Retrospective Analysis of 17 Liveborn Neonates with Hydrops Fetalis

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Background: Hydrops fetalis (HF) is a condition with a high mortality rate.The cause may be due to a variety of underlying diseases. In the majority of cases, death occurs antepartum and intrapartum. For those that are born alive, it is difficult to survive. The purpose of this study was to analyze the clinical manifestations, etiologies and outcomes of liveborn babies with hydrops fetalis.

Methods: From October 1995 through May 2001, 17 liveborn neonates that presented with HF were admitted to our neonate intensive care unit (NICU). We were retrospectively reviewed their records. Clinical data including gestational age (GA) at diagnosis and birth, birth weight, Apgar score, maternal and fetal presentations, laboratory data, etiology and outcome were retrospectively collected and analyzed.

Results: The mean GA at diagnosis was 30.5 weeks and the mean GA at birth was 33.8 weeks. The male to female ratio was 8:9. Most cases presented with ascites (12/17) and cardiomegaly (8/17). The most common problem faced by the liveborn HF neonates was cardiovascular anomalies (7/17). Seven of these liveborn HF neonates survived. The overall mortality rate of HF in this review was 59%. In comparison with survival cases, those that died were diagnosed earlier, had lower Apgar scores, had more severe acidosis, and had pericardial effusion.

Conclusion: Recent advances in prenatal ultrasonographic examinations have made early detection of fetal hydrops possible. The mortality rate of these liveborn hydropic neonates without receiving prenatal therapy was high. More effort in prenatal intervention is needed in order to decrease the mortality rate and improve the outcome of neonates with HF.

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Key words: **hydrops fetalis, liveborn.**

Hydrops fetalis (HF) is a condition with high morbidity rates caused by a variety of fetal, placental, and maternal diseases.[1,2] Although it has been described for many years, recent advances in prenatal ultrasound have made it possible to identify fetal hydrops earlier in gestation.[3,4] In spite of in utero medical and surgical therapy in most cases, fetuses with HF still die antepartum or intrapartum with a mortality rate of 20-90%.[5-7] Those neonates who survive beyond perinatal period also exhibit varying degrees of morbidity.[8,9] In the present study, we reviewed liveborn neonates with HF from

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October 1995 through May 2001 admitted to our neonatal intensive care unit (NICU) and analyzed the etiologies and outcomes of these patients.

METHODS

From October 1995 through May 2001, 17 liveborn newborns diagnosed with HF prenatally or postnatally were admitted to our NICU. Hydrops fetalis was diagnosed according to the criteria suggested by Mahoney et al.[10] by observing the presence of generalized skin thickening of greater than 5 mm and at least two of the following conditions: ascites, pleural effusion, pericardial effusion or placental enlargement. All medical records were reviewed and clinical data including gestational age (GA) at diagnosis, GA at birth, birth weight, Apgar score, maternal and fetal presentations, laboratory data, etiology and outcome were retrospectively collected and analyzed.

RESULTS

Clinical manifestations

The clinical data of the 17 newborns are shown in Table 1. The maternal age ranged from 22 to 36 years (mean, 28.3 ¡ 3.6 years). The GA at diagnosis was between 19 to 36 weeks (mean, 30.5 ¡ 4.9 weeks) and the GA at birth was between 28 to 38 weeks (mean, 33.8 ¡ 2.4 weeks). The mean Apgar score was 3.7 (0 to 9) at 1 minute and 5.6 (0 to 10) at 5 minutes. The male to female ratio was 8:9. Birth weight ranged from 1120 to 3900 g (mean, 2802 ¡ 748 g) (Table 2). There were eight neonates born that were large for GA. In the majority of cases, the maternal pregnancy were complicated with polyhydramnios (4/17), oligohydramnios (1/17), pre-term rupture of membrane (2/17), amnionitis (2/17), or placenta previa (1/17). Fetal presentations included ascites (12/17), cardiomegaly (8/17), pericardial effusion (3/17), and pleural effusion (7/17). Laboratory data are summarized in Table 2. White blood cell counts and C-reactive protein (CRP) levels were within normal limits. Marked anemia was noted in four cases and thrombocytopenia in five cases. There was only one case of hyponatremia. All infants had hypoalbuminemia except for those who had not been checked. Acidosis with a pH value less than 7.1 was noted in nine of 13 cases.

