Original Article
Obstet Gynecol Sci 2015;58(2):90-97
http://dx.doi.org/10.5468/ogs.2015.58.2.90
pISSN 2287-8572 · eISSN 2287-8580

Obstetrics & Gynecology Science

Clinical characteristics and perinatal outcome of fetal hydrops

Wonkyung Yeom, E Sun Paik, Jung-Joo An, Soo-young Oh, Suk-Joo Choi, Cheong-Rae Roh, Jong-Hwa Kim

Department of Obstetrics and Gynecology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Objective
To investigate the clinical characteristics of fetal hydrops and to find the antenatal ultrasound findings predictive of adverse perinatal outcome.

Methods
This is a retrospective study of 42 women with fetal hydrops who delivered in a tertiary-referral center from 2005 to 2013. Fetal hydrops was defined as the presence of fluid collection in ≥2 body cavities: ascites, pleural effusion, pericardial effusion, and skin edema. Predictor variables recorded included: maternal characteristics, gestational age at diagnosis, ultrasound findings, and identifiable causes. Primary outcome variables analyzed were fetal death and neonatal death.

Results
The mean gestational age at diagnosis was 29.3±5.4 weeks (range, 18 to 39 weeks). The most common identifiable causes were cardiac abnormality (10), followed by syndrome (4), aneuploidy (3), congenital infection (3), twin-to-twin transfusion syndrome (3), non-cardiac anormaly (2), chorioangioma (2), inborn errors of metabolism (1), and immune hydrops by anti-E antibody isoimmunization (1). Thirteen cases had no definite identifiable causes. Three women elected termination of pregnancy. Fetal death occurred in 4 cases. Among the 35 live-born babies, only 16 survived (54.0% neonatal mortality rate). Fetal death and neonatal mortality rate was not significantly associated with Doppler velocimetry indices or location of fluid collection, but increasing numbers of fluid collection site was significantly associated with a higher risk of neonatal death.

Conclusion
The incidence of fetal hydrops in our retrospective study was 24.4 per 10,000 deliveries and the perinatal mortality rate was 61.9% (26/42). The number of fluid collection sites was the significant antenatal risk factor to predict neonatal death.

Keywords: Fetal death in utero; Hydrops fetalis; Infant mortality; Ultrasonography

Introduction

Fetal hydrops is defined as an abnormal fluid collection in two or more areas of the fetal body, such as ascites, pleural effusion, pericardial effusion and skin edema [1-3]. The etiologies of fetal hydrops are classified as immune or non-immune hydrops. Immune hydrops develops due to fetal hemolysis mediated by circulating maternal antibodies to fetal red blood cell antigens. Non-immune hydrops can result from a large number of causes including cardiac and non-cardiac anomaly, syndromes, aneuploidy, congenital infection, twin-to-twin transfusion syndrome, chrioangioma and other conditions. Cardiac abnormalities that cause fetal hydrops include structural anomalies, cardiomyopathies and arrhythmias. Toxoplasmosis,

Received: 2014.5.30. Revised: 2014.9.5. Accepted: 2014.10.5.
Corresponding author: Suk-Joo Choi
Department of Obstetrics and Gynecology, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 135-710, Korea
Tel: +82-2-3410-3546 Fax: +82-2-3410-0630
E-mail: drmaxmix.choi@samsung.com

This study was presented at the Annual Congress of Korean Society of Ultrasound in Obstetrics and Gynecology, Mungyeong, October 19, 2013 (abstract no. 16K10022).

cytomegalovirus, herpes simplex virus, syphilis, and Parvovirus B19 are the most common congenital infections that cause fetal hydrops. But, the precise cause of non-immune hydrops may remain unknown in 15% to 25% of cases [4,5].

The incidence of fetal hydrops is reported to be 0.3 to 2.4 per 1,000 live births [6,7]. Recent advances in obstetric and neonatal medicine made some improvements in diagnosis, prevention and management of fetal hydrops. Specifically, immune hydrops has been decreased by routine screening and prophylaxis of Rhesus iso-immunization [1,5]. However, the incidence of non-immune hydrops is largely unchanged [8] and mortality rate of non-immune hydrops, either during fetal or neonatal period, is still high, up to 75.5% [5,9,10].

