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Author(s)	Hayasaka, Itaru; Cho, Kazutoshi; Uzuki, Yutaka; Morioka, Keita; Akimoto, Takuma; Ishikawa, Satoshi; Takei, Kohta; Yamada, Takahiro; Morikawa, Mamoru; Yamada, Takashi; Ariga, Tadashi; Minakami, Hisanori
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Title: **Frequency of malformed infants in a tertiary center over a period of ten years in Hokkaido, Japan**

Running title: **Malformed newborns in a tertiary center**

Itaru Hayasaka[1], Kazutoshi Cho[1], Yutaka Uzuki[1], Keita Morioka[1], Takuma Akimoto[1], Satoshi Ishikawa[1], Kohta Takei[1], Takahiro Yamada[1], Mamoru Morikawa[1], Takashi Yamada[1], Tadashi Ariga[2], Hisanori Minakami[1]

[1]Maternity and Perinatal Care Center, Hokkaido University Hospital
[2]Department of Pediatircs, Hokkaido University Hospital, Sapporo, Japan

Corresponding author: Kazutoshi Cho
Maternity and Perinatal Care Center, Hokkaido University Hospital
TEL +81-11-706-5846
FAX +81-11-706-7981
E-mail chotarou@med.hokudai.ac.jp
All authors contributed significantly to this study.

Abstract

Aim: The widespread availability of ultrasound in obstetric practice may result in disproportionately high prevalence rates of maternities with malformed infants in tertiary centers in Japan. This retrospective study was performed to determine the frequency of malformed infants born at a tertiary center in Hokkaido, Japan.

Materials and Methods: An observational study was performed on all of 1509 and 1743 newborn infants at a single center during the 1st (2005 – 2009) and 2nd 5-year (2010 – 2014) study periods. Minor anomalies (accessory auricle, nevus, and fistula auris congenita) were not included.

Results: In total, 274 and 569 malformations were identified in 191 and 337 newborn infants in the 1st and 2nd periods, respectively. The number of malformed infants increased significantly over time (13% [191/1509] vs. 19% [337/1743], respectively, $P < 0.001$) mainly due to increased numbers of congenital heart disease (CHD) cases from 59 to 141 (31% [59/191] vs. 42% [141/337] of all malformed infants in 1st and 2nd periods, respectively). The overall accurate prenatal diagnosis rate improved over time from 47% (128/274) to 58% (329/569) due to significant improvements in accurate prenatal diagnosis of CHD subtypes (23% [16/70] vs. 65% [151/232] in 1st and 2nd periods, respectively, $P < 0.0001$).

Conclusions: The frequency of malformed newborns was higher in the tertiary center than the general population. The increased number of cases with prenatal suspicion and diagnosis of CHD contributed to the increased frequency of malformed infants during the study period.

Key words: congenital malformations, congenital heart defects, fetal echocardiography, prenatal diagnosis, tertiary care

Introduction

Ultrasound examination is widely used in obstetric practice in Japan, leading to antenatal suspicion or diagnosis of fetal malformation. Some malformed infants require prompt treatment specific for individual anomalies soon after birth. Mothers carrying fetuses with suspected or diagnosed malformations are frequently referred to tertiary centers for detailed investigation and subsequent care.

Most university hospitals play a role as tertiary centers in the care of pregnant women with complications. Therefore, it is expected that the frequency of malformed newborn infants would be higher among infants born at tertiary centers than among those in the general population. However, it has not been extensively studied how many women gave birth to malformed infants in tertiary centers in Japan.

Hokkaido University Hospital (HUH), located in Sapporo, is a tertiary center for pregnant women with complications, including fetal anomalies requiring pediatric surgery covering Sapporo area in Hokkaido, the northernmost and the second largest island in Japan, with a population of 5467000 and 39392 newborn infants in 2011. The Sapporo area has a population of 2000000 and 17000 births annually. Sapporo City launched a system called Sapporo Obstetric System for Emergency Patients (SOS) to shorten the time interval until admission to an appropriate hospital after the occurrence of an obstetric emergency in October 2008.[1] Six centers in Sapporo including the HUH participated in the SOS system and were considered as having a sufficient number of beds available for such emergency cases. However, neonatal intensive care unit (NICU) at the six centers, especially at the HUH, suffered from chronic shortages of NICU-beds available for otherwise healthy premature infants. This suggested an increased number of maternal referral for fetal malformations to the HUH from community hospitals remote from the Sapporo area.