Etiology and outcome

From the reviewed data, the etiologies of HF

Table 1. Clinical Presentations of 17 Liveborn Babies with Hydrops Fetalis

Case	Gender	GA at birth	GA at diagnosis	Ma Age	Apgar score (1 min/5 min)	Maternal presentation	Fetal Presentation	Cause	Outcome
1	M	38	19	36	8/9		Cm	Arrhythmia	Died
2	M	34	34	25	5/5		As+Cm	PS	Survived
3	M	28	28	31	1/1	Poly	Abd mass	Neoplasm	Died
4	F	35	34	27	3/5		As+Pc+Pl	TGA	Died
5	F	33	32	31	4/5		As+Cm+Pc	TGA	Died
6	F	36	25	25	9/10	Poly	As+Cm	Congenital CMV infection	Survived
7	F	35	24	22	3/7	Poly	As+H	Congenital anomaly	Died
8	F	32	28	28	2/5		As+Cm+Pl	Congenital Infection	Survived
9	M	36	39	28	0/0	Amnionitis	As+Cm	Hypertrophic cardiomyopathy	Died
10	M	38	37	28	8/9		As	Idiopathic	Survived
11	F	29	29	31	4/5	Oligo	Cm	Hemoglobin Bart's disease	Died
12	F	34	30	24	3/6		As+Pc+Pl	PDA	Died
13	F	33	32	30	4/6	PROM	Pl	Idiopathic	Survived
14	F	36	35	24	1/1		Pl	Trisomy 18	Died
15	M	32	31	33	3/6	Poly	As+Pl	Hemoglobin Bart's disease	Survived
16	M	32	32	30	4/8		As	Twin to twin transfusion	Survived
17	M	34	30	29	3/7		As+Cm+Pl	Hypoplastic left heart	Died

Abbreviations: Abd: abdominal; As: ascites; Cm: cardiomegaly; CMV: cytomegalovirus; F: female; GA: gestational age (weeks); H: hydrocephalus; M: male; Ma: maternal; Oligo: oligohydramnio; Pc: pericardial effusion; PDA: patent ductus arteriosus; Pl: pleural effusion; Poly: polyhydramnio; PROM: preterm rupture of membrane; PS: pulmonary valve stenosis; TGA: transposition of great arteries.

Table 2. Clinical Data of 17 Liveborn Babies with Hydrops Fetalis

No	BBW	WBC	Hb/Hct	PLT¡ 10^3	Na	CRP	Alb	pH
1	2348	23700	8.8/34	20	138	2.5	ND	6.905
2	2185	11400	14/41.7	ND	140	2.6	2.8	7.356
3	2990	ND	ND	ND	ND	ND	ND	ND
4	3040	20600	14.2/43	405	135	10.7	ND	6.58
5	2108	7390	17.4/32	205	137	ND	ND	7.488
6	3675	6800	15.3/45	205	137	5	3.3	7.338
7	3604	25200	18.9/54	105	135	3.6	2.15	7.031
8	3110	14900	10.5/30	39	127	3.6	1.2	7.023
9	3830	7670	15.6/52	205	146	13.1	2.83	6.852
10	3900	9100	16.3/49.1	214	142	3.1	2.5	7.376
11	1120	ND	ND	ND	ND	ND	ND	ND
12	3500	14000	13.9/41	205	142	ND	2.1	6.878
13	2367	12300	17.7/52.4	354	142	3.5	1.9	7.039
14	2390	27200	15.9/51.6	151	139	3.5	1.4	6.636
15	2280	4800	6.0/24.8	25.9	138	3.7	1.7	6.929
16	2490	7380	6.4/21.6	13.8	142	3.7	1.2	ND
17	2670	6300	15.6/48.1	89	152	3.5	1.4	ND

