Journal of Pediatric Surgery 50 (2015) 50–54

Contents lists available at ScienceDirect

Journal of Pediatric Surgery

journal homepage: www.elsevier.com/locate/jpedsurg

The many faces of hydrops

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ARTICLE INFO

Article history:
Received 29 September 2014
Accepted 6 October 2014

Key words:
Hydrops fetalis
Hydrops
Fetal echocardiography
Fetal ultrasonography
Cardiovascular profile score

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 to 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 nonsurvivors. 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.

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 because of 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.

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http://dx.doi.org/10.1016/j.jpedsurg.2014.10.027
0022-3468/

1. Methods

1.1. Study population

Following IRB approval (number 10-04093), we queried our Fetal Treatment Center's database to identify patients evaluated from 1996 to 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, because of variability in the definition of these parameters in the literature.

1.2. 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.

1.3. 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 antiarrhythmic 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.

1.4. 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.

2. 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 nonsurvivors (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

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
No. 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. p-Values calculated by Mann–Whitney U test or chi-square test.

[a] 36 IUFDs excluded.

[b] 32 MCA Dopplers reviewed (nonsurvivors $n = 17$; survivors $n = 15$).