Etiology And Outcome Of Pregnancies Complicated By Fetal Hydrops

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Abstract

Objective: To identify causes, outcomes and management options of pregnancies complicated by fetal hydrops.

Methods: Medical records of all singleton pregnancies complicated by hydrops fetalis at two McGill University affiliated hospitals over a 10 year period were reviewed. Comprehensive perinatal evaluation was performed on all cases. Gestational age at diagnosis and delivery, results of investigations, ultrasound findings, interventions performed, delivery and neonatal data were recorded.

Results: 44 cases of fetal hydrops were identified during the 10-year period. 4.5 % of these cases could be classified as immune hydrops, the remaining being non-immune in origin. Thoraco-pulmonary abnormalities were the most common causes, accounting for 22.7% of fetal hydrops, followed by cardiovascular and multiple structural abnormalities, each accounting for 9% of cases. Despite thorough investigation, the etiology remained undetermined in 16% of the cases.

The mean gestational age at diagnosis was 28 weeks and at delivery was 30 weeks. The mean interval between diagnosis and delivery was 11 ± 21 days. The cesarean delivery rate exceeded 75 % and only 31 % of infants (excluding terminations of pregnancy) survived to NICU discharge.

Conclusion: Fetal hydrops is a heterogeneous disease with multiple etiologies and an overall poor prognosis and poor survival beyond the neonatal period.

INTRODUCTION:

Hydrops is defined as an abnormal accumulation of fluid in 2 or more body cavities which may include ascites, pleural effusion, pericardial effusion or skin edema (1). The cause of hydrops can be divided into two groups; immune and non immune hydrops. When the hydrops occurs in the absence of antigen-antibody mediated red cell hemolysis it is referred to as non immune hydrops (NIH) (2). The routine use of anti-D immunoglobulin and the active management of pregnancies with Rhesus incompatibility have led to a decline in immune mediated hydrops. There has been however, no reduction in NIH which is currently the most common cause of fetal hydrops, accounting for >90% of hydrops cases in the western world (3, 4).

The objective of this study was to identify the causes and outcomes of pregnancies complicated by fetal hydrops in a tertiary care institution and compare it to the reported literature.

METHODOLOGY:

This was a retrospective descriptive study including all singleton gestations complicated by fetal hydrops between 2001 and 2010 at two McGill University affiliated hospitals; the Jewish General Hospital (JGH) and the Royal Victoria Hospital (RVH). A search of computerized databases identified all the cases of fetal hydrops seen at these institutions. Medical charts were extracted and reviewed for results of all perinatal evaluations performed including; blood group, antibody screen, complete blood count (CBC), serological evaluation for maternal infection - including Parvovirus, hepatitis B virus (HBV), hepatitis C virus (HCV), syphilis, cytomegalovirus (CMV), toxoplasmosis and human immunodeficiency virus (HIV). Ultrasound findings were recorded as well as details of any associated maternal medical conditions and the results of hemoglobin

electrophoresis, Kleihauer–Betke test, fetal echocardiography, fetal karyotype, fetal body fluid evaluation and postmortem autopsy results where available. Note was made of any interventions undertaken.

The following outcome variables were recorded: gestational age at diagnosis, gestational age at delivery, mode of delivery, any maternal complications and neonatal outcomes including final diagnosis and duration of survival. Early neonatal death (END) was defined as death within the first 7 days of life. Late neonatal death (LND) was defined as death between 8 and 28 days of life. Infant death (ID) was defined as death during the first year of life.

The study was approved by the McGill University and the Jewish General Hospital's research ethics committees.