Fetal hydrops is easily recognized by routine ultrasound examination. When it is found by a routine ultrasound, a detailed ultrasound examination should be done to figure out the etiology and nature of hydrops, including the location, number and amount of fluid collections, amniotic fluid index, placental thickness, fetal echocardiography and Doppler velocimetry. However, there is limited information regarding the association between the ultrasound findings and perinatal outcomes of fetal hydrops [11-13]. Specifically, it is not well known whether the location or number of fluid collection sites is associated with fetal or neonatal mortality. Therefore, the aim of this study is to investigate the clinical characteristics of fetal hydrops and to find out whether the antenatal ultrasound findings, especially the location or number of fluid collection sites, are associated with adverse perinatal outcomes.

Materials and methods

A retrospective chart review was performed in pregnant women with fetal hydrops who delivered in a tertiary referral center in Seoul, Korea, from January 2005 to August 2013. Fetal hydrops was defined as an abnormal fluid collection in two or more areas of the fetal body: ascites, pleural effusion, pericardial effusion, and skin edema. Polyhydramnios and placentomegaly are frequently associated with fetal hydrops, but they are not used as diagnostic criteria. This was a retrospective study and approved to be exempt from full IRB review in the Samsung Medical Center.

The standard diagnostic work up for fetal hydrops in our institute is described in the Table 1. But not all tests were per-

Table 1. Diagnostic work up for fetal hydrops

	Tests
Maternal blood	ABO & Rh (0%, 0/42), antibody screen (2.4%, 1/42), indirect Coombs' test (5%, 1/20), Kleihauer-Betke test (0%, 0/3), Serological test: toxoplasmosis (0%, 0/30), rubella (3.3%, 1/30), cytomegalovirus (0%, 0/30), herpes simplex virus (0%, 0/30), parvovirus B19 (3.3%, 1/30), syphilis (2.4%, 1/42)
Ultrasound	Estimated fetal weight, amniotic fluid index, biophysical profile[a)] Site and number of fluid collection[a)] Fetal structural investigation including fetal echocardiography (57.1%, 24/42) Placental thickness (60%, 15/25) Doppler velocimetry: umbilical artery (27.2%, 9/33), middle cerebral artery (53.8%, 14/26), ductus venosus (50.0%, 8/16)
Amniocentesis	Karyotype (0%, 0/21) Serologic tests for specific suspicious congenital infections (0%, 0/1)
Cordocentesis	Karyotype (100%, 1/1) Fetal hemoglobin or hematocrit (if fetal anemia is suspected) (100%, 1/1) Serologic tests for specific suspicious congenital infections (0%, 0/0)
Postnatal work up	Gross morphological assessment (73.8%, 31/42) Ultrasonography including echocardiography (50.0%, 14/28) Karyotype (12.5%, 3/24) Congenital infection study: toxoplasmosis (0%, 0/31), rubella (3.2%, 1/31), cytomegalovirus (3.2%, 1/31), herpes simplex virus (0%, 0/31), parvovirus B19 (4%, 1/25), syphilis (33.3%, 1/3) Neonatal hemoglobin (43.2%, 16/37) Autopsy (recommended in fetal death cases) (85.7%, 6/7) Placenta pathology (14.6%, 6/41) Neonatal screening (inborn error of metabolism) (3.6%, 1/28)

Numbers in the parenthesis is the test positive rate for each test (positive results/number of test performed) in our study population.
[a)]Performed in all cases.

formed in all cases. If available, the prenatal diagnosis was confirmed or changed by postnatal or postmortem examination. The cause of fetal hydrops was classified into 10 categories: cardiac abnormality, non-cardiac structural anomaly, syndrome, aneuploidy, congenital infection, twin-to-twin transfusion syndrome, chorioangioma, inborn errors of metabolism, immune, and unknown. If the cause of fetal hydrops is indefinite or multiple, the most probable one was defined as the cause.

