Singapore Med J 2013; 54(8): 432-436
doi:10.11622/smedj.2013149

Antenatally diagnosed congenital diaphragmatic hernia in Singapore: a five-year series

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INTRODUCTION We aimed to investigate the epidemiology, diagnosis, prognostication, follow-up care and outcomes of antenatally diagnosed congenital diaphragmatic hernia (CDH) in KK Women's and Children's Hospital (KKH), Singapore. The objective of this study was to identify trends in current practice, and evaluate and improve the management of CDH.

METHODS We retrospectively reviewed cases of antenatally diagnosed CDH from 2006 to 2010.

RESULTS A total of 22 cases of CDH were found, bringing its incidence in KKH to 3.6 per 10,000 live births. The mean gestational age at diagnosis was 22.7 weeks, with 14 (63.6%) cases diagnosed at < 22 weeks and 8 (36.4%) diagnosed at ≥ 22 weeks. All cases were left-sided – 15 (68.2%) were isolated CDH and 7 (31.8%) were associated with other anomalies. Of the 22 cases, counselling about the prognosis of pregnancy based on the lung-to-head ratio was provided in 9 (40.9%). Overall, 10 (45.5%) cases resulted in termination of pregnancy (TOP), 9 (40.9%) resulted in live birth and 1 (4.5%) in stillbirth; 2 (9.1%) cases were lost to follow-up prior to delivery. Of the 9 live births, 3 (33.3%) resulted in neonatal death. In the 10 births, 5 (50.0%) were delivered by normal vaginal delivery, 4 (40.0%) by emergency Caesarean section and 1 (10.0%) by elective Caesarean section.

CONCLUSION CDH is a challenging perinatal problem with a low overall survival rate. Almost half of the cases opt for TOP. The data in this study can help clinicians better undertake the task of adequately counselling parents with qualitative and quantitative prognostic factors, using an evidence-based approach.

Keywords: antenatal diagnosis, congenital diaphragmatic hernia, epidemiology, outcome, prognosis

INTRODUCTION

Congenital diaphragmatic hernia (CDH), a rare malformation with an incidence of 1.7–5.7 per 10,000 live births, remains one of the most fatal causes of severe respiratory failure.[1,2] CDH was first described by Riveriusin 1672,[3] with the types of defects classified by Morgagni in 1769.[4] The posterolateral defect that we now know as the most common type of CDH was described by Bochdalek in 1848.[3] The developmental defect in CDH results from abnormal maturity of the septum transversum and incomplete fusion of the pleuroperitoneal membrane, thus allowing the abdominal viscera to herniate into the thoracic cavity. This can interfere with normal lung development and lead to pulmonary hypoplasia and pulmonary hypertension, which are often life-threatening.

Antenatal diagnosis is currently achieved with the use of ultrasonographic studies, but detection rates vary widely.[5] Typical sonographic findings include the presence of a stomach bubble in the thoracic cavity, and/or cardiac displacement by abdominal viscera.[6] Up to 59% of cases have associated anomalies such as chromosomal abnormalities, and cardiovascular and gastrointestinal defects.[7] Prognostication of CDH is based on the presence of associated anomalies, sonographic measurement of lung-to-head ratio (LHR), Doppler flow studies of the diameter of the main pulmonary artery (MPA) and magnetic resonance (MR) imaging assessment of fetal lung volume (FLV).[6]

With the growing use of routine antenatal ultrasonographic screening in recent years, early detection of fetal anomalies allows for better planning of antenatal counselling and optimisation of postnatal care.[8] Therefore, in this study, we aimed to investigate the epidemiology, diagnosis, prognostication, follow-up care and outcomes of antenatally diagnosed CDH in KK Women's and Children's Hospital (KKH), Singapore, during the period 2006–2010. We wished to identify the current trends in perinatal practice that pertain to pregnancies with CDH, in order to allow us to evaluate and improve the management of CDH in Singapore.

