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The Many Faces of Hydrops

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Abstract

Purpose—Fetal hydrops arises from multiple disease processes and can portend a grim prognosis. We reviewed our experience with hydropic fetuses to understand relevant antenatal anatomic and physiologic predictors of survival.

Methods—We reviewed fetal ultrasounds and echocardiograms of hydropic fetuses evaluated from 1996-2013.

Results—Overall neonatal survival in 167 fetuses was 44% (range, 0-75%) and was influenced by the underlying disease process. The anatomic distribution of fluid varied and was not significantly different between survivors and non-survivors. Univariate analysis indicated that resolution of hydrops and delivery at a later gestational age were predictive of survival (OR:5.7 (95% CI:2.5-13.2) and OR:1.3 (95% CI:1.1-1.4), respectively). Fetal intervention also improved survival in some diseases. Echocardiograms were reviewed to group fetuses with similar cardiac physiology and defined categories with high or low/normal cardiothoracic ratio (CTR). Among patients with a high CTR, the cardiovascular profile score was predictive of survival (p=0.009).

Conclusion—Survival in hydrops depends on the underlying disease, available fetal therapies to resolve hydrops, and the gestational age of delivery and not on the specific anatomic manifestations of hydrops. In hydropic fetuses with high CTRs, the cardiovascular profile score may be a useful prognostic indicator.

Keywords

Hydrops fetalis; hydrops; fetal echocardiography; fetal ultrasonography; cardiovascular profile score

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INTRODUCTION

Hydrops fetalis, also known as *hydrops*, manifests as the accumulation of extravascular fluid within two or more body cavities in utero. Hydrops may result from various underlying congenital anomalies that cause either increased central vascular pressure, decreased lymph flow, or decreased plasma oncotic pressure, leading to a net imbalance of fluid movement between the intravascular and interstitial compartments (1). Rh alloimmunization, once the most common cause of hydrops, is now more rare due to routine immunization of Rhesus negative mothers. Non-immune fetal hydrops now accounts for 85%-90% of cases (2-4). Underlying diseases associated with development of hydrops are diverse and range from chest occupying lesions that compress the mediastinum to highly vascularized tumors that increase cardiac demand. Management and outcomes are often dependent on the underlying disease process (5), although in up to 18% of cases the cause remains unknown (6). Historically, hydrops was felt to be a harbinger of fetal demise, but advancements in fetal treatment have improved outcomes for diseases such as primary hydrothorax (7) and chest masses (8-10). Nevertheless, mortality still approaches 40-50% when considering hydropic fetuses overall (3, 11, 12) and predicting survival remains a challenge.

Ultrasonography and echocardiography have been used to predict outcomes and dictate management for fetuses with congenital abnormalities, particularly in the setting of hydrops. Most institutions define hydrops by the accumulation of fluid within two or more body cavities. Polyhydramnios may result from impaired renal function (13) and placentomegaly from a disrupted oncotic gradient (1); however, there is a lack of consistency among institutions regarding their diagnostic utility (14). Echocardiography is particularly critical to evaluate the hemodynamic effects of numerous congenital anomalies. The ultrasound-derived cardiovascular profile score (CVPS) is a clinical tool which accounts for both cardiac function and Doppler velocimetry by calculating the extent of derangement in five parameters: fetal hydrops, heart size, cardiac function, and arterial and venous Doppler flow through the umbilical vessels and ductus venosus. Since hydrops is the anatomic endpoint of significant physiologic derangements, echocardiogram measurements and other biomarkers could be more predictive of survival than ultrasound measurements of fluid.

We reviewed our 17-year experience in evaluating and managing hydropic fetuses in order to identify etiologies, anatomic distributions of fluid, and echocardiographic parameters that may predict survival.

METHODS

Study Population

Following IRB approval (number 10-04093), we queried our Fetal Treatment Center's database to identify patients evaluated from 1996-2013 diagnosed with fetal hydrops. In twin-to-twin transfusion syndrome (TTTS), the hydropic recipient was included. We defined hydrops as fluid within two or more compartments on prenatal ultrasound, including the skin, thorax, pericardium, and abdomen. We considered placentomegaly and

polyhydramnios as potential predictors of survival but did not include them in our definition of hydrops, due to variability in the definition of these parameters in the literature.