Ultrasound findings reviewed for the analysis were the location and number of fluid collection sites, amniotic fluid index, placental thickness and Doppler velocimetry. Abnormal umbilical artery Doppler velocimetry was defined as systolic/diastolic ratio >90 percentile or absent/reversed end diastolic flow. Abnormal middle cerebral artery (MCA) Doppler velocimetry was defined as pulsatility index <10 percentile or peak systolic velocity >1.5 multiples of median. Abnormal ductus venosus Doppler velocimetry was defined as an absent/reversed a-wave.

The primary outcome variables were fetal death and neonatal death. Other secondary outcome variables analyzed were gestational age at delivery, gender, birth weight, Apgar scores and neonatal hemoglobin. Neonatal anemia was defined as hemoglobin <14.5, and severe anemia was defined as hemoglobin <10.0.

The Mann-Whitney *U*-test was used for the comparison of continuous variables. For the comparison of multiple means, Kruskal-Wallis test was used. Proportions were compared using the chi-square test or Fisher's exact test, as appropriate, and linear-by-linear association was used to identify trends. The results were considered statistically significant when *P*-values were <0.05.

Results

During the 8-year period of review, 42 cases of fetal hydrops were identified from a total of 17,217 deliveries (incidence 24.4/10,000 delivery). Four cases were twin pregnancy. The mean gestational age at diagnosis was 29.3 weeks (range, 18.2 to 39.4 weeks). Sixteen cases were diagnosed during the second trimester and 26 cases were diagnosed during the third trimester. Three women elected to terminate their pregnancies at 18, 20, and 22 weeks of gestation, respectively (Fig. 1). Fetal death occurred in 4 cases (18, 26, 26, and 34 weeks of gestation, respectively). Among the 35 live-born babies, 16 survived and 19 died (54.0% neonatal mortality rate).

Five cases were diagnosed before 22 weeks of gestation, and there were no perinatal survivor (termination of pregnancy in 2 cases, fetal death in 2 cases, and neonatal mortality in 1 case). Among the 11 cases diagnosed between 22 and 28 weeks of gestation, there was only 1 perinatal survivor (termination of pregnancy in 1 case, fetal death in 2 cases, neonatal mortality in 7 cases). Among the 16 cases diagnosed between 29 and 33 weeks of gestation, there were 10 perinatal survivors (no termination of pregnancy, no fetal death, neonatal mortality in 6 cases). Seven cases were diagnosed between 34 and 39 weeks of gestation, and there were 2 perinatal survivors (no termination of pregnancy, no fetal death, neonatal mortality in 5 cases).

The most common identifiable cause was cardiac abnormality (10) followed by syndrome (5), aneuploidy (3), congenital infection (3), twin-to-twin transfusion syndrome (3), non-cardiac structural anomaly (2), chorioangioma (2), inborn errors of metabolism (1), and immune hydrops by anti-E antibody isoimmunization (1). Thirteen cases had no definite identifiable causes. The causes of fetal hydrops of the 35 live-born babies are described in the Table 2. There was no significant difference in the proportion of causes of fetal hydrops between the survivors and neonatal mortality cases (*P*=0.599, by chi-square test), as well as between the survivors and perinatal mortality (fetal death or neonatal death) cases (*P*=0.660, by chi-square test).

Prenatal intervention was offered to 13 fetuses: amnioinfusion in parvovirus infection case (1), cordocentesis and

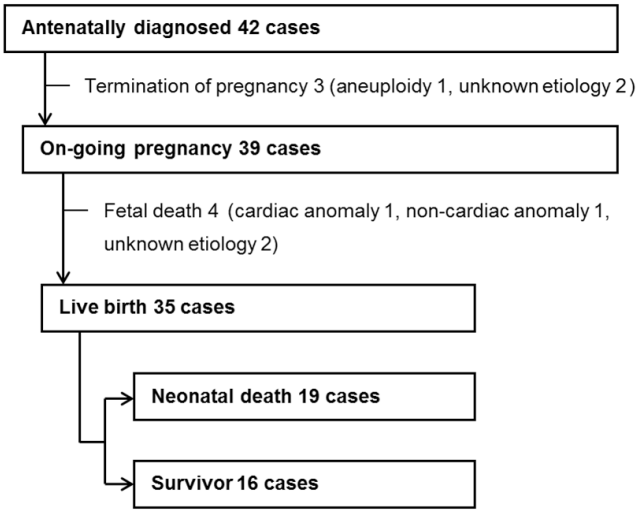

Fig. 1. A flowchart of the pregnancy and perinatal outcome of the pregnancies with fetal hydrops.