METHODS

All CDH cases diagnosed antenatally in KKH between January 2006 and December 2010 were obtained using the discharge summary codes and retrospectively reviewed. Population denominators were obtained from KKH's perinatal statistics database. The incidences were calculated according to the format used by the National Birth Defects Registry.[9] Detailed information was collected from the maternal medical records, which included demographic characteristics such as gestational age at diagnosis, method of diagnosis, ultrasonographic findings, prognostication factors (e.g. LHR, FLV and MPA diameter), presence of other anomalies, follow-up care (e.g. karyotyping, frequency of follow-up appointments and referral to paediatric surgical service), outcome of

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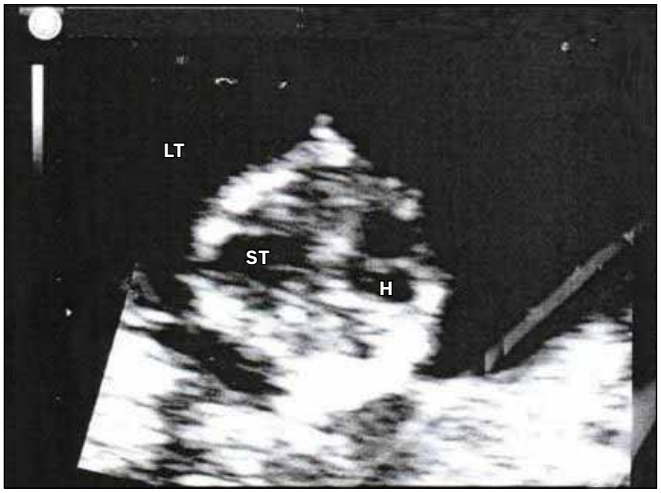

Fig. 1 First trimester fetal viability US image at 13 weeks of gestation shows the presence of a stomach bubble in the left chest and cardiac displacement to the right chest.
H: heart; LT: left side; ST: stomach

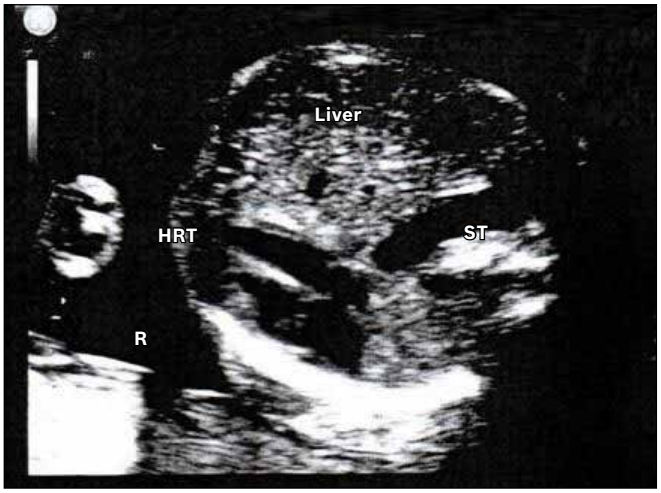

Fig. 2 Fetal anomaly US image shows a large left diaphragmatic hernia with the heart displaced to the right, the stomach in the posterior thorax and the liver in the thorax.
HRT: heart; R: right side; ST: stomach

pregnancy, mode of delivery and gestational age at delivery. Ultrasonographic investigations done in KKH were performed by experienced and accredited sonographers using the Hitachi Aloka SSD-4000 (Hitachi Aloka Medical Ltd, Tokyo, Japan) and Voluson E8 (General Electric, Wauwatosa, WI, USA) ultrasonography machines.

Statistical analyses were performed using the Statistical Package for the Social Sciences Windows version 17.0 (SPSS Inc, Chicago, IL, USA). Categorical data were summarised with frequency and crosstab distributions. This research project was approved by the SingHealth Institutional Review Board.

