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Etiology and outcome of fetal hydrops - a 17-years single-centre experience

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Abstract

Objective: Recent advances in neonatal medicine have led to the improvements in diagnosis, prevention and management of fetal hydrops (HF). Although incidence of immune HF has significantly decreased, the incidence of non-immune HF has remained largely unchanged and mortality rate continues to be high, with rates up to 75.5%.

Methods: A retrospective chart review of newborns who were admitted due to HF to the Institute of Child and Youth Healthcare of Vojvodina, Novi Sad, Serbia, from January 1st, 2001 to January 1st, 2018. It involved the analysis of demographic, antenatal, and postnatal parameters as well as examination of etiology and outcome.

Results: There were 18 cases of HF, comprising 12/18 (66.66%) males, 6/18 (33.34%) females. Mean gestational age was 34.96±3.15gw (min-max 29.43-41.00); mean birth weight 2564.44±652.45g (min-max 1510.00-3650.00), Etiology of fetal hydrops was determined in 14/18 (77.78%), newborns; in 6/18 (33.33%) newborns was of immune, and in 8/18 (44.45%) of non-immune origin. Death occurred in 10/18 (55.56%) newborns. Patients who did not survive were more frequently born from multiple pregnancies (p=0.03), had lower values of Apgar score 1st and 5th minutes (p=0.011; p=0.001, respectively), more frequently presented with pericardial effusions (p=0.002) and multiple sites of effusions (p=0.02), cardiac insufficiency (p=0.019), acute kidney injury (p=0.004) and lower values of pH (p=0.035). High-frequency oscillatory ventilation was more frequently used in this group (p=0.018).

Conclusion: Mortality among newborn with HF remains high. Poor prognosis is associated with multiple pregnancies, lower Apgar scores, severe acidosis, as well as the presence of pericardial effusion, multiple sites of effusions, cardiac insufficiency and acute kidney injury, and use of high-frequency oscillatory ventilation as a life-saving mode of ventilation.

Keywords: Fetal hydrops, newborn, etiology, outcome

Introduction

Fetal hydrops (HF) is a clinical condition defined as an excessive fluid accumulation in two or more areas of the fetal body, such as ascites, pleural effusion, pericardial effusion plus skin edema. The incidence of HF is reported to be 0.3 to 2.4 per 1000 live births.[1,2]

According to the etiology, HF is classified as immune or non-immune hydrops. Immune HF develops due to a hemolysis mediated by circulating maternal antibodies to fetal red blood cell antigens. Disorders or mechanisms leading to the non-immune HF include cardiovascular (21.7%), idiopathic (17.8%), genetic (13.4%), hematological (10.4%), infectious (6.7%), and metabolic (1.1%) issues, as well as chest tumors (6.7%), urogenital anomalies (2.3%), monochorionic twin pregnancy and related complications: twin-to-twin transfusion syndrome (TTTS), twin reversed arterial perfusion (TRAP) sequence) (5.6%) and gastrointestinal problems (0.5%).[3,4]

Recent advances in obstetric and neonatal medicine made some improvements in diagnosis, prevention and management of HF. Incidence of immune HF has been significantly decreased by routine screening and prophylaxis of Rhesus isoimmunization. However, the inci-

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dence of non-immune HF remains largely unchanged and mortality rate of non-immune HF, both during fetal or neonatal period, is still high, up to 75.5%, and dependent on gestational age and its etiology.[5,6] In the literature, there are limited data about prognostic factors in newborn infants with HF and these include some perinatal interventions and demographic and clinical features.[7,8,9] In this study, our aim was to analyze etiology and outcome of newborns with HF in a single tertiary neonatal intensive care unit (NICU) over a 17-years period.

Methods

A retrospective chart review was performed on newborns admitted due to HF to the tertiary referral neonatal intensive care unit, Institute of Child and Youth Healthcare of Vojvodina, Novi Sad, Serbia, from January 1st, 2001 to January 1st, 2018. Fetal hydrops was defined as an abnormal fluid collection in two or more areas of the fetal body: ascites, pleural effusion, pericardial effusion or in one area plus skin edema (skin thickness greater than 5mm). Demographic (gender, gestational age, mode of delivery, Apgar score at 1st and 5th minute, birth weight, birth length, head circumference, ponderal index), antenatal (maternal age, parity, presence of polyhydramnios, co-morbidity, gestational age at the time of HF diagnosis, antenatal corticosteroid use, diagnostic/therapeutic procedures: amniocentesis, cordocentesis, chorionic villus sampling, intrauterine fetal transfusion) and postnatal (resuscitation at birth, presence of skin edema, pleural and/or pericardial effusions, ascites, presence of respiratory and/or cardiac insufficiency and acute kidney injury, need for surfactant treatment, use of conventional and high-frequency oscillatory mechanical ventilation, laboratory findings on admission (leukocytes, hemoglobin, hematocrit, thrombocytes, sodium, C-reactive protein, procalcitonin, proteins, albumin, pH)) were analyzed. Etiology and outcome have also been examined.