This study was performed to determine how many malformed infants were born at the HUH during a 10-year study period from 2005 to 2014. Accurate prenatal diagnosis rates according to malformations were also invetigated.

Materials and Methods

This retrospective observational study was conducted after receiving approval from the Institutional Review Board of Hokkaido University Hospital (016-0053, May 2, 2016).

A total of 3252 infants were born on or after gestational week 22 at the HUH during the last 10-year study period between January 1, 2005, and December 31, 2014. The study period was divided into two 5-year periods (1st period, 2005 – 2009; 2nd period, 2010 – 2014). We identified newborn infants with malformation(s) using the hospital discharge record database. Thus, malformations were defined as those found during the hospital stay after birth at the HUH. The medical charts of each infant with malformation(s) were reviewed in detail regarding malformation types.

Classification of malformations

Minor anomalies, such as accessory auricle, nevus, and fistula auris congenita, were not included as malformations in this study. Malformations were classified based on

phenotypes regardless of chromosomal/genetic abnormalities or syndrome. Congenital heart disease (CHD) were divided into following subtypes; pulmonary atresia, pulmonary stenosis, pure pulmonary atresia, atrial septal defect (ASD), tetralogy of Fallot (TOF), extreme TOF, aortostenosis, aortic valve stenosis, coarctation of aorta (CoA), CoA complex, aortic arch interruption (AAI), AAI with ventricular septal defect (VSD), transposition of great arteries (TGA), corrected TGA, endocardial cushion defect (ECD), double outlet right ventricle (DORV), total anomalous pulmonary venous connection (TAPVC), single ventricle, hypoplastic left heart syndrome (HLHS), tricuspid atresia, Ebstein's anomaly, truncus arteriosus communis (TAC), and VSD alone accompanied by neither DORV, TOF, TGA, nor CoA complex and others. Patent ductus arteriosus alone was not included in the CHD subtypes.

Accurate prenatal diagnosis of malformations was defined as that concordant pre- and postnatal diagnoses of malformations. Small for gestational age (SGA) was diagnosed based on normative birthweight for Japanese infants.[2]

Statistical analyses were performed using the JMP8© statistical software package (SAS, Cary, NC). Differences between the frequencies were analyzed using Fisher's exact test. In all analyses, $P < 0.05$ was taken to indicate statistical significance.

Results

In total, 1509 and 1743 infants were born at the HUH during the 1st and 2nd periods, respectively (Fig. 1). Of these, 191 (13%) and 337 (19%) were identified as having at least one malformation, respectively. Thus, the number of infants with malformation(s) increased significantly over time, from 13% (191/1509) in the 1st period to 19% (337/1743) in the 2nd period ($P < 0.001$). These 191 and 337 infants had 274 and 569 malformations, respectively (Fig. 1). Each malformation was treated separately in infants with multiple malformations when they were not affected by trisomy 18 and 13.

A CHD was detected in 200 of the 528 malformed infants (38%) and was the leading malformation. CHD infants accounted for 31% (59/191) vs. 42% (141/337) ($P = 0.015$) of all malformed infants born during the 1st vs. 2nd periods, respectively. As many as 3.9% (59/1509) vs. 8.1% (141/1743) ($P < 0.001$) of all infants born in the 1st vs. 2nd periods had at least one CHD subtype, respectively. A total of 302 CHD subtypes were seen in the 200 CHD infants (Table 1). VSD alone, pulmonary stenosis, and DORV were the leading three CHD subtypes (Table 1). However, the accurate prenatal diagnosis rate for each subtype varied markedly from 3.6% for VSD to 100% for defects such as tricuspid atresia, HLHS, Ebstein's anomaly, and pure pulmonary atresia. Thus, the accurate prenatal diagnosis rate for VSD alone was low perhaps due to a relatively smaller defect compared to VSD accompanied by other CHD subtypes. Overall, the accurate prenatal diagnosis rate for CHD subtypes was 55% (167/302) (Table 1). CHD subtypes accounted for 26% (70/274) vs. 41% (232/569) ($P < 0.001$) of all malformations in the 1st vs. 2nd periods, respectively.