RESULTS

A total of 22 fetuses were antenatally diagnosed with CDH during the study period. There were 60,510 live births from 2006 to 2010, bringing the incidence of CDH in KKH to 3.6 per 10,000 births. The average maternal age was 31.3 (range 22–40) years. Of the 22 fetuses, 8 (36.4%) were Chinese, 5 (22.7%) were Malay, 3 (13.6%) were Indian and 6 (27.3%) were either Eurasian or of other ethnicities. 11 (50.0%) cases were primiparous, while the other 11 (50.0%) comprised multiparous women. Out of the 22 cases, only 1 (4.5%) mother had a poor obstetric history of a previous pregnancy with CDH. The mean gestational age at diagnosis was 22.7 (range 13–39) weeks. While 14 (63.6%) cases were diagnosed at < 22 weeks of gestation, 8 (36.4%) were diagnosed at ≥ 22 weeks. Diagnoses made at ≥ 22 weeks were accounted for as follows: (a) 4 (50.0%) cases defaulted on follow-up; (b) 2 (25.0%) were initially diagnosed late at gestational ages of 28 and 36 weeks, respectively, in foreign countries; (c) 1 (12.5%) was initially diagnosed late at a gestational age of 25 weeks, at a local private hospital; and (d) 1 (12.5%) was a 'late booker'.

In total, 3 (13.6%) cases were diagnosed in the first trimester, with 2 (9.1%) of these cases diagnosed on viability scan in the first trimester (Fig. 1), which is usually performed at 11–14 weeks of gestation, and 1 (4.5%) diagnosed on pre-chorionic villus sampling, which is usually done at 11–13 weeks of gestation. 11 (50.0%) cases were diagnosed in the second trimester, at < 22 weeks of gestation, via fetal anomaly imaging (Fig. 2), which is usually performed at 18–22 weeks of gestation. The remaining 8 (36.4%) cases were diagnosed at ≥ 22 weeks of gestation. Of these 8 cases, 7 (87.5%) were diagnosed via fetal anomaly imaging, while 1 (12.5%) was picked up on follow-up imaging after fetal anomaly imaging.

All cases were found to be left-sided. 20 (90.9%) cases had ultrasonographic findings of a stomach bubble in the left chest, as well as cardiac displacement to the right chest. Bowel loops were found in the thoracic cavity in 9 (40.9%) cases and liver herniation in 2 (9.1%). In total, 4 (18.2%) cases of lung hypoplasia or agenesis were detected at diagnosis. Polyhydramnios (defined as amniotic fluid index > 25 cm) was found in 4 (18.2%) cases. There were 15 (68.2%) cases of isolated CDH and 7 (31.8%) cases of associated fetal anomalies (Table I). Cardiovascular malformations were the most common (85.7%) associated fetal anomalies, and TOP was found to be more common in cases with associated fetal anomalies than those with isolated CDH (57.1% vs. 40.0%). In 6 (27.3%) cases, the fetus was small for gestational age at some point during the pregnancy.

Fetal karyotyping was performed in 9 (40.9%) cases, of which 3 (33.3%) were chorionic villus samplings and 6 (66.7%) were amniocenteses. Of these, 4 (44.4%) were done prior to diagnosis of CDH, while 5 (55.6%) were carried out after diagnosis. Of these 9 cases, 7 (77.8%) and 2 (22.2%) had normal and abnormal karyotypes, respectively. A balanced translocation t(11;17)(q21;p13.3) and a ring chromosome 15 were respectively detected. Based on prognostic factors such as the presence of associated fetal anomalies, fetal hydrops, LHR, and right-sided CDH, as well as patient preference,

Table I. Summary of associated fetal anomalies in CDH cases in Singapore during the period 2006–2010.

Associated fetal anomaly	Frequency
Cardiovascular system	
Ventricular septal defect	3
Tricuspid regurgitation	1
Dextrocardia	1
Left ventricular outflow tract obstruction	1
Absent ductus venosus	1
Aberrant course of umbilical vein	1
Nervous system	
Choroid plexus cyst	1
Prominent ventricle	1
Absent cavum septum pellucidum	1
Others	
Cystic hygroma	1
Short nasal bone	1
Thickened nuchal fold	2

appropriate counselling about the risks, implications and prognosis of the pregnancies was provided in all the cases by the obstetricians and neonatologists. The counselling provided was documented in the medical records. In all, 9 (40.9%) cases were counselled about the prognosis of the pregnancy based on LHR (Fig. 3). The mean LHR in the present study was 1.26 (range 0.550–3.000). Of these 9 cases, 3 (33.3%) had LHR < 1.0, 5 (55.6%) had LHR of 1.0–1.4 and 1 (11.1%) had LHR > 1.4. TOP was also more common in cases where LHR was < 1.0, as compared to cases where LHR was > 1.0 (33.3% vs. 20.0%).