Abbreviations: BBW: birth body weight (gm); WBC: white blood cell count (/mm^3); Hb: hemoglobin (gm/dl); Hct: hematocrite (ml/dl); PLT: platelet (/mm^3); Na: sodium (meq/l); CRP: C-reactive protein (mg/l); Alb: albumin (mg/dl); ND: not done.

were categorized into cardiovascular anomalies (7/17), hematological disorder (2/17), congenital infection (2/17), twin-to-twin transfusion (1/17), chromosomal anomalies (1/17), multiple anomalies (1/17), neoplasm (1/17) and idiopathic (2/17) (Table 1). None of these patients received prenatal medical or surgical intervention. Eight neonates died on the day of birth, while two died the day after birth. The overall mortality rate in neonatal period was 10/17 (59%). Seven cases survived initially, three cases survived to the present with normal growth and development and four patients died beyond the perinatal period due to sepsis (cases 2 and 15) and heart failure (cases 8 and 14). When compared with the patients that survived, the patients that died were diagnosed at an earlier GA (29 vs. 31 weeks), had lower Apgar scores on 1 minute / 5 minutes (3/5 vs. 5/7), and showed severe acidosis with their pH value less than 7.1. In contrast, the survivors were diagnosed after 28 weeks of gestation age and had a normal pH values.

DISCUSSION

The classification of HF is traditionally categorized into two groups; immune HF and non-immune HF.[1,10] Immune hydrops is mainly caused by Rh incompatibility. With the declining incidence of Rh isoimmunization due to the introduction of Rh immune globulin in the 1960s, the majority of HF cases are now is due to non-immune causes. In the present review, there was no immune HF case. Instead, we categorized our non-immune cases into several groups based on the organ systems involved. Cardiovascular anomalies, which included structural and functional defects, were the most common cause in our liveborn HF patients (36%). The other causes were hematological disease, chromosomal abnormalities, congenital infection, twinning, neoplasm, and idiopathic. Most of our patients with cardiovascular anomalies were structural anomalies such as transposition of great arteries, pulmonary stenosis, and hypoplastic left heart syndrome. Hydrops fetalis was caused by fetal arrhythmia in only one patient. Fetal arrhythmia such as supraventricular tachyarrhythmia can lead to HF, which may be explained because the fast ventricular rate decreases the cardiac output and then the patient develops congestive heart failure.[10,11]

The mortality rate of patients with cardiovascular anomalies was 86%, which was higher than the mortality rate of the cases as a whole (59%). Our overall mortality rate of liveborn neonates with HF

was lower than those reported by Castillo (82%) and Thompson (67%),[12,13] but was the same as that reported by Nakayama (59%).[9] The reason of this discrepancy might due to different patient populations or the recent advances in neonatal care.

A number of hematologic disorders can lead to non-immune HF. Among these hemoglobinopathies, alpha-thalassemia is the leading cause of HF in Southeast Asia, where it accounts for 57 to 81% of non-immune HF.[14,15] A fetus with alpha-thalassemia lacks normal alpha globin genes and is unable to synthesize alpha chains, leading to anemia and heart failure due to chronic hemolysis. Alpha-thalassemia should be suggested when the baby develops hydrops without any significant structural anomalies. The parents may be screened for their carrier status by evaluation of their mean corpuscular volumes. It is difficult to distinguish the etiologies of HF from alpha-thalassemia to other types of non-immune HF using conventional ultrasound. However, by calculating the diameter and blood flow of the umbilical vein, one can differentiate alpha-thalassemia-induced HF from other causes of non-immune HF.[16]