Other malformations with accurate prenatal diagnosis rates are shown in Table 2. Hydronephrosis (n=75), hydrocephaly (n=36), cryptorchidism (n=26), hypoplasia of the lung (n=22), corpus callosum agenesis (n=19), hypospadias (n=17), CDH (n=16),

duodenal stenosis/atresia (n=16), cleft lip with cleft palate (n=16), multicystic kidney (n=15), and intestinal atresia/stenosis (n=15) were relatively common malformations at our hospital (Table 2). Among these malformations with higher frequencies, the accurate prenatal diagnosis rate was more than 60% in CDH (94% [14/15]), hypoplasia of the lung (91% [20/22]), hydrocephaly (89% [32/36]), multicystic kidney (87% [13/15]), duodenal stenosis/atresia (81% [13/16]), and corpus callosum agenesis (68% [13/19]).

Both intestinal atresia/stenosis and hypospadias are rare in the general population, with prevalence rate of 8.7 for the former and 5.6 for the latter per 10000 newborn infants in Japan.[3] The accurate prenatal diagnosis rate was low for both malformations (13% [2/15] for intestinal atresia/stenosis and 5.9% [1/17] for hypospadias) in this study (Table 2). However, frequencies were very high at our hospital; 15 intestinal atresia/stenosis and 17 hypospadias in 3252 infants, corresponding to 46 and 52 per 10000 infants, respectively. Other malformations/abnormalities were reasons for referral to our hospital in most patients. In the 13 infants with intestinal atresia/stenosis, but without accurate prenatal diagnosis, dilated intestine with (n=6) or without ascites (n=5) were seen in 11 fetuses. Cystic abdominal mass was pointed out in one of the remaining two fetuses. In the 16 infants with hypospadias, but without accurate prenatal diagnosis, 9 were twins born to 9 twin pregnancies (7 monochorionic and 2 dichorionic), and 6 of the remaining 7 singletons had multiple anomalies other than the hypospadias including hydrocephaly (with corps callosum agenesis and SGA), SGA (with cleft lip, cleft palate, cerebellar hypoplasia, DORV, and trisomy 18), hydronephrosis (with sacrum deformity, left kidney hypoplasia, and anal atresia), SGA (with ASD, VSD, and cryptorchidism), hydrocephaly (with hydronephrosis, cryptorchidism, and Schinzel-Giedion syndrome), and SGA (with cryptorchidism). Thus, twins were likely to have hypospadias, and fetal growth restriction was likely to occur in fetuses with hypospadias.

The overall accurate prenatal diagnosis rate was 54% (457/843) for the 10-year study period. However, the accurate prenatal diagnosis rate was significantly higher for the 2nd period than the 1st period (58% [329/569] vs. 47% [128/274], respectively, P = 0.0212). This was mainly due to improvement in accurate prenatal diagnosis rate of CHD for the 2nd period (Table 3). The accurate prenatal diagnosis rate did not change significantly over time for malformations arising from organs/sites other than the heart (Table 3).

We had 20, 10, and 1 newborns with trisomy 21, trisomy 18, and trisomy 13, respectively, during the study period. Of them, 15 (75%), 9 (90%) and 1 (100%) of infants with trisomy 21, trisomy 18, and trisomy 13, respectively, had malformation(s). The CHD was seen in as many as 9 (45%) and 8 (80%) infants with trisomy 21 and trisomy 18, respectively. Number of infants with these anomalies was 11 (0.73%) for the 1st period (2005 – 2009) and 20 (1.1%) for the 2nd period (2010 – 2014).

Discussion

As expected, the frequency of malformed infants was much higher in our center compared to that in the general Japanese population in 2011 based on the Annual Report 2013 released by the International Clearinghouse Center for Birth Defect

Surveillance and Research (ICBDSR)[3] in which a limited number of malformations or malformation subtypes are listed. With regard to malformations classified in a similar way to our method and listed in the ICBDSR report, the frequency of most malformations were much higher in infants born at the HUH compared to those in Japan described in the ICBDSR report. For example, the frequency of hydrocephaly was 169.1 per 10000 births in this study, far exceeding the rate of 7.8 per 10000 births in the ICBDSR report, representing a 21.7-fold higher prevalence rate at our center than the general Japanese population. This suggested that the number of mothers referred to us for suspected fetal malformations and other fetal anomalies suggestive of malformations was high among maternities at the HUH. This may have reflected the widespread use of ultrasound examination in antenatal care provided at primary/secondary facilities in Hokkaido.