Table 2. Causes of fetal hydrops in live-born cases: survivors vs. neonatal mortality cases

	Survivor (16)	Neonatal death (19)
Cardiac abnormality	n=3 Severe tricuspid regurgitation (1), pulmonary stenosis with hypertropic cardiomyopathy (1), fetal tachycardia (atrial flutter) (1)	n=6 Pulmonary atresia with ventricular septal defect (1), cardiomyopathy (1), complex cardiac anomaly (1), right heart failure (1), ventricular septal defect (1), myocardial dysfunction (1)
Non-cardiac structural anomaly	n=1 Meconium peritonitis due to jejunoileal atresia (1)	n=0
Syndrome	n=2 Prader-Willi/Angelman syndrome (1), Pierre-Robin syndrome (1)	n=2 Haddad syndrome (1), mitochondrial disease (1)
Aneuploidy	n=1 Down syndrome (1)	n=1 Down syndrome (1)
Infection	n=1 Congenital cytomegalovirus infection (1)	n=2 Parvovirus infection (1), congenital syphilis (1)
TTTS	n=3	n=0
Chorioangioma	n=1	n=1
Inborn errors of metabolism	n=0	n=1 Glycogen storage disease (1)
Immune	n=0	n=1
Unknown etiology	n=4	n=5

TTTS, twin-to-twin transfusion syndrome.

transfusion in chorioangioma case (1), amnioreduction and microseptostomy in twin-to-twin transfusion syndrome case (1), amnioreduction, thoracentesis and pleurodesis in unknown cases (3), paracentesis in congenital cytomegalovirus infection case (1) and amnioreduction in Haddad syndrome, twin-to-twin transfusion syndrome, mitochondrial disease, and unknown case (4).

We compared maternal and pregnancy characteristics, antenatal ultrasound findings and perinatal outcome between fetal death group and live birth group (Table 3). The mean gestational age at diagnosis of fetal hydrops was significantly lower in the fetal death group compared to the live birth group. Antenatal ultrasound findings, including the location of fluid collection, polyhydramnios, placental thickness and Doppler velocimetry results, were not significantly different between the two groups. Maternal and pregnancy characteristics, antenatal ultrasound findings and perinatal outcome of the neonatal death group and perinatal survivor group were also comparable, except for a lower cesarean section rate and lower Apgar scores in the neonatal death group (Table 3).

Among the 4 sites of fluid collection (ascites, pleural effusion, pericardial effusion and skin edema), 17 cases had 2 sites, 19 cases had 3 sites, and 3 cases had all 4 sites of fluid collection (Table 4). None of the Doppler velocimetry indices was associated with the number of fluid collection sites. The incidence of neonatal anemia and severe anemia increased with increasing number of fluid collection sites, but the trend was not statistically significant. Increasing number of fluid collection site was not associated with the fetal death rate, but it was significantly associated with a higher neonatal death rate and a more neonates with Apgar score of less than 4. However, we could not find any combination of fluid collection sites that was significantly associated with either fetal death or neonatal death rate (Table 5).

Discussion

In this study, we reviewed the clinical characteristics and outcomes of fetal hydrops in a tertiary-referral center during 8-year period. We found that the incidence of fetal hydrops was 24.4 per 10,000 deliveries and the overall perinatal mortality rate was 61.9% (26/42). The higher incidence of fetal hydrops in our study, compared to the other previous studies, may be due to the high proportion of fetal hydrops referred to our tertiary-care hospital from the community. The major find-

Table 3. Comparisons of maternal and pregnancy characteristics, antenatal ultrasound findings and perinatal outcome