The pathogenesis of HF is abnormal transport of water between the capillary plasma and extravascular tissue leading to excessive fluid accumulation in the serous cavities presenting as ascites, pericardial effusion and pleural effusion.[17] As we know, the outcome of HF mainly depends on the etiologies. Thus, treatment of HF should be based on the underlying disease. However, certain prognostic factors such as pleural effusion, pericardial effusion, and congenital malformation affect the outcome of HF.[5,8,12] Carlson et al. measured the biventricular outer dimension in diastole (BVOD) using real-time-directed M mode echocardiography and showed that enlarged BVOD was an excellent prognostic factor of fetal death.[18] In our review, we found that the presence of pleural effusion or ascites did not correlate with a poor prognosis. However, three patients with pericardial effusion died. It has been suggested that ascites is an early presentation of HF, which may then progress to pleural effusion and/or pericardial effusion. Our review also demonstrated the presence of ascites in a majority of the cases. This suggested that pericardial effusion represents a more advanced form of HF and may be used as a prognostic factor. Therefore, early delivery of hydropic baby with ascites, before the development of pericardial effusion, should be considered. Three cases with pericardial effusion in our review were caused by cardiovascular anomalies with structural defects. We also recommend that congenital heart disease should be considered if a hydropic fetus has pericardial effusion.

Once the HF is recognized, the first step in management of the disease is to identify the etiology. Maternal blood studies including the blood type, presence of antibodies, and serological studies for viruses should be performed to rule out isoimmunization or congenital infection as the cause of HF. Fetal blood examinations, including metabolic studies and karyotype should be performed in order to rule out metabolic disorders or chromosomal abnormalities. Serial sonographic examinations should be arranged as spontaneous resolution of HF may occur.[19] Prenatal intrauterine fetal therapy might be considered in severe cases of HF. Serial paracentesis and/or thoracocentesis may decompress the thoracic cavity and prevent lung hypoplasia.[20] Successful treatment of HF by intrauterine albumin and blood transfusion has been reported for many years.[21] Maternal antiarrhythmia drug administration or fetal ventricular pacing for HF caused by tachyarrhythmia have also been utilized.[11,22] Recently, surgical intervention for infants with correctable structural anomalies such as congenital diaphragmatic hernia and obstructive hydronephrosis has also been reported.[23,24] In summary, various forms of prenatal intervention may decrease the mortality rate and improve the outcome of HF. The mean gestational age at diagnosis in our study was approximately 30 weeks, with one case as early as 19 weeks, however, due to limitations in prenatal intervention, the mortality rate was still high.

In conclusion, recent advances in prenatal ultrasonographic examinations have made early detection of fetal hydrops easier. However, the importance of early detection lies in evaluation of the etiology of fetal hydrops. To improve outcomes for the survivors, proper management is needed early in the prenatal or postnatal period. In this study, we concluded that early detection of fetal hydrops was possible, but early prenatal intervention seemed to play the major role in improving outcomes and needs further effort. The overall mortality rate of liveborn babies with HF was 59%. Poor prognosis was associated with diagnosis early in gestation, lower Apgar scores, severe acidosis, and the presence of pericar-

dial effusion. Due to the strong positive effects of early intervention, we believe that more research into early intervention strategies for HF is required.

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回溯性分析17例胎兒水腫之活產新生兒

劉倢安　黃新純　周英英

背 景： 造成胎兒水腫的原因很多，隨著時代進步，雖然產前診斷與胎內治療已有相當的進步，但胎兒水腫仍是一個少見而高死亡率的新生兒疾病。絕大多數患嬰在產前即死亡，至於那些得以存活到出生者，也難以繼續存活下去。此一回溯性研究主要是收集活產的胎兒水腫的病例，並分析其臨床表現，致病因及相關預後。

方 法： 我們回溯性收集自1995年10月至2001年5月出生的17例患有胎兒水腫之活產新生兒，根據其診斷週數及出生週數、出生體重、Apgar score、母親及胎兒的表現、實驗室檢查、發生原因及預後加以分析。

結 果： 平均診斷年齡爲懷孕30.5週，平均出生週數爲33.8週，男女比例爲8:9。大多數病嬰出生時有腹水和心臟擴大的現象。造成胎兒水腫的主因是心血管疾病，死亡率爲59%。分析結果發現，預後較差的因子包括：懷孕時期較早發現診斷的、Apgar score偏低、嚴重酸中毒和心包膜積水者。

結 論： 雖然早期診斷胎兒水腫已較爲容易，但產前的胎兒治療經驗仍有限，若能在發現胎兒致病因時隨即進行胎內治療，可望改善活產胎兒水腫病人之預後。

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關鍵字： 胎兒水腫，活產。

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