After diagnosis, the frequency of subsequent visits to the obstetrician was increased to weekly in 12 out of 16 (75.0%) cases that were followed up, once in two weeks in 2 (12.5%) cases and once in three weeks in 2 (12.5%) cases. These results excluded six patients who either defaulted on follow-up, opted for TOP immediately or whose first presentation to the hospital was for delivery. In all, 10 (45.5%) cases resulted in TOP, 9 (40.9%) in live birth and 1 (4.5%) in stillbirth. The outcomes of the other two cases were unknown as they were lost to follow-up. The mean gestational age at birth was 37.2 (range 32–42) weeks. A total of 4 out of 9 (44.4%) live births and 2 of 10 (20.0%) terminated pregnancies were referred to paediatric surgical service, with documentation in the medical records regarding the counselling received about the prognosis of the pregnancies, postnatal outcomes and management.

Of the 10 births in the present study, 5 (50.0%) cases were delivered by normal vaginal delivery (NVD), 4 (40.0%) by emergency Caesarean section and 1 (10.0%) by elective Caesarean section. Of the 9 live births, the mean birth weight was 2448.6 g, and only 1 (11.1%) neonate was small for gestational age, while the remaining 8 (88.9%) were normal for gestational age. 2 (22.2%) neonates out of the 9 live births had Apgar scores of 9 at both 1 min and 5 mins, and another 2 (22.2%) had Apgar scores ≥ 7 at both 1 min and 5 mins. The remaining 5 (55.6%) neonates had Apgar scores of 4–6 at

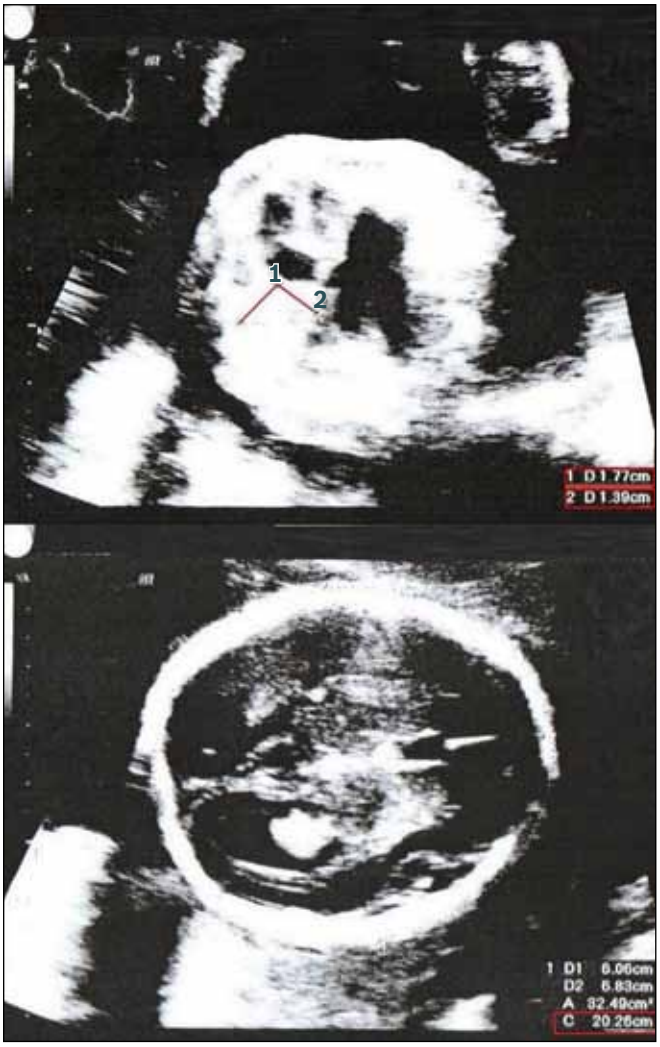

Fig. 3 US images show the dimensions of the (a) lung and (b) brain. These images were used for the calculation of the lung-to-head ratio – dividing the area of the lung by the circumference of the head (i.e. [1.77 × 1.39]/20.26 = 0.121).