Fetal Echocardiography

Subjects underwent a standard of care fetal echocardiogram using Sequoia C256, C512, and S2000 ultrasound systems (Acuson; Siemens, Mountain View, Calif., USA). Images were stored digitally in standard Digital Imaging and Communications in Medicine (DICOM) format. Measurements obtained from the studies included the cardiothoracic ratio (CTR) (the area occupied by the heart in diastole divided by the thoracic area in a standard axial image of the fetal thorax), combined ventricular output indexed to fetal weight (CVO_i; velocity time integral × heart rate × semilunar valve area for left and right ventricular outflows, as appropriate) and the CVPS, as previously described [9]. Images were reviewed by two pediatric cardiologists (S.P. and A.M-G.) blinded to the underlying disease process and outcome.

Fetal Therapy and Clinical Outcomes

To analyze the effects of fetal intervention on survival, hydropic fetuses were divided into five groups: no intervention, medical therapy, percutaneous intervention, fetoscopic intervention, or open fetal surgery. In cases where multiple procedures were performed, the most invasive was used for categorization. Medical therapy included maternal administration of betamethasone for congenital pulmonary airway malformation (CPAM) given prior to 24 weeks gestation and maternal anti-arrhythmic medications administered for fetal cardiac arrhythmias. Interventions were therapeutic measures and not diagnostic; therefore, amniocentesis and chorionic villus sampling were not considered interventions. The primary outcome was infant survival to hospital discharge.

Statistics

Data are presented as median with interquartile range (IQR) or frequency (%). Data were analyzed by the Mann-Whitney rank sum, Fisher’s exact test or chi-square test. Significant predictors were then entered into a multivariable logistic regression model (Stata 12, StataCorp LP, College Station, Texas). A p-value of <0.05 was considered statistically significant.

RESULTS

We evaluated 231 fetuses with hydrops during the study period. Forty-nine elected termination of pregnancy and 15 were lost to follow up, leaving 167 patients for analysis. Maternal demographics, underlying diagnoses/etiologies, and fluid distributions are detailed in Table 1. Overall survival was 73/167 (44%), and varied between 0% and 75% depending on the underlying disease process. Among patients with more common diseases ($n>10$), survival was highest (50-55%) among those with CPAM, primary hydrothorax, and anemia, while it was lowest (10%) among those with sacrococcygeal teratoma (SCT).

We performed a univariate analysis to examine factors related to survival. We determined that resolution of hydrops and delivery at a later gestational age both portend a better

survival regardless of the underlying disease process. The odds ratio for survival after resolution of hydrops was 5.7 (95% CI 2.5-13.2, P<0.001). In addition, patients who delivered at a later gestational age were 1.3 (95% CI: 1.1-1.4) times more likely to survive for each week they remained in utero (p<0.001, Table 1). After stratifying by resolution of hydrops and adjusting for fetal intervention, delivery at a later gestational age remained a significant predictor of survival only for fetuses whose hydrops persisted (OR: 1.6, 95% CI: 1.2-2.0, p<0.001), but not for those whose hydrops resolved (OR: 1.2, 95% CI: 0.9-1.6, p=0.161).

We next asked whether the anatomic distribution of fluid indicates a more or less severe disease processes. We determined that the anatomic distribution of fluid varied by etiology and did not significantly differ between survivors and non-survivors (Tables 1 and 2). The combination of ascites, pleural effusion and skin edema was the most frequent constellation of fluid accumulation (28% of cases). Interestingly, the absolute number of involved compartments did not correlate with survival: 46% of patients survived when two compartments were involved compared to 42% when three or more compartments were involved (p=0.623), suggesting that increasing fluid does not necessarily indicate a more severe disease state.