Indeed, frequencies of intestinal atresia/stenosis and hypospadias were much higher at our hospital than the general Japanese population[3] despite that these anomalies were hardly diagnosed prenatally (Tables 2, 3). However, as fetuses with intestinal atresia/stenosis were likely to show dilated intestines, those with this anomaly were referred to us, resulting in a high frequency at our hospital. Fetuses with hypospadias were likely to exhibit other detectable complications/anomalies such as twin pregnancy and growth restriction, consistent with results of previous studies.[4,5]

Congenital malformations occur in 2.3% of newborns in the USA[6] after exclusion of fetuses terminated for severe/lethal malformations.[7] CHD is the most common malformation occurring in approximately 0.8% – 1.0% of all live born infants.[8-10] Thus, CHD infants accounted for approximately 30% – 40% of all malformed infants. Indeed, 38% (200/528) of all malformed infants had CHD in this study. In addition, the CHD frequency increased significantly over time during the study period, with rates of 3.9% (59/1509) and 8.1% (141/1743) of all newborns at the HUH during the 1st and 2nd periods, respectively. This suggested that Hokkaido physicians responsible for antenatal care had increased their attention to CHD over the past 10 years.

Some CHDs are lethal in the absence of intervention[11,12] and prenatal diagnosis followed by planned delivery and appropriate postnatal care improve perioperative morbidity.[13,14] National health insurance began covering the cost of testing with fetal echocardiography targeting women with suspected fetal CHD in 2010. Screening echocardiography of spatiotemporal image correlation (STIC)[15,16] was introduced in seven facilities located in Sapporo in 2013. In addition, the HUH participated in a multicenter clinical trial of noninvasive prenatal testing (NIPT) in 2013 resulting in markedly increased number of women at high risk with respect to fetal anomalies at the HUH.[17] Fraction of infants with trisomy 21, 18, and 13 was 0.73% (11/1509) for the 1st period and 1.1% (20/1743) for the 2nd period. All of these may have contributed to the markedly higher frequency of CHD at the HUH and to the significantly improved accurate prenatal diagnosis rate for CHD (Table 3). As may as 45% (9/20) of infants with trisomy 21 had CHD in this study consistent with a previous study[18] in which CHD is seen in 44% (323/728) of all registered infants with trisomy 21 in Europe.[18] Japanese law prohibits any induced abortion on and after gestational week 22. Even in women with gestational week less than 22, induced abortion is allowed only in women with

maternal health and/or economic problems, but not in women whose reason for induced abortion is “fetal anomaly”. These also may have been associated with the increase in CHD infants at the HUH despite the improved accurate prenatal diagnosis rate for CHD.

The total number of malformed newborns increased over the study period, from 191 during the 1st period to 337 during the 2nd period at the HUH. This was mainly due to the increased number of CHD infants; the net increase in number of CHD infants was 82, accounting for 56% of the net increase of 146 in number of all malformed newborns. This may have been ascribed to the following situations in Hokkaido; cardiac surgeries for CHD newborns were available only at a limited number of tertiary centers in Hokkaido, including HUH, but we had no predefined systems for maternal referral for fetal malformations from community hospitals and back transport of infants to community hospitals for convalescent care. Most infants with malformations required NICU causing chronic shortages of bed available for otherwise healthy premature infants at our NICU. The development of new policies regarding the acceptance of maternal referral with suspected fetal malformations as well as back transport of very low-birthweight infants to community hospitals is urgently needed.

In conclusion, this study demonstrated that the number of malformed infants increased significantly over the past 10 years due mainly to the increase in number of infants with CHD. The overall rate of accurate prenatal diagnosis improved over time mainly due to a significant improvement in accurate prenatal diagnosis of CHD. This caused chronic bed shortages for otherwise healthy premature infants at our NICU.

Conflict of Interest
None declared.

