the fetus, showing the discordance between the abdominal cavity circumference (depressed anterior wall of the abdomen – red arrow) and the thorax circumference; (b2) Transversal section of the thorax, showing the intrathoracic organs: heart (H), displaced to the right, left lung (L) displaced to the right and anteriorly, left lobe of the liver (L liver), spleen and small bowel loops (B). Sp – Spine; (b3) After the removal of the anterior abdominal and thoracic walls: diaphragm (red arrows), heart (H), left lobe of the liver (L liver), right lobe of the liver (R liver); (b4) Lateral view from the left side of the fetal thorax, after lifting up the left lobe of the liver (L liver). Intrathoracic organs revealed: the stomach (S), small bowel loops (B). Heart also seen (H).*

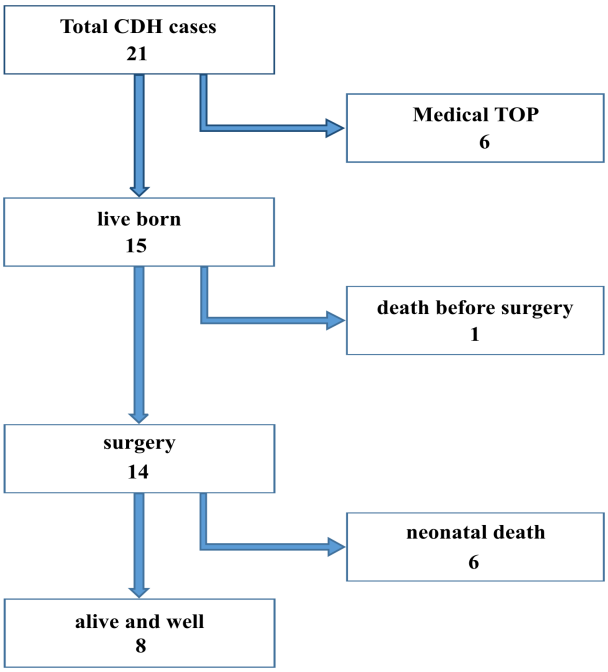

Figure 7 – *Flow diagram. CDH: Congenital diaphragmatic hernia; TOP: Termination of pregnancy.*

Many sonographic parameters have been proposed to predict the prognosis of CDH. Polyhydramnios in the third semester, early diagnosis (less than 25 weeks' gestation), presence of an intrathoracic stomach, small lung-thorax transverse area ratio, small lung volumes, surfaces and area, underdevelopment of the left heart, LHR, the o/e LHR and visceral herniation have all been evaluated, but none of these has been widely accepted or applied clinically [4–6, 8, 9, 21, 22, 25, 32–34]. It seems that the most reliable sonographic prognostic factors are the presence of intrathoracic liver herniation and the LHR, which is why we chose to assess these US parameters. In our series, the most important feature in predicting the fetal/neonatal death was the liver-up, confirming the recent published data [35].

The results demonstrate that other structural abnormalities are frequently associated with CDH and that perinatal mortality remains high, even in neonates with isolated CDH.

In our case series termination of pregnancy (TOP) was performed, thus it was not possible to fully evaluate the natural history of CDH in cases with or without associated structural malformations or chromosomal abnormalities.

Table 1 – *Prenatal US characteristics and measurements, related to the maternal demographic data and pregnancy outcome*