The study was approved by the Institute`s Ethics Committee No 215/2018. All infants with HF underwent a diagnostic flow chart according to our NICU protocol. Ultrasonography examinations including echocardiography were performed on all infants. Fetal or neonatal karyotyping was offered in all cases. The presence of lymphatic dysplasia was evaluated by microscopic and biochemical investigation (lipid profile) of ascites, pleural, or pericardial fluids. Hematologic disorders were evaluated by complete blood count, peripheral blood or bone marrow smear, blood group and Coombs test. Inherited metabolic diseases were evaluated with blood and urine amino acid analysis, urine organic acid analysis, and, if necessary, specific genetic analysis. All infants were screened for intrauterine infections such as toxoplasmosis, rubella, cytomegalovirus, herpes simplex, parvovirus, and syphilis.

Statistical data were analyzed by using SPSS version 16.0 software (SPSS Inc. Chicago IL, USA). Data were shown as a percentage or mean/median and standard deviation. Continuous variables were compared by two-tailed t test for parametrically distributed data or Mann-Whitney test for non-parametrically distributed data. Categorical variables were analyzed by chi2 test or Fisher exact test. A p-value of <0.05 was accepted as statistically significant.

Results

During the study period, 18 cases of HF were identified; 12/18 (66.66%) males, and 6/18 (33.34%) females. Mean gestational age was 34.96±3.15 weeks` gestation (min-max 29.43-41.00); mean birth weight 2564.44±652.45 g (min-max 1510.00-3650.00), mean birth length 45.61±3.40 cm (min-max 41.00-50.00), mean head circumference 32.36±2.11cm (28.50-37.00), mean ponderal index 2.68±0.56 (min-max 2.08-4.28). Median Apgar score at 1st minute and 5th minute were 4±2.56 (min-max 1-8) and 5±2.27 (min-max 1-9), respectively.

As for mode of delivery, 12/18 (66.66%) newborns were born by Cesarean section, 6/18 (33.34%) were born vaginally. Mean maternal age was 27.64±5.03 years (min-max 19-37); 2/18 (11.12%) newborns were born out of multiple pregnancies. Prenatal diagnosis was available in 9/18 (50%) newborns, averagely at 29.52±5.69 weeks gestation (min-max 26-36); prenatal diagnostic and therapeutic interventions were carried out in 7 newborns, most frequently cordocentesis and intrauterine transfusions.

Etiology of fetal hydrops was determined in 14/18 (77.78%), newborns; in 6/18 (33.33%) newborns of immune, and in 8/18 (44.45%) of non-immune origin. Etiology of fetal hydrops was not determined in 4/18 (22.22%) newborns. Etiology of HF is summarized in Table 1.

Table 1. Etiology of fetal hydrops

	No of cases (%)
Rh-isoimmunisation	6 (33.34%)
Intrauterine infection (Coxsackie. Parvo B19)	2 (11.12%)
TRAP sequence	1 (5.56%)
Chromosomopathy (46.XX+1 metaphase 46XX del(8)p21	1 (5.56%)
MADD/glutaric aciduria type II	1 (5.56%)
Galactosaemia	1 (5.56%)
Fetal atrial flutter	1 (5.56%)
Total anomalous pulmonary veins return	1 (5.56%)
Unknown etiology (Idiopathic)	4 (22.22%)

TRAP - Twin reversed arterial perfusion; MADD - Multiple Acyl CoA Dehydrogenase Deficiency

Death occurred in 10/18 (55.56%) newborns, while 8/18 (44.44%) newborns survived. Demographic parameters of newborns who survived and who died are summarized in Table 2.