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Figure legend

Figure 1 Number of newborn infants with malformations

Fig. 1

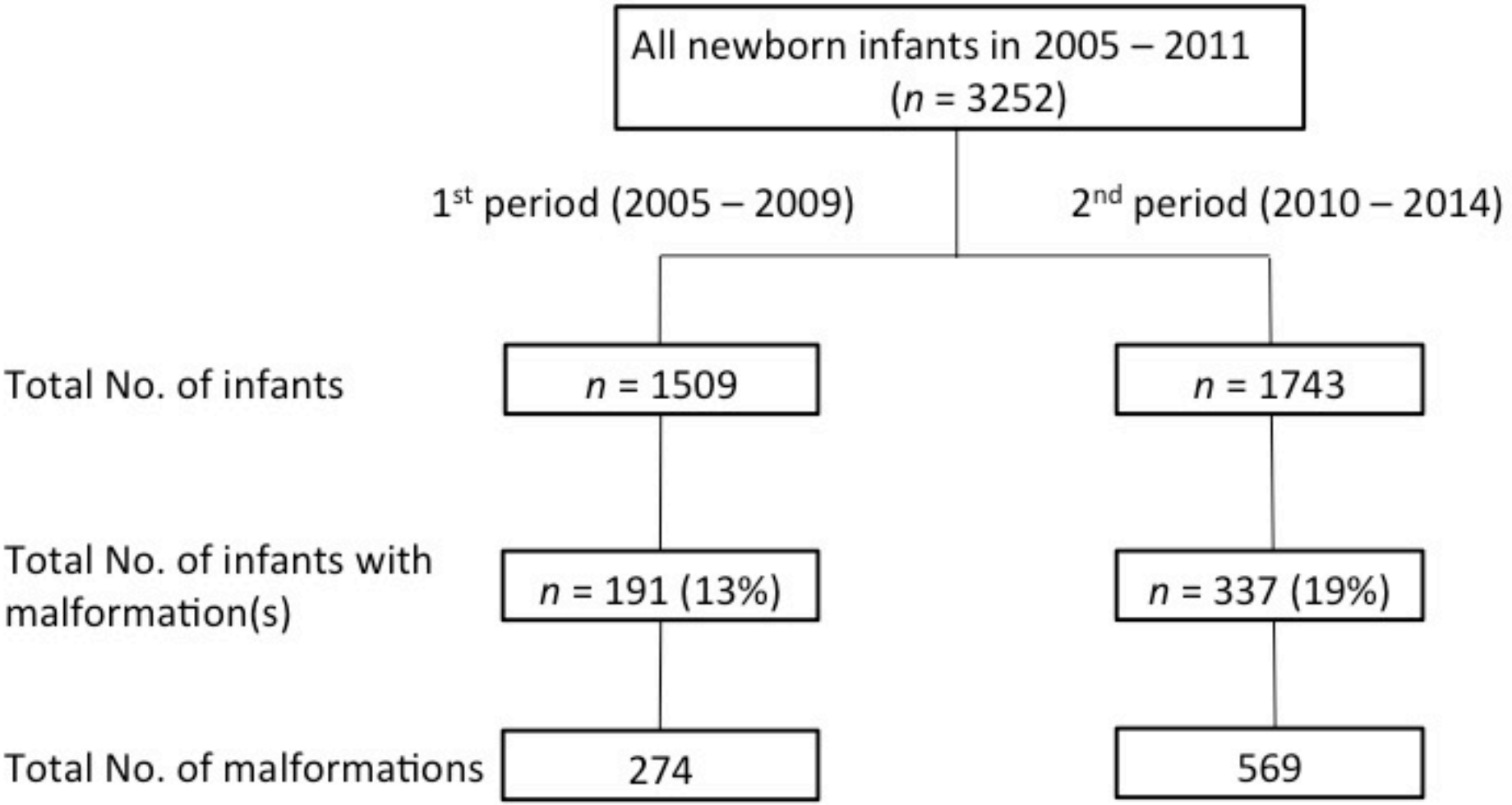
All newborn infants in 2005 – 2011
(n = 3252)
1st period (2005 – 2009)
2nd period (2010 – 2014)
Total No. of infants
n = 1509
n = 1743
Total No. of infants with malformation(s)
n = 191 (13%)
n = 337 (19%)
Total No. of malformations
274
569

Table 1. CHD seen in the 200 infants and rate of accurate prenatal diagnosis of subtypes

Subtypes	No. of infants affected	Accurate prenatal diagnosis
Tricuspid atresia	7	7 (100%)
HLHS	6	6 (100%)
Ebstein's anomaly	5	5 (100%)
Pure pulmonary atresia	4	4 (100%)
Truncus arteriosus communis	1	1 (100%)
Corrected TGA	1	1 (100%)
ECD	24	20 (83%)
Extreme TOF	6	5 (83%)
CoA complex	6	5 (83%)
TGA	10	8 (80%)
Single ventricle	10	8 (80%)
TAPVC	13	10 (77%)
TOF	14	10 (71%)
AAI with VSD	3	2 (67%)
Pulmonary atresia	13	8 (62%)
Aortic valve stenosis	5	3 (60%)
DORV	32	19 (59%)
Coarctation of aorta (CoA)	7	4 (57%)
Pulmonary stenosis	33	16 (48%)
Aortic arch interruption (AAI)	3	1 (33%)
ASD	16	3 (19%)
VSD	56	2 (3.6%)
Others	27	19 (70%)
Overall	302	167 (55%)