No.	Age at dg	GA at the PE	Liver up/ down	PHA	LHR	Circ/ Area RL	o/e LHR [%]	Fetal weight [g]	Associations	KT	MoD	DoS	Outcome	Maternal age [years]	G	P	Place of birth	A
1.	AN: 16 WA	16	Up	No	-	-	-	100	ASD, radial agenesy	T 18	-	-	Death	26	1	0	UCH Cv	No
2.	AN: 22 WA	24	Up	No	1.28	**50.1/ 179 mm²**	**54.23**	350	Early IUGR, holopros-encephaly	T 13	-	-	Death	21	2	1	UCH Cv	No
3.	AN: 24 WA	24	Down	Yes	0.67	**37.6/ 100 mm²**	**28.38**	500	OSB, hidrocephaly	N	-	-	Death	20	2	0	UCH Cv	Yes
4.	AN: 21 WA	22	Up	No	0.54	**34.3/ 94 mm²**	**27.13**	360	Renal agenesy	Ukn	-	-	Death	27	1	0	Secondary center	Yes
5.	AN: 21 WA	22	Up	Yes	1.38	**47.7/ 171 mm²**	**69.34**	380	None	N	-	-	Death	25	1	0	UCH Cv	Yes
6.	PN	40	Up	-	-	-	-	3620	CHD–VSD	Ukn	V	3	Death	29	3	3	UCH Cv	No
7.	PN	39	Down	-	-	-	-	4000	None	N	V	2	Discharged Day 9	27	2	2	Rural area	-
8.	PN	33	Up	-	-	-	-	1950	Agen stern, AVSD	Ukn	CS	2	Death Day 2	31	3	3	UCH Cv	No
9.	PN	39	Down	-	-	-	-	3100	None	N	V	3	Discharged Day 29	22	1	1	Secondary center	-
10.	PN	34	Down	-	-	-	-	2400	None	Ukn	CS	3	Discharged Day 15	23	2	2	Secondary center	-
11.	PN	39	Down	-	-	-	-	3100	None	N	V	33	Discharged Day 21	25	1	1	Rural area	-
12.	PN	39	Down	-	-	-	-	3100	None	Ukn	CS	2	Discharged Day 16	24	3	2	Secondary center	-
13.	PN	40	Down	-	-	-	-	3700	None	N	V	5	Discharged Day 60	27	3	1	Rural area	-
14.	AN: 32 WA	39	Up	Yes	0.92	**72.8/ 273 mm²**	**30.16**	3300	None	Ukn	V	6	Death	26	1	1	UCH Cv	No
15.	AN: 37 WA	40	Up	Yes	1.15	**51.9/ 195 mm²**	**32.39**	3380	Splenic hemangioma	N	V	2	Death Day 4	35	1	1	UCH Cv	No
16.	PN	38	Up	-	-	-	-	5200	None	Ukn	CS	2	death	22	1	1	Rural area	No
17.	AN: 34 WA	35	Up	Yes	1.2	**93.33/ 350.7 mm²**	**36.92**	2600	None	Ukn	V	1	Death Day 12	21	1	1	UCH Cv	No
18.	AN: 34 WA	40	Down	No	1.63	**126.6/ 475 mm²**	**50**	3800	None	N	CS	1	Discharged Day 26	25	2	2	UCH Cv	-
19.	PN	39	Down	-	-	-	-	3400	CHD (ASD)	N	V	4	Discharged	24	1	1	Rural area	-
20.	AN: 33 WA	34	Up	Yes	0.46	**37.1/ 100 mm²**	**14.6**	1720	CHD (CAT)	Ukn	V	-	Early death	26	4	2	UCH Cv	Yes

No.	Age at dg	GA at the PE	Liver up/ down	PHA	LHR	Circ/ Area RL	o/e LHR [%]	Fetal weight [g]	Associations	KT	MoD	DoS	Outcome	Maternal age [years]	G	P	Place of birth	A
21.	AN: 16 WA	24	Up	No	-	-	-	180	None	Ukn	-	-	Death	24	1	0	UCH Cv	Yes

dg – Diagnosis; AN – Antenatal; WA – Weeks of amenorrhea; PN – Postnatal; GA – Gestational age; PE – Pregnancy ending; PHA – Polyhydramnios; LHR – Lung-to-head ratio; Circ/area – Circumference/area; RL – Right lung; o/e – Observed/expected; ASD – Atrial septal defect; IUGR – Intrauterine growth restriction; OSB – Open spina bifida; CHD – Congenital heart disease; VSD – Ventricular septal defect; Agen – Agenesis; AVSD – Atrioventricular septal defect; CAT – Common arterial trunk; KT – Karyotype; T – Trisomy; N – Normal; Ukn – Unknown; MoD – Mode of delivery; V – Vaginal; CS – Caesarean section; DoS – Day of surgery; G – Gestation range; P – Parity; UCH Cv – University Clinic Hospital, Craiova; A – Autopsy.