	Fetal death (n=4)	Live birth (n=35)	Live birth	
			Neonatal death (n=19)	Survivor (n=16)
Maternal age (yr)	31.0±1.4	31.3±4.2	31.3±3.9	31.4±4.6
Nulliparity	3 (75.0)	16 (45.7)	8 (42.1)	8 (50.0)
Twin	1 (25.0)	3 (8.6)	0 (0)	1 (6.3)
GA at diagnosis (wk)	22.3±4[a]	30.9±4.2[a]	31.5±4.8	30.2±3.5
Location of fluid collection				
Ascites	4 (100)	26 (74.3)	14 (73.7)	12 (75.0)
Pleural effusion	2 (50.0)	24 (68.6)	15 (78.9)	9 (56.3)
Pericardial effusion	1 (25.0)	16 (45.7)	9 (47.4)	7 (43.8)
Skin edema	4 (100)	26 (74.3)	16 (84.2)	10 (62.5)
Polyhydramnios	1 (25.0)	23 (65.7)	10 (52.6)	13 (81.3)
Placental thickness	29.8±0.4	49.4±19.1	47.6±22.2	52.0±14.4
Doppler[b]				
UA S/D ratio >90 percentile	0/2 (0)	7/30 (23.3)	2/15 (13.3)	5/15 (33.3)
UA A/R EDF	0/2 (0)	3/30 (10.0)	1/15 (6.7)	2/15 (13.3)
MCA PI <10 percentile	1/2 (50.0)	11/24 (45.8)	4/12 (33.3)	7/12 (58.3)
MCA PSV >1.5 MoM	2/2 (100)	6/19 (31.6)	3/10 (30.0)	3/9 (33.3)
DV A/R a-wave	1/1 (100)	7/15 (46.7)	5/10 (50.0)	2/5 (40.0)
GA at delivery (wk)	26.5±6.3[a]	32.7±3.6[a]	33.0±4.0	32.3±3.1
Cesarean delivery	1 (25.0)[a]	24 (68.6)[a]	10 (52.6)[b]	14 (87.5)[b]
Male	2 (50.0)	16 (45.7)	9 (47.4)	7 (43.8)
Birth weight (kg)	1.4±0.8[a]	2.2±0.7[a]	2.3±0.7	2.2±0.7
1 Minute Apgar score <4	-	17 (48.6)	15 (78.9)[b]	2 (12.5)[b]
5 Minute Apgar score <7	-	19 (54.3)	14 (73.7)[b]	5 (31.3)[b]
Neonate hemoglobin at birth (mg/dL)	-	14.2±5.1	13.3±6.2	15.1±3.3
Anemia[c]	-	14/34 (41.2)	8/18 (44.4)	6/16 (37.5)
Severe anemia[c]	-	6/34 (17.6)	5/18 (27.8)	1/16 (6.3)

Data are expressed by mean±standard deviation or no. (%).
GA, gestational age; UA, umbilical artery; S/D, systolic/diastolic; A/R, absent/reversed; EDF, end-diastolic flow; MCA, middle cerebral artery; PI, pulsatility index; PSV, peak systolic velocity; MoM, multiple of median; DV, ductus venosus.
[a]Fetal death vs. live birth, $P<0.05$ by Mann-Whitney U-test; [b]Neonatal death vs. survivor, $P<0.05$ by Fisher's exact test; [c]Denominators are numbers of patients who were tested for each test.

ing of our study was the association between the number of fluid collection sites and neonatal death rate. Although limited by the relatively small sample size, our study also showed that the incidence of neonatal anemia and severe anemia increased with increasing number of fluid collection sites.

Fetal hydrops is not an uncommon complication of pregnancy and it results from multifactorial causes. Although Rhesus isoimmunzation is the most well-known cause of fetal hydrops, we found only one case of immune hydrops during the 8-year period of review. This may be due to routine screening of maternal antibody during early pregnancy and prophylactic Rh immune globulin injection in women with Rh negative blood type [14]. Instead, cardiac abnormality and syndrome were the most common causes of fetal hydrops in our study. However, distribution of causes of fetal hydrops are different among studies because of regional and ethnic differences and because most studies are retrospective and have small number of cases. The cause of fetal hydrops is known to be signifi-

Table 4. Doppler findings and perinatal outcome according to the numbers of fluid collection sites