We detected improved survival in patients who were able to undergo fetal treatment (for diseases in which a treatment exists, Table 3). For example, fetuses who were treated medically (OR: 8.8, 95% CI: 2.7-28.8), percutaneously (OR: 4.5, 95% CI: 2.0-10.2) or fetoscopically (OR: 5.1, 95% CI: 1.6-16.6) were more likely to survive than those who were untreated. Because prenatal therapies evolve over time, we also asked whether there are differences in survival in patients who presented earlier or later during this study period. We found that approximately half (n=85) of our cases presented up to 2006 and half (n=82) presented after 2006. The frequency of survival was not significantly different between the early or late groups (38% and 50%, respectively; p=0.11 by chi square test).

Although hydrops is an anatomic definition, we were interested to understand whether echocardiograms could be used as a better marker of physiologic or functional derangements in these patients. Seventy-eight (47%) patients had echocardiograms available for analysis of CTR, CVO_i, and CVPS. We determined that CTR measurements identified two distinct groups of patients: those with cardiomegaly (SCT, anemia, cardiac disease, and TTTS) and those without (primary hydrothorax, congenital diaphragmatic hernias (CDH), congenital high airway obstruction syndrome (CHAOS), and CPAM) (Figure 1A). Thus, although different disease processes all result in fluid accumulation in various cavities, the cardiac manifestations can be strikingly different. The CVO_i did not vary significantly among diseases (p=0.094, data not shown) and fetuses within the low CTR group were more likely to have a prenatal therapy.

We have previously shown that CVPS correlates with favourable outcomes among fetuses with SCT or twin-reversed arterial perfusion sequence (TRAP) (15). We therefore examined CVPS in patients with high or low CTRs. Interestingly, among those with a larger CTR, survival was better when the CVPS was higher (p=0.009, Figure 1B), whereas CVPS was not predictive of survival in fetuses with diseases that do not increase the CTR.

DISCUSSION

We have performed detailed ultrasonographic and echocardiographic evaluations of a large cohort of hydropic fetuses over a 17-year period to understand both anatomic and physiologic factors related to prognosis. We report that resolution of hydrops and delivery at a later gestational age portend a better prognosis while the precise anatomic manifestations do not impact outcome. Moreover, hydropic fetuses can be considered as having low or high CTRs according to the disease process and among fetuses with high CTRs, a high CVPS is associated with increased survival.

The physiologic process leading to hydrops are likely different depending on the underlying disease. For example, in diseases such as anemia and SCT, hydrops develops in the face of high output cardiac failure (16, 17), likely a combination of increased myocardial oxygen demands, decreased ability of the heart to meet these end-organ demands, and subsequent elevation in venous pressure and alterations in myocardial compliance as a late finding. Chest occupying lesions may result in impaired cardiac output secondary to reduced preload and increased afterload (18) without alteration in myocardial compliance or function *per se*. Cass and colleagues demonstrated that among hydropic fetuses with lung masses, abnormal fetal cardiac function parameters were strong predictors of demise, while hydropic fetuses without cardiac parameter abnormality almost universally survived (19). Among fetuses with SCT or TRAP, cardiac abnormalities including chamber enlargement and tricuspid regurgitation have been shown to predict poor outcome even prior to development of hydrops (15). Hofstaetter et al. analyzed the CVPS in patients with hydrops (in a series containing a larger proportion (21%) of patients with anemia) and determined that it had prognostic significance (20). Our paper builds on these findings and makes the further observation that CVPS is most useful among fetuses with cardiomegaly.

The actual correlation of the underlying pathophysiology to the resultant hydrops (types of hydropic compartments) is interesting to consider. In fetuses with etiologies resulting in a larger CTR, higher cardiac output may initially be tolerated, but with time and increasing imbalance in myocardial oxygen supply-demand, anasarca initially manifests by small pleural effusions and ascites. Later, integumentary edema and finally overt heart (myocardial) failure might be expected; at this point, a decline in CVPS might then herald imminent demise. On the other hand, chest masses with associated impairment in venous return might initially be accompanied by normal cardiac function and oxygen delivery to tissues, albeit with lower net cardiac output, but an increase in venous pressure and resultant pleural and ascites fluid out of proportion to cardiac findings (and therefore a better CVPS). Unfortunately, our sample size was not large enough to test this in terms of actual cardiac output measurements and although a trend toward higher CVO_i in the larger CTR group was evident, this was not statistically significant.