Published reports place the incidence of chromosomal and structural abnormalities in association with CDH at 35% to 50%, including trisomies, most commonly trisomy 18. In this study, 42.8% of the neonates had associated malformations, and 9.5% had chromosomal abnormalities. The two neonates with chromosomal abnormalities had other associated structural malformations. Among the neonates with abnormal karyotyping, trisomy 18 and 13 was diagnosed. Cases with abnormal karyotyping usually have the poorest prognosis, with almost 100% perinatal mortality. Although we perform invasive maneuvers on daily routine, we obtained fetal or neonatal karyotyping in less than half cases. Our series is too small to draw definite conclusions and our results are probably biased by the low rate of genetic assessment. For the moment, none of the prenatal genetic tests, including the conventional karyotype, is free of charge for patient, through the Health Insurance Institution, the process of subsidize being still ongoing.

Moreover, many cases were diagnosed postpartum (47.6%), and the majority of these cases had no prenatal care. These results underline the difficulties encountered still in implementing routine prenatal care and screening US exam in rural area.

None of the surgically managed cases benefited from additional information, obtained by (magnetic resonance imaging) MRI technique. Most studies report that fetal lung volume measurement by MRI is a potential predictor of pulmonary hypoplasia and postnatal outcome, leading to a better selection and preoperative measures, and to a better costs/benefits balance [36–40]. Recent studies confirm the positive correlation between US and MRI preoperative information and found that, in expectantly managed CDH fetuses, the assessment of the ratio of the volume of the liver that is herniated into the thoracic cavity to the volume of the thoracic cavity using MRI provides prediction of postnatal survival independently from observed/expected total fetal lung volume [8].

From the two cases with associated structural malformation but normal karyotype, one died. One infant who had an associated ASD and normal karyotype survived, probably because of the less severe herniation of abdominal organs into the fetal thorax.

Both categories of fetuses (severe associated congenital anomalies and chromosomal anomalies) are candidates for medical TOP in most European countries.

In cases with isolated CDH, postnatal mortality was lower in our series (20%) than reported in the international literature (50–70%). These results may be explained by the small figure of cases in our retrospective study. Moreover, TOP was performed in all second trimester diagnosed cases. The main prognostic factors considered were the liver-up and the pulmonary size and/or volume, which was evaluated by the lung-over-head ratio (LHR) and the observed/expected fetal lung volume ratio (o/e-FLV). Cases with LHR<1.0 and o/e-FLV<0.35 are associated with poorer outcome (approximately 90%). In cases with LHR<1.0 or liver herniation and CDH diagnosed before 20 weeks, TOP was performed.

We included in our study all cases, prenatally or postnatally diagnosed, and it is known that prenatally diagnosed cases have higher mortality rate and a worse prognosis than those with only postnatal diagnosis [41].

Harrison *et al.* recently demonstrated that adequate and specialized neonatal care can improve neonatal survival to about 70% in cases with prenatally diagnosed isolated CDH, even in those cases without prenatal treatment [17]. This finding means that each hospital may have different neonatal mortality rates based on the prenatal selection of population, prenatal interventions, degree of specialization of neonatal care group, and type of postnatal treatment. Consequently, meta-analysis and multicenter studies should be analyzed carefully. Nevertheless, in our series, the surgically treated cases had a modest outcome, with a survival rate of 57.14%.

The present study is important, being the first report in Romania on CDH cases. It is reporting the US features in prenatally diagnosed cases, and it is describing detailed correlations between them and conventional perinatal autopsy data. Also, it reports our experience in the pre- and postnatally diagnosed cases. Moreover, it motivates us to review our prenatal evaluation of prognosis and our neonatal care, as well as to consider the reasons for intrauterine transfer in superior centers, for fetal interventions, in selected cases. By improving the prenatal prediction of perinatal outcome and the neonatal care and complex management in cases with isolated CDH, as well as the multidisciplinary approach, we will be able to better counsel the couples that have to cope with this severe diagnosis and eventually we will improve the reported results.

Conclusions

The overall and perinatal mortality rate in congenital diaphragmatic hernia was still high in our series. Early perinatal deaths are associated with early diagnosis and with the presence of other structural defects. The prevalence of chromosomal abnormalities in perinatal death could not be determined from these data. In isolated congenital diaphragmatic hernia, mortality is related to the presence of herniated liver and severe pulmonary hypoplasia, this being well correlated with antenatal ultrasound parameters used for the estimation of fetal lung volumes. The antenatal diagnosis allowed better counseling of the parents, description of associations and improving the neonatal care.

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