Table 2. Demographic parameters on admission

	Survived (n=8)	Died (n=10)	p
Gender (m/f)	5/3	7/3	0.738
GA (gw)	35.29±2.61	34.70±3.54	0.708
AS 1.min	4.50±1.93	1.50±1.29	0.011*
AS 5.min	6.50±1.66	4.00±0.74	0.001**
BW (g)	2453.75±669.14	2653.00±621.66	0.536
BL (cm)	45.50±3.50	45.70±3.30	0.905
HC (cm)	31.56±1.83	33.00±2.11	0.157
Ponderal index	2.53±0.16	2.62±3.55	0.319

GA - gestational age; AS 1.min - Apgar score 1. minute; AS 5. min - Apgar score 5. minute; BW - birth weight; BL - birth length; HC - head circumference

The demographics of the cohort is displayed in Table 2. Compared to patients who survived, patients who died had significantly lower values of the median Apgar score at the 1st and 5th minute. There were no significant differences between groups in gender, gestational age, birth weight, birth length, and head circumference or ponderal index. The perinatal parameters of the cohort are displayed in Table 3. Compared to patients who survived, patient who died were born more frequently from multiple pregnancies and were more frequently aggressively resuscitated at birth. There were no significant differences between groups in maternal age, presence of polyhydramnios, antenatal use of steroids, the incidence and timing of antenatally diagnosed HF.

Table 3. Perinatal parameters

	Survived (n=8)	Died (n=10)	p
Maternal age	28.25±4.17	2.62±3.55	0.293
Parity (singleton/multiple)	2/6	0/10	0.030*
Polyhidramnios (%)	6/8 (75%)	7/10 (70%)	0.055
Maternal co-morbidity (%)	2/8 (25%)	4/10 (40%)	0.450
Antepartal corticosteroids (%)	2/8 (25%)	2/10 (20%)	0.064
Prenatal diagnosis (%)	4/8 (50%)	5/10 (50%)	0.897
Prenatal diagnosis (GA)	30.67±3.45	30.40±2.24	0.635
Prenatal procedures (%)	4/8 (50%)	4/10 (40%)	0.671
Resuscitation at birth (%)	3/8 (37.5%)	9/10 (90%)	0.019*

GA - gestational age

The clinical parameters of the cohort are displayed in Table 4. Compared to patients who survived, patients who died had more frequently pericardial effusions and multiple sites of effusions, as well as cardiac insufficiency and acute kidney injury. High-frequency oscillatory ventilation, as a life-saving mode of mechanical ventilation, was more frequently used in this group. There were no significant differences between groups in the presence of skin edema, pleural effusions, ascites, respiratory insufficiency and need for surfactant therapy. Laboratory data are summarized in Table 5.

Table 4. Clinical parameters on admission

	Survived (n=8)	Died (n=10)	p
Skin edema (%)	6/8 (75%)	10/10 (100%)	0.09
Pleural effusions (%)	4/8 (50%)	9/10 (90%)	0.0597
Pericardial effusions (%)	0/8 (0%)	7/10 (70%)	0.002**
Ascites (%)	8/8 (100%)	9/10 (90%)	0.867
Multiple effusions (1/2/3)	4/4/0	1/3/6	0.020*
Respiratory insufficiency (%)	7/8 (87.5%)	9/10 (90%)	0.967
Cardiac insufficiency (%)	3/8 (37.5%)	9/10 (90%)	0.019*
Acute kidney injury (%)	1/8 (12.5%)	8/10 (80%)	0.004**
Need for surfactant therapy (%)	6/8 (75%)	9/10 (90%)	0.832
Mechanical ventilation (%)	8/8 (100%)	10/10 (100%)	0.024*
HFOV (%)	1/8 (12.5%)	8/10 (80%)	0.018*

Multiple effusions (1/2/3) - Multiple effusions (1 site/2 sites/3 sites); HFOV - high frequency oscillatory ventilation

Table 5. Laboratory data on admission

	Survived (n=8)	Died (n=10)	p
Leukocytes	24.51±18.54	22.81±23.92	0.876
Hemoglobin	122.31±35.31	105.30±53.28	0.456
Hematocrit	0.367±0.11	0.30±0.15	0.339
Thrombocytes	178.87±98.29	181.5±56.72	0.947
Sodium	135.87±10.76	135.60±7.96	0.953
CRP	5.32±8.17	0.7±0.97	0.133
Procalcitonin	2.74±1.88	0.51±0.35	0.287
Proteins	37.15±8.43	31.56±6.31	0.141
Albumin	22.80±6.08	20.64±3.79	0.390
pH	7.19±0.16	7.05±0.08	0.035*

CRP - C-reactive protein

Compared to patients who survived, patients who died had lower values of pH, i.e. more severe decompensated acidosis. There were no significant differences between groups in the values of complete blood count parameters, sodium, C-reactive protein, procalcitonin, proteins and albumin.