Prior studies have suggested that fluid accumulation is predictive of survival, with increased survival in fetuses who have fluid within 2 compartments (21, 22) and decreased in those with fluid within 3 or more compartments (11). In our large cohort, we did not find the number of compartments involved to be a predictor of survival. However, the nature of compartments affected is likely related to the underlying disease as well, and given the

above pathophysiologic rationale, one might expect that three-compartment hydrops is simply a late manifestation of all of the disease processes, whether primary myocardial failure or failure secondary to compromised output. While placentomegaly can be associated with high cardiac output disease processes such as SCT (16), we did not find it to be a particular useful predictor of survival. Perhaps the concurrent presence of polyhydramnios in many fetuses compresses the placenta, obscuring an accurate measurement. Prospective studies with longitudinal assessment of other echocardiographic measurements are necessary to develop these findings into a more sophisticated scoring scheme that may predict prognosis in all patients. In addition, relevant biomarkers of fetal cardiac distress may be even more useful in the earlier stages, prior to the onset of hydrops.

Our series reinforces the accepted practice that fetal intervention in well-selected patients improves survival. Those who received medical therapy, percutaneous or fetoscopic intervention were more likely to survive than those who received no treatment. We also found that there is still a high rate of mortality in hydropic fetuses undergoing open fetal surgery. We speculate that this is secondary to a significant inflammatory response from the surgery coupled with the underlying disease state, which often leads to preterm delivery. Developing a better understanding of the underlying physiology that leads to hydrops may lead to changes in perioperative medical management to ameliorate this problem.

Patients with hydrops who are able to have fetal intervention for their underlying condition now benefit from improved survival, especially when hydrops can resolve and there is no preterm delivery. While particular physiologic parameters such as the middle cerebral artery peak systolic velocity did not predict survival, we did find the CVPS to be a useful adjunct to predict survival when the underlying cause results in a high CTR. Furthermore, the fact that patients with such variable disease processes and cardiac manifestations can converge on the simple anatomic finding of fluid in two compartments suggests a basic fetal distress mechanism that is yet to be discovered.

Appendix Discussion

The Many Faces of Hydrops

Presented by S.C. Derderian, San Francisco, CA

OLUYINKA OLUTOYE (Houston, TX): That’s a fantastic study.

Congratulations. I think you bring up an important point which is what we agree very much with, that the whole concept of hydrops and looking at fluid was just a surrogate for cardiac function and really focusing on the cardiovascular function is really what is key. Reading your abstract, though, I was a little surprised by your findings that you really didn’t see much of a difference in survival in those with higher cardiac output versus those that did not. It looks like your presentation is a little different. Can you elaborate a little further on that?

S. CHRISTOPHER DERDERIAN: Sure. We found that among those with larger cardiothoracic ratios, we originally had it grouped into a group that was a high cardiac output group which makes sense in that hydrops that develops from cardiac failure

echocardiography would be predictive of it. The reason I switched it from the high cardiac output to the size of the heart is that in twin-to-twin transfusion syndrome the cardiac output can be a little bit tricky in that some people argue that they are in a high cardiac output state and some argue that they are not, so we just kept it simple with heart size. For all other diseases processes, those with high cardiac output failure also fell into that category.

THOMAS TRACY (Providence, RI): Just really quickly, a couple of years ago Francois Luks described the inconsistent progression of stage with twin-to-twin transfusion that what you see is what you get. It may progress, it may not. I wonder if your analysis of fluid in the other conditions that you pointed out also had that erratic nonprogressive distribution. In other words, it can come and it can go. If you have a comment on that.

S. CHRISTOPHER DERDERIAN: Sure. We did see some rare cases of spontaneous resolution of hydrops, and we defined resolution of hydrops with going from two compartments involved to one or less. That was rare, particularly with twin-to-twin transfusion syndrome. More likely to resolve were patients that had underlying disease processes like CPAMs where we have medical therapies available to treat them or anemia where we had in utero transfusions as a potential therapy.