	2 Sites (n=17)	3 Sites (n=19)	All 4 sites (n=3)	*P*-value[a]
Doppler				
UA increased S/D ratio	2/13 (15.4)	5/16 (31.3)	0/3 (0)	0.901
UA A/R EDF	0/13 (0)	3/16 (18.8)	0/3 (0)	0.378
MCA PI <10 percentile	5/9 (55.6)	7/14 (50.0)	0/3 (0)	0.178
MCA PSV >1.5 MoM	2/6 (33.3)	3/13 (23.1)	1/2 (50.0)	0.909
DV A/R a-wave	1/2 (50.0)	6/11 (54.5)	1/3 (33.3)	0.663
Neonatal anemia	5/16 (31.3)	6/15 (40.0)	3/3 (100)	0.073
Neonatal severe anemia	2/16 (12.5)	2/15 (13.3)	2/3 (100)	0.113
1 Minute Apgar score <4	5/16 (31.3)	9/16 (56.3)	3/3 (100)	0.024
5 Minute Apgar score <7	7/16 (43.8)	9/16 (56.3)	3/3 (100)	0.108
Fetal death	1/17 (5.9)	3/19 (15.8)	0/3 (0)	0.714
Neonatal death	6/17 (37.5)	10/19 (62.5)	3/3 (100)	0.033
Perinatal death	7/17 (41.2)	13/19 (68.4)	3/3 (100)	0.027

Data are expressed by no. (%) and denominators are numbers of patients who were tested for each test.
UA, umbilical artery; S/D, systolic/diastolic; A/R, absent/reversed; EDF, end-diastolic flow; MCA, middle cerebral artery; PI, pulsatility index; PSV, peak systolic velocity; MoM, multiple of median; DV, ductus venosus.
[a]Statistically significant trend by linear-by-linear association.

Table 5. Fetal death, neonatal mortality and perinatal survivor rate according to the location and number of fluid collection sites

	No.	Fetal death	Neonatal death	Perinatal survivor	*P*-value
2 Sites	17	1 (5.9)	6 (35.3)	10 (58.8)	0.135
Ascites + pleural effusion	1	0 (0)	0 (0)	1 (100)	0.478
Ascites + pericardial effusion	4	0 (0)	1 (25.0)	3 (75.0)	0.329
Ascites + skin edema	5	1 (20.0)	1 (20.0)	3 (60.0)	0.367
Pleural effusion + pericardial effusion	0				
Pleural effusion + skin edema	6	0 (0)	4 (66.7)	2 (33.3)	0.522
Pericardial effusion + skin edema	1	0 (0)	0 (0)	1 (100)	0.478
3 Sites	19	3 (15.8)	10 (52.6)	6 (31.6)	0.363
Ascites + pleural effusion + pericardial effusion	4	0 (0)	2 (50.0)	2 (50.0)	0.761
Ascites + pleural effusion + skin edema	10	2 (20.0)	5 (50.0)	3 (30.0)	0.439
Ascites + pericardial effusion + skin edema	3	1 (33.3)	2 (66.7)	0 (0)	0.198
Pleural effusion + pericardial effusion + skin edema	2	0 (0)	1 (50)	1 (50)	0.879
All 4 sites	3	0 (0)	3 (100)	0 (0)	0.181
Ascites + pleural effusion + pericardial effusion+ skin edema	3	0 (0)	3 (100)	0 (0)	0.181
Total	39	4	19	16	

Values are presented as no. or no. (%).

cantly associated with prognosis [5,13]. But, we could not find an association between the cause of fetal hydrops and fetal or neonatal death, because their causes were heterogeneous and the number of cases in each cause was too small. We found that the mean gestational age at diagnosis of fetal hydrops was lower in the fetal death cases than the live birth cases. This may represent that the risk of fetal death is higher if fetal hydrops is diagnosed at an earlier gestational age.

With the recent advances in prenatal ultrasound, fetal hydrops is almost always diagnosed by antenatal ultrasound. Therefore, we focused on prediction of perinatal outcome of fetal hydrops by antenatal ultrasound findings. Doppler velocimetry is the one of the most important predictor for fetal or neonatal mortality in various fetal compromise conditions, including fetal growth restriction [15,16] and fetal hydrops [17]. But, none of the Doppler velocimetry indices were associated with fetal or neonatal death rate. The pattern of abnormal Doppler velocimetry indices may depend on different cause of fetal hydrops. For example, abnormal umbilical artery Doppler or MCA pulsatility index reflects fetal hypoxia [15], abnormal MCA peak systolic velocity may reflects fetal anemia [18], and abnormal ductus venosus Doppler occurs as a result of fetal cardiac decompensation [19]. But, a full comprehensive Doppler study was not done in all cases, and we were not able to analyze the fetal vessel Doppler indices according to the heterogeneous cause of fetal hydrops.