1 min, which subsequently improved to ≥ 7 at 5 mins. The 2 (22.2%) neonates with Apgar scores of 9 were postnatally transferred to the special care nursery. The remaining 7 (77.8%) neonates were transferred to the neonatal intensive care unit. 3 (33.3%) of these live births resulted in neonatal deaths.

Both cases that had accompanying partial or full liver herniation visualised on ultrasonography resulted in midtrimester TOPs. Out of the 9 cases that were antenatally prognosticated with LHR, 4 (44.4%) resulted in live births, 1 (11.1%) in stillbirth and 4 (44.4%) in midtrimester TOPs. Of the 4 live births, 1 (25.0%) resulted in neonatal death on the third day of life, while 3 (75.0%) survived the neonatal period.

DISCUSSION

Access to outcome data can better help clinicians provide adequate counselling to parents in situations such as that presented in this study, where CDH is antenatally diagnosed (Fig. 4). Quantitative prognostic factors such as LHR should be used to guide parents toward making informed decisions in an evidence-based manner.[10] Notably, our data suggest that

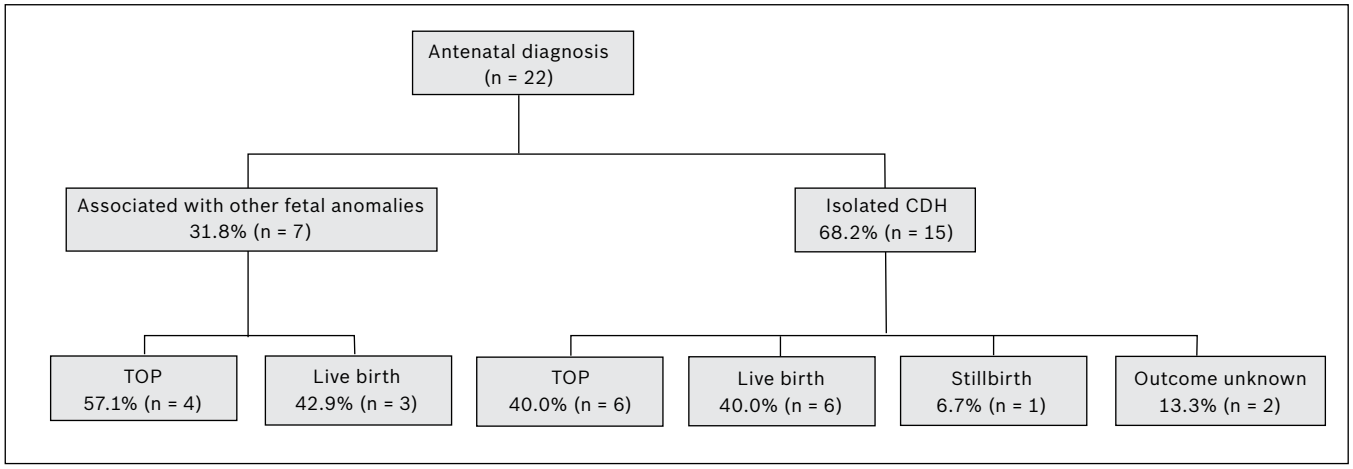

Fig. 4 Flowchart shows the outcomes of antenatally diagnosed congenital diaphragmatic hernia (CDH) cases in KKH from 2006 to 2010. TOP: termination of pregnancy

the incidence of CDH in Singapore is not associated with advanced maternal age, any particular ethnicity, parity or poor obstetric history such as malformations. The incidence of CDH in Singapore is similar to that in Norwegian and European meta-analyses, as well as studies conducted in the United Kingdom, United States and Australia.[1,5,11-18]