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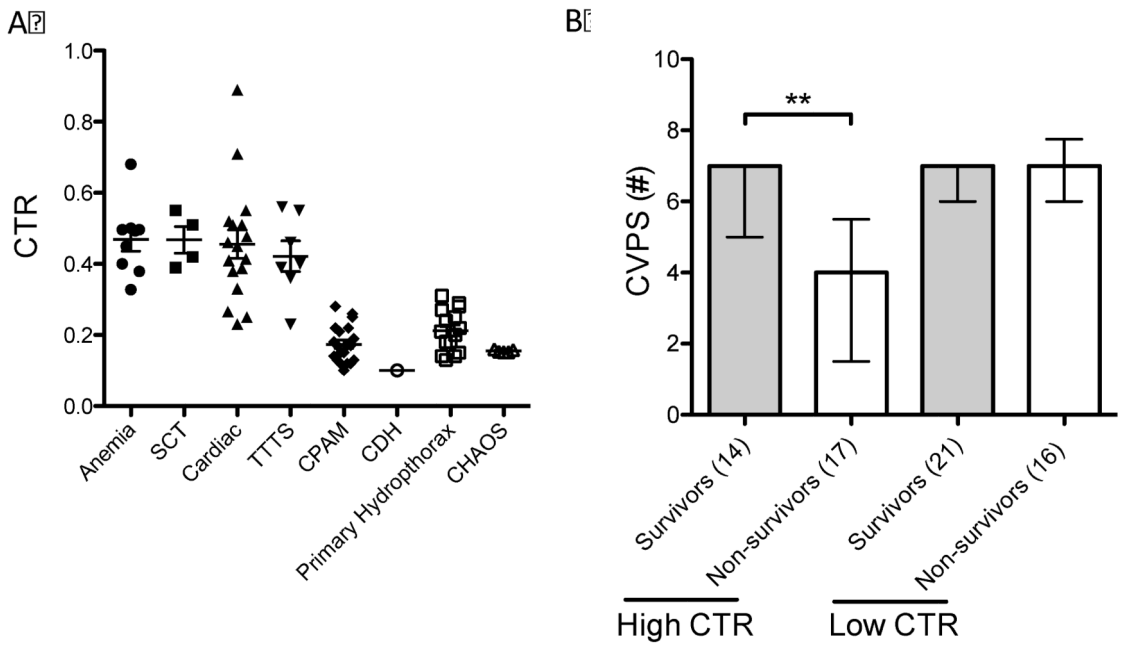

Figure 1. Echocardiography measurements among fetuses with hydrops

(A) CTR, cardiothoracic ratio, among fetuses with various underlying disease processes. SCT, sacrococcygeal teratoma; TTTS, twin-to-twin transfusion syndrome; CPAM, congenital pulmonary airway malformation; CDH, congenital diaphragmatic hernia; CHAOS, congenital high airway obstruction syndrome. **(B)** CVPS, cardiovascular profile score. Data represent median and error bars represent interquartile range. Patients with an elevated cardiothoracic ratio included SCT, anemia, cardiac anomalies, and TTTS and those with a low cardiothoracic ratio included CDH, CPAM, CHAOS, and primary hydrothorax. **p=0.009 by Mann-Whitney U test.