Previous studies reported that presence of pleural effusion was a poor prognostic factor of fetal hydrops [13,20]. In our study, pleural effusion was more frequently found in the case of neonatal death compared to the survivors (78.9% vs. 56.3%), but the difference was not statistically significant. In addition, we were not able to find a significant difference in fetal or neonatal death among any combination of fluid collections including pleural effusion.

The most important finding of this study was that the number of fluid collection sites was highly correlated with neonatal outcome including low Apgar score and neonatal death. Interestingly, none of the 3 neonates with presence of all 4 sites of fluid collection survived. A similar result was found in a recent study by Kim et al. [21] who studied 43 women with non-immune fetal hydrops. They developed an 'ultrasonographic severity scoring of non-immune hydrops (USNIH)' defined as a total number of abnormal fluid collections. Perinatal mortality rate, defined as stillbirth or neonatal death ≤28 completed days after birth, was significantly higher in cases with USNIH of ≥3 than in those with USNIH of 2. These results, taken together with our current study, may suggest that the number of fluid collection sites is the most strong antenatal ultrasound risk factor for prediction of poor outcome in fetal hydrops.

There are several limitations of our study. First, the main limitation of this study is small sample size which made our study underpowered, especially the numbers of cases in each cause was not enough to show a significant difference in primary outcomes. Second, as a retrospective chart review, our study has potential biases including selection bias and information bias. And our study included only the cases which were delivered as hydrops, and we were not able to include prenatal spontaneous resolution cases, which may occur in cases with parvovirus infection, aneuploidy, lymphatic dysplasia and unknown [22-26]. Last, perinatal outcome of our study may have been affected by intrauterine therapeutic procedure, but the number of cases who had intrauterine therapeutic procedure was not large enough to be analyzed statistically and therapeutic procedure performed in each case was largely heterogeneous.

In summary, the incidence of fetal hydrops in our retrospective study was 24.4 per 10,000 deliveries and the neonatal mortality rate and perinatal mortality rate was 54.0% and 61.9%, respectively. The most important antenatal ultrasound finding that is predictive of neonatal death was the number of fluid collection sites. These results may provide an useful information on counselling for women with fetal hydrops. However, more comprehensive, well-designed studies with adequate sample sizes are needed to confirm our findings.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

References

1. Bellini C, Hennekam RC. Non-immune hydrops fetalis: a short review of etiology and pathophysiology. Am J Med Genet A 2012;158A:597-605.
2. Randenberg AL. Nonimmune hydrops fetalis part I: etiology and pathophysiology. Neonatal Netw 2010;29:281-95.
3. Favre R, Dreux S, Dommergues M, Dumez Y, Luton D, Oury JF, et al. Nonimmune fetal ascites: a series of 79 cases. Am J Obstet Gynecol 2004;190:407-12.
4. Randenberg AL. Nonimmune hydrops fetalis part II: does etiology influence mortality? Neonatal Netw 2010;29:367-80.
5. Abrams ME, Meredith KS, Kinnard P, Clark RH. Hydrops fetalis: a retrospective review of cases reported to a large national database and identification of risk factors asso-