The mean gestational age at diagnosis in our study corresponds to that in other studies, which ranges from 19 to 29 weeks.[6,18-21] The majority of cases are similarly diagnosed via fetal anomaly imaging, which is conducted from 18 to 20 weeks of gestation.[22] Although left-sided CDH has been found to be most common,[11,19,22-24] our study is unique in that right-sided, bilateral and central forms of CDH were not detected. The topmost ultrasonographic findings are stomach bubble in the thoracic cavity, cardiac displacement and polyhydramnios.[6,18,22,24] Sonographers should hence be advised to suspect CDH when faced with such ultrasonographic evidence.

An increase of more than 20% in TOP rates when CDH is associated with other fetal malformations is confirmed by other studies, where the most commonly associated anomalies are cardiovascular in nature.[10,25-27] To aid parents in their decision-making process on whether to carry on with the pregnancy, associated anomalies should be investigated in fetuses diagnosed with CDH. The outcomes of pregnancies with CDH in our study were similar to that in studies by Colvin et al[18] and Gallot et al,[20] where close to half of the cases opted for TOP. However, this is in contrast to other studies where TOP rates ranged from 21% to 44%.[1,5,7,22,24] As there is no general consensus on the counselling and management of CDH, there can be many reasons for this discrepancy, which are not within the scope of this paper.

As investigated by Jani et al,[10] an LHR of 1.0 is taken as the threshold for high fetal mortality, with a mortality rate as high as 100.0% reported in some studies.[28-30] Separately, an LHR of > 1.4 is associated with virtually no mortality in two studies.[28,30] Hence, it can be surmised that quantitative factors could play a crucial role in prognostication and counselling, despite the fact that the significance of LHR has yet to be validated.[30-32] No other prognosticating factors such as FLV and MPA diameter were recorded in our cases of CDH. This can be attributed to the need for further investigations (such as MR imaging and Doppler flow studies for measurement of FLV and MPA diameter, respectively), which are more costly than the measurement of LHR, as LHR can be calculated at the same ultrasonography session.[6] In our study, we did not find any difference in outcome with regard to other postulated prognostic factors such as liver herniation, polyhydramnios, or lung hypoplasia or agenesis. The literature also states that survival of the fetus with CDH is not influenced by the mode of delivery.[6,23] Correspondingly, other studies, as well as ours, show almost equal rates of NVDs and Caesarean sections.[19]

Although CDH can be diagnosed antenatally, it continues to have a high perinatal mortality rate, as demonstrated by an overall survival past the neonatal period of only 60.0% in our present study. However, this survival rate is higher than that in other similar studies, where the overall survival rates were consistently below 50.0%.[11,22,33,34] CDH is known to be associated with hidden mortality, which is accounted for by TOP, intrauterine fetal deaths and postnatal deaths.[6,20,35] We have explored deaths caused by the former two causes, but further postnatal follow-up may help to better explain the difference in overall survival rates.

As the sample size of our study is small, the number of cases within each analytical subgroup is limited. It is thus possible that insignificant findings could be misconstrued. Since sonography is an operator-dependent investigation, ultrasonographic findings are subjective, especially in cases that were not diagnosed in KKH. Additionally, due to the observational and retrospective nature of our study, we were not able to influence the care of any of the pregnancies. As expressed by Wright et al,[11] well-organised randomised controlled trials would be the most challenging but most ideal way to reach a consensus to guide the future management of CDH.

In conclusion, CDH is a challenging perinatal problem with almost half of the cases opting for TOP and a low overall

survival rate. With the data in this study, clinicians can provide adequate counselling to parents, with both qualitative and quantitative prognostic factors using an evidence-based approach. We aim to further our knowledge of this rare condition by investigating postnatal outcomes, so as to ultimately devise an optimal clinical protocol for future practice.

ACKNOWLEDGEMENTS

The authors would like to thank Mr Ng Mor Jack, KKH Division of Obstetrics and Gynaecology Research, for his kind assistance throughout this study, and Ms Asmah, KKH Department of Document Management Services, for tracking the medical folders during data collection.

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