Table 1

Overview of Hydropic Fetuses

	Overall (n=167)	Neonatal Death + IUFD (n=94)	Survival at Discharge (n=73)	p-value
GA at Initial Hydrops	25.3 (22.0-28.6)	25.7 (21.4-28.6)	24.9 (22.9-28.6)	0.795
<24 wks	64 (38%)	36 (56%)	28 (44%)	0.994
>= 24 wks	103 (62%)	58 (56%)	45 (44%)	
GA at Delivery[a]	32.4 (29.7-36.1)	30.7 (27.4-34.0)	34.0 (31.7-37.9)	**<0.001**
Resolution	41 (32%)	10 (24%)	31 (76%)	**<0.001**
Underlying Etiology				0.166
Anemia	12 (7%)	6 (50%)	6 (50%)	
Cardiac	19 (11%)	11 (58%)	8 (42%)	
CDH	8 (5%)	5 (63%)	3 (38%)	
CHAOS	4 (2%)	1 (25%)	3 (75%)	
Chromosomal	5 (3%)	3 (60%)	2 (40%)	
CPAM	42 (25%)	19 (45%)	23 (55%)	
GU	3 (2%)	1 (33%)	2 (67%)	
Lymphatic	4 (2%)	4 (100%)	0 (0%)	
Unknown/Multiple	18 (11%)	13 (72%)	5 (28%)	
Primary Hydrothorax	20 (12%)	9 (45%)	11 (55%)	
TTTS	22 (13%)	13 (59%)	9 (41%)	
SCT	10 (6%)	9 (90%)	1 (10%)	
Hydrops Description				
Ascites	144 (87%)	78 (54%)	66 (46%)	0.217
Pleural Effusion	92 (56%)	52 (57%)	40 (44%)	0.824
Pericardial Effusion	57 (35%)	32 (56%)	25 (44%)	0.943
Skin edema	128 (77%)	76 (59%)	52 (41%)	0.110
Polyhydramnios	98 (59%)	54 (55%)	44 (45%)	0.774
Placentomegaly	86 (52%)	48 (56%)	38 (44%)	0.955
# of Compartments				
Two	83 (51%)	47 (58%)	34 (42%)	0.623
Three	71 (43%)	41 (58%)	30 (42%)	0.710
Four	10 (6%)	6 (60%)	4 (40%)	0.797
MCA MoM[b]	1.3 (1.0-1.6)	1.4 (1.0-1.5)	1.3 (1.0-1.6)	0.583

Neonatal death indicates death prior to discharge. IUFD, in utero fetal demise; Cardiac, structural/arrhythmias; CDH, congenital diaphragmatic hernia; CHAOS, congenital high airway obstruction syndrome; CPAM, congenital pulmonary airway malformation; GU, genitourinary; TTTS, twin-to-twin transfusion syndrome; SCT, sacrococcygeal teratoma; MCA, middle cerebral artery; MoM, multiples of the median.

[a] 36 IUFDs excluded.

[b] 32 MCA Dopplers reviewed (non-survivors n=17; survivors n=15) P-values calculated by Mann-Whitney U test or chi-square test.

Table 2

Etiology and description of hydrops

	# of Cases	# of Compartments	Ascites	Pleural Effusion	Pericardial Effusion	Skin Edema	Poly	Placento-megaly	Poly + Placento-megaly	Poly or Placento-megaly	Most Common Compartment Combination
SCT	10 (6%)	4.0 ± 0.7	6 (67%)	5 (56%)	6 (67%)	7 (78%)	6 (60%)	7 (78%)	4 (44%)	8 (89%)	(Card+Skin) &(Abd+PE+Skin)
Anemia	12 (7%)	3.7 ± 1.0	12 (100%)	4 (33%)	8 (67%)	8 (67%)	2 (17%)	10 (83%)	2 (17%)	10 (83%)	(Abd+Card) & (Abd+Card+Skin)
Primary Hydrothorax	20 (12%)	3.9 ± 1.0	15 (75%)	20 (100%)	3 (15%)	15 (75%)	15 (75%)	9 (45%)	7 (35%)	17 (85%)	(Abd+PE+Skin)
CPAM	42 (25%)	3.5 ± 0.8	40 (95%)	13 (32%)	8 (20%)	34 (81%)	24 (59%)	28 (67%)	16 (39%)	35 (85%)	(Abd+Skin)
CHAOS	4 (2%)	3.5 ± 0.6	4 (100%)	1 (25%)	4 (100%)	3 (75%)	2 (50%)	4 (100%)	2 (50%)	4 (100%)	(Abd+Skin)
CDH	8 (5%)	4.0 ± 1.1	5 (63%)	7 (88%)	3 (38%)	6 (75%)	6 (75%)	5 (63%)	3 (38%)	8 (100%)	(Abd+PE+Skin)
TTTS	22 (13%)	3.7 ± 0.8	21 (96%)	7 (32%)	12 (55%)	21 (95%)	17 (77%)	3 (14%)	2 (9%)	18 (82%)	(Abd+Card+Skin)
Cardiac	19 (11%)	3.4 ± 1.0	18 (95%)	10 (53%)	10 (53%)	11 (58%)	8 (42%)	8 (42%)	4 (21%)	12 (63%)	(Abd+Card) & (Abd+PE+Skin)
Other	30 (18%)	3.6 ± 1.0	23 (77%)	25 (83%)	7 (23%)	23 (77%)	18 (60%)	12 (40%)	9 (30%)	21 (70%)	(Abd+PE+Skin)
Lymph	4 (2%)	3.5 ± 0.6	2 (50%)	4 (100%)	4 (100%)	4 (100%)	3 (75%)	1 (25%)	1 (25%)	3 (75%)	(PE+Skin) &(Abd+PE+Skin)
Chrom	5 (3%)	4.0 ± 1.0	4 (80%)	4 (80%)	1 (20%)	5 (100%)	3 (60%)	3 (60%)	2 (40%)	4 (80%)	(Abd+PE+Skin)