Discussion

Nowadays, with the declining incidence of Rh-isoimmunization due to introduction of anti-RhD-immunoglobulin prophylaxis in developed countries, up to 76-87 % of cases are of non-immune origin.[2] However, this was not a case in our study, where 6/18 (33.33%) patients had immune HF, probably due to a small sample size, but perhaps also due to a inadequate prenatal monitoring of pregnancies at risk for developing immune HF. This emphasizes the importance of more precocious management of these pregnancies. Zwiers et al. showed that the incidence of severe immune HF can be significantly influenced by routine early alloantibody screening, use of national guidelines, and pooling of expertise in national reference laboratories and a referral to the center for fetal therapy.[10] Etiology remained unknown in 4/18 (22.22%) newborns with HF, which is slightly below recent data where the etiological diagnosis of HF was achieved in 86.3% cases.[11]

Most studies emphasize the importance of timing of HF development during pregnancy. Mean gestational age in our study was 34.96±3.15 weeks, and is in accordance with the results of previous studies.[12,13] The birth weight of most newborns with HF is higher compared to the mean newborn`s birth weight for gestational age. Higher birth weight and ponderal index are probably due to an excessive fluid accumulation in the body and organomegaly.[14,15] Mean ponderal index in our study was 2.68±0.56, which is above 50. percentile, but not above 90. percentile for the gestational age. Most of newborns in our study were born in perinatal asphyxia. Median Apgar score at 1st minute and 5th minute were 4±2.56, and 5±2.27, respectively. This was previously reported and is probably due to a higher incidence of prematurity and significant hemodynamic disturbance as the most important pathophysiological feature in newborns with HF that lead to maladaptation during transition from intrauterine to extrauterine life conditions.[16]

Overall mortality rate of neonates with HF in our study was lower than those reported by Castillo (82%)[14] and Thompson (67%)[15], but similar as that reported by Nakayama (59%)[16] and Liu.[17] Early prenatal detection and timely treatment may decrease the mortality rate and improve the outcome of HF.[18] The mean gestational age at the time of the diagnosis in our study was approximately 30 weeks, however, due to lack of prenatal interventions, the mortality rate still remained high. Also, presence of decompensated acidosis on admission, with mean blood pH 7.12±0.16 is yet one more sign of the poor health condition of newborns with HF. Significant decompensated acidosis with pH<7.1 was present in 69.23% of cases, and, when accompanied by severe anemia, was one of the signs of poor outcome.

Liu et al. found that the death in newborns with HF occurred primarily in the first week of life (average of 4.55 ± 4.2 days), most often as a result of complications associated with hypervolemia, such as cardiac, renal, and/or respiratory insufficiency.[17] This was also the case in our study, where acute cardiac insufficiency and acute kidney injury were present significantly more frequently in patients with unfavorable outcome (p=0.019 and p=0.004, respectively). Takci et al. reported skin edema in 54.8%, ascites in 48.4%, and pleural effusions in only 19.4% of cases with HF.11 In our study, generalized skin edema was found in all cases, while ascites and pleural effusions were found in 77.78% of cases with HF, respectively. It has been suggested that ascites is an early presentation of HF, which may then progress to pleural and/or pericardial effusion. Our study also demonstrated the presence of ascites in a majority (17/18) of the cases. Nassr et al. found that the presence of ascites is associated with a higher perinatal death among all fetuses with NIHF.[19] In our study, the presence of ascites or pleural effusions was not associated with a poor prognosis. On the other hand, 7/10 (70%) newborns who died had pericardial effusions. This suggests that presence of pericardial effusions could be used as a prognostic factor.[17]

It has previously been reported that an increasing number of sites of fluid collection are associated with lower Apgar scores and an increased neonatal death rate.[20] A similar result was found in a study by Kim et al. who developed an ultrasonographic severity scoring of non-immune hydrops (USNIH). The presence of an abnormal fluid collection in each body compartment, such as subcutaneous edema, pleural effusion, pericardial effusion, or ascites was assigned a score of 1 point per each body compartment, and the absence of abnormal fluid collection was scored as 0 point. The total number of abnormal fluid collections was converted to a numeric score. 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.[21] These results, as well as the results of our study, where cases of multiple effusions were more frequently observed in patients who died (p=0.02), may suggest that the number of fluid collection sites is the important risk factor for

prediction of poor outcome in newborns with HF.

There are several limitations of our study. First, the main limitation of this study is a small sample size which could influence some of the study findings. Second, as a retrospective chart review, our study has potential biases, including selection bias and information bias. Last, perinatal outcome of our study may have been affected by intrauterine therapeutic procedures, but the number of cases who had the intrauterine therapeutic procedures was not large enough to be analyzed statistically.

Conclusion

Poor prognosis was associated with multiple pregnancies, lower Apgar scores, resuscitation at birth, severe acidosis, presence of pericardial effusions, multiple sites of effusions, cardiac insufficiency and acute kidney injury, as well as with the use of high-frequency oscillatory ventilation as a life-saving mode of mechanical ventilation.

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