ciated with death. Pediatrics 2007;120:84-9.
6. Liao C, Wei J, Li Q, Li J, Li L, Li D. Nonimmune hydrops fetalis diagnosed during the second half of pregnancy in Southern China. Fetal Diagn Ther 2007;22:302-5.
7. Heinonen S, Ryynanen M, Kirkinen P. Etiology and outcome of second trimester non-immunologic fetal hydrops. Acta Obstet Gynecol Scand 2000;79:15-8.
8. Hutchison AA, Drew JH, Yu VY, Williams ML, Fortune DW, Beischer NA. Nonimmunologic hydrops fetalis: a review of 61 cases. Obstet Gynecol 1982;59:347-52.
9. Simpson JH, McDevitt H, Young D, Cameron AD. Severity of non-immune hydrops fetalis at birth continues to predict survival despite advances in perinatal care. Fetal Diagn Ther 2006;21:380-2.
10. Moreno CA, Kanazawa T, Barini R, Nomura ML, Andrade KC, Gomes CP, et al. Non-immune hydrops fetalis: a prospective study of 53 cases. Am J Med Genet A 2013;161A:3078-86.
11. Fukushima K, Morokuma S, Fujita Y, Tsukimori K, Satoh S, Ochiai M, et al. Short-term and long-term outcomes of 214 cases of non-immune hydrops fetalis. Early Hum Dev 2011;87:571-5.
12. Sohan K, Carroll SG, De La Fuente S, Soothill P, Kyle P. Analysis of outcome in hydrops fetalis in relation to gestational age at diagnosis, cause and treatment. Acta Obstet Gynecol Scand 2001;80:726-30.
13. Nakayama H, Kukita J, Hikino S, Nakano H, Hara T. Long-term outcome of 51 liveborn neonates with nonimmune hydrops fetalis. Acta Paediatr 1999;88:24-8.
14. Bellini C, Hennekam RC, Fulcheri E, Rutigliani M, Morcaldi G, Boccardo F, et al. Etiology of nonimmune hydrops fetalis: a systematic review. Am J Med Genet A 2009;149A:844-51.
15. Baschat AA. Arterial and venous Doppler in the diagnosis and management of early onset fetal growth restriction. Early Hum Dev 2005;81:877-87.
16. Bilardo CM, Wolf H, Stigter RH, Ville Y, Baez E, Visser GH, et al. Relationship between monitoring parameters and perinatal outcome in severe, early intrauterine growth restriction. Ultrasound Obstet Gynecol 2004;23:119-25.
17. Hofstaetter C, Hansmann M, Eik-Nes SH, Huhta JC, Luther SL. A cardiovascular profile score in the surveillance of fetal hydrops. J Matern Fetal Neonatal Med 2006;19:407-13.
18. Mari G, Deter RL, Carpenter RL, Rahman F, Zimmerman R, Moise KJ Jr, et al. Noninvasive diagnosis by Doppler ultrasonography of fetal anemia due to maternal red-cell alloimmunization. Collaborative Group for Doppler Assessment of the Blood Velocity in Anemic Fetuses. N Engl J Med 2000;342:9-14.
19. Berg C, Kremer C, Geipel A, Kohl T, Germer U, Gembruch U. Ductus venosus blood flow alterations in fetuses with obstructive lesions of the right heart. Ultrasound Obstet Gynecol 2006;28:137-42.
20. Smoleniec J, James D. Predictive value of pleural effusions in fetal hydrops. Fetal Diagn Ther 1995;10:95-100.
21. Kim SA, Lee SM, Hong JS, Lee J, Park CW, Kim BJ, et al. Ultrasonographic severity scoring of non-immune hydrops: a predictor of perinatal mortality. J Perinat Med 2014 May 15 [Epub]. DOI: 10.1515/jpm-2013-0208.
22. Suwanrath-Kengpol C, Kor-anantakul O, Suntharasaj T, Leetanaporn R. Etiology and outcome of non-immune hydrops fetalis in southern Thailand. Gynecol Obstet Invest 2005;59:134-7.
23. Mostello DJ, Bofinger MK, Siddiqi TA. Spontaneous resolution of fetal cystic hygroma and hydrops in Turner syndrome. Obstet Gynecol 1989;73:862-5.
24. Swain S, Cameron AD, McNay MB, Howatson AG. Prenatal diagnosis and management of nonimmune hydrops fetalis. Aust N Z J Obstet Gynaecol 1999;39:285-90.
25. Petrikovsky BM, Baker D, Schneider E. Fetal hydrops secondary to human parvovirus infection in early pregnancy. Prenat Diagn 1996;16:342-4.
26. Henrich W, Heeger J, Schmider A, Dudenhausen JW. Complete spontaneous resolution of severe nonimmunological hydrops fetalis with unknown etiology in the second trimester: a case report. J Perinat Med 2002;30:522-7.