All subtypes of CHD seen in 200 infants are listed in this table. ASD, atrial septal defect; CoA, coarctation of aorta; DORV, double outlet right ventricle; ECD, endocardial cushion defect; NA, not applicable; TAPVC, total anomalous pulmonary venous connection; TGA, transposition of great arteries; TOF, tetralogy of Fallot; VSD, ventricular septal defect. Patent ductus arteriosus (PDA) was diagnosed in two newborns, but not included in CHD subtypes in this study. These two with PDA had other anomaliesi ncludingVSD in one and multicystic kidney in another.

Table 2. Accurate prenatal diagnosis rates according to malformations in the site other than the heart

	No. of infants affected	Accurate prenatal diagnosis
Polysplenia	9	9 (100%)
Gastroschisis	6	6 (100%)
CCAM	5	5 (100%)
Achondroplasia	4	4 (100%)
Myotonic dystrophy	3	3 (100%)
Campomelic dysplasia	2	2 (100%)
CDH	16	15 (94%)
Hypoplasia of the lung	22	20 (91%)
Hydrocephaly	36	32 (89%)
Spina bifida	9	8 (89%)
Omphalocele	8	7 (88%)
Multicystic kidney	15	13 (87%)
Asplenia	6	5 (83%)
Chiari malformation	6	5 (83%)
Duodenal stenosis/atresia	16	13 (81%)
Osteogenesis imperfecta	7	5 (71%)
Corpus callosum agenesis	19	13 (68%)
Persistent cloaca/BE	3	2 (67%)
Pulmonary sequestration	5	3 (60%)
Renal agenesis/hypoplasia	5	3 (60%)
Ovarian cyst	12	7 (58%)
Hydronephrosis	75	40 (53%)
Cerebellar hypoplasia	6	3 (50%)
Arthrogryposis multiple congenita	2	1 (50%)
Esophageal atresia	9	3 (33%)
Cleft lip with cleft palate	16	5 (31%)
Ectopic gray matter	4	1 (25%)
Cleft lip alone	7	1 (14%)
Intestinal atresia/stenosis	15	2 (13%)
Cryptorchidism	26	2 (7.7%)
Hypospadias	17	1 (5.9%)
Anal atresia	6	0 (0.0%)
Polydactyly (foot)	6	0 (0.0%)
Cleft palate without cleft lip	5	0 (0.0%)
Syndactyly (foot)	4	0 (0.0%)
MMIHS	3	0 (0.0%)
Biliary dilatation	2	0 (0.0%)
Facial cleft	2	0 (0.0%)
Natal teeth	2	0 (0.0%)
Syndactyly (hand)	2	0 (0.0%)

Malformations seen in two or more of the 528 newborns are listed in this table. BE, bladder extrophy; CCAM, congenital cystic adenomatoid malformation; CDH, congenital diaphragmatic hernia; MMIHS, megacystis-microcolon-intestinal hypoperistalsis syndrome.

Table 3 Change in rate of accurate prenatal diagnosis over time

	1st period (2005 – 2009)	2nd period (2010 – 2014)
Hydrocephaly	83% (15/18)	94% (17/18)
CDH	100% (5/5)	91% (10/11)
Duodenal stenosis/atresia	67% (4/6)	90% (9/10)
Hypoplasia of the lung	100% (6/6)	88% (14/16)
Corpus callosum agenesis	56% (5/9)	80% (8/10)
Multicystic kidney	100% (6/6)	78% (7/9)
Ovarian cyst	40% (2/5)	71% (5/7)
CHD subtypes	23% (16/70)	65% (151/232) *
Hydronephrosis	57% (21/37)	50% (19/38)
Cleft lip with cleft palate	100% (2/2)	21% (3/14)
Cryptorchidism	17% (1/6)	5.0% (1/20)
Intestinal atresia/stenosis	20% (2/10)	0.0% (0/5)
Hypospadias	14% (1/7)	0.0% (0/10)

*, $P < 0.05$ vs. 1st period. Malformations seen in 10 or more infants are listed in this table.