	# of Cases	# of Compartments	Ascites	Pleural Effusion	Pericardial Effusion	Skin Edema	Poly	Placento-megaly	Poly + Placento-megaly	Poly or Placento-megaly	Most Common Compartment Combination
GU	3 (2%)	2.7 ± 1.2	3 (100%)	1 (33%)	1 (33%)	2 (67%)	3 (100%)	1 (33%)	0 (0%)	1 (33%)	N/A
Other/ Mult	18 (11%)	3.7 ± 1.0	14 (78%)	16 (89%)	5 (28%)	12 (67%)	12 (67%)	7 (39%)	6 (33%)	13 (72%)	(Abd+PE+Skin)

Data expressed as n (%) or mean ± S.D. SCT, sacrococcygeal teratoma; CPAM, congenital pulmonary airway malformation; CHAOS, congenital high airway obstruction syndrome; CDH, congenital diaphragmatic hernia; TTTS, twin-to-twin transfusion syndrome; lymph, lymphatic malformations; chrom, chromosomal abnormality; GU, genitourinary anomaly; mult, multiple congenital abnormalities; poly, polyhydramnios; card, pericardial effusion; skin, edema; abd, ascites; PE, pleural effusion; N/A, not applicable.

Table 3
Fetal therapy among fetuses with hydrops

Fetal Therapy	Neonatal Death + IUFD (n=94)	Survival at Discharge (n=73)
None	51 (77%)	15 (23%)
Anemia=3 (5%), CDH=6 (9%), CHAOS=3 (5%), CPAM=5 (8%), Cardiac=12 (18%), Chrom=4 (6%), GU=2 (3%), Lymph=4 (6%), Unknown/multiple=15 (23%), Primary hydrothorax=3 (5%), SCT=4 (6%)		
Medical	5 (28%)	13 (72%)
CPAM=10 (56%), Cardiac=6 (33%), Unknown/multiple=2 (11%)		
Percutaneous Procedure	21 (43%)	28 (57%)
Anemia=9 (18%), CDH=1 (2%), CPAM=13 (27%), Chrom=1 (2%), GU=1 (2%), Unknown/multiple =1 (2%), Primary hydrothorax=17 (35%), TTTS=4 (8%), SCT=2 (4%)		
Fetoscopic Surgery	6 (40%)	9 (60%)
CDH=1 (7%), CHAOS=1 (7%), TTTS=13 (87%)		
Open Surgery	11 (58%)	8 (42%)
CPAM=14 (74%), Cardiac=1 (5%), SCT=4 (21%)		

CDH, congenital diaphragmatic hernia; CHAOS, congenital high airway outflow obstruction; CPAM, congenital pulmonary airway malformation; Chrom, chromosomal abnormality; GU, genitourinary; Lymph, lymphatic malformation; TTTS, twin-to-twin transfusion syndrome; SCT, sacrococcygeal teratoma.