RESULTS:

During the study period 44 cases of fetal hydrops were identified among 76,414 deliveries, yielding an incidence of 1:1737 deliveries. Only 2 cases (4.5%) were of immune origin. There was a slight predominance of male fetuses (57% versus 43%). The mean maternal age was 29.3±5.3 years. The mean gestational age at diagnosis was 28.3±5.1weeks and the mean gestational age at delivery was 30.0±4.6 weeks. The mean interval between diagnosis and delivery was 11±21 days and the median interval was 2 days. Four cases were diagnosed at delivery (9.1%). The mean birth weight was 2022±912 grams and the mean placental weight was 712±294 grams. (Table 1)

Of the 44 cases of fetal hydrops, 5 (11.4%) underwent termination of pregnancy (TOP) before 22 weeks of gestation. These included 2 cases with an identified fetal chromosomal abnormality (one case each of Trisomy 21 and Monosomy X), one case of congenital high airway obstruction syndrome (CHAOS), a case with cystic hygroma hypoplastic right heart and intestinal malrotation and a case of early hydrops of undetermined etiology.

Intrauterine fetal demise (IUFD) occurred in 6 cases (13.6%). One death occurred during intrauterine fetal blood transfusion for fetal anemia due to erythroblastocis fetalis caused by parvovirus infection. The other cases resulting in IUFD were complicated by an Ebstein anomaly, Smith-Lemli-Otiz syndrome, duodenal atresia with reversed rotation of the large bowel and an intracranial hemorrhage secondary to neonatal alloimmune thrombocytopenia (NAIT). These findings were confirmed at autopsy examination although in the sixth case the etiology remained undetermined. All these cases had a euploid karyotype.

There were 13 (29.5%) early neonatal deaths, 4 late neonatal deaths (9.1%) and 4 infant deaths (9.1%). Excluding the five terminated cases, the overall fetal, neonatal and infant mortality rate was 69% (27 out of 39 cases).

Table 1

Characteristics of study group:

Table 2

Outcome of Hydrops According to Etiology

Table 3

Details of pregnancies complicated by fetal hydrops
Excluding the pregnancies ending by termination (5) or IUFD (6), twenty five of the remaining 33 cases were delivered by cesarean section (75.7%). The main indication for cesarean delivery was non-reassuring fetal heart rate monitoring (12/25 cases, 48%). Other indications included previous cesarean section (7 cases), breech presentation (2 cases), maternal request (2 cases), severe preeclampsia (1 case) and fetal arrhythmia (1 case).

Intrauterine interventions were undertaken in 14 cases (31.8%). Amnio-reduction was performed in 5 cases to treat severe polyhydramnios. Fetal intrauterine blood transfusion was undertaken in 3 cases, 2 for parvovirus related anemia and one in a case of Kell allo-immunization. Three of the cases that underwent amnio-reduction also had a toracocentesis performed. In 2 cases a pleuro-amniotic shunt was inserted. Of the five case that had pleural fluid drainage three had congenital chylothorax, in one the etiology appeared to be a subacute fetomaternal hemorrhage as evident by the Kleihaur Betke test and one remained undiagnosed. There was one case of drainage of cytic hygroma and one case with drainage of a macrocystic Congenital Cystic Adenomatoid Malformation (CCAM) and ascitic fluid.

Two women with fetal cardiac dysfunction were treated with oral digoxin. The first case was for a fetal tachyarrhythmia (atrial flutter with 2:1 conductance) with a good outcome. The second case that was complicated by unexplained fetal heart failure, was subsequently attributable to alpha thalassemia.

There were two patients who experienced recurrence of fetal hydrops. One patient had a 1st healthy child, followed by pregnancy complicated by hydrops secondary to congenital heart disease that resulted in an early neonatal death. Her 3rd

pregnancy, which contributed to this series, was complicated by an IUFD at 33 weeks of gestation with abdominal dystocia requiring drainage of fetal ascites to permit delivery. The diagnosis in this pregnancy was Smith-Lemli-Opptiz syndrome. The second patient had 2 hydropic fetuses that are both included in this series. The first was attributed to cardiac failure resulting from a large (7cm) placental chorioangioma . The subsequent pregnancy was complicated by hydrops of unknown etiology that developed at 27 weeks.

Maternal complications arose in 8 cases, these included; 4 cases of placental abruption, 4 cases of maternal mirror syndrome, one with isolated pulmonary edema, the other with isolated ascites and 2 associated with severe preeclampsia.

DISCUSSION:

As would be expected in tertiary referral centers, the incidence of hydrops we observed (1: 1737 deliveries) is greater than the incidence typically reported in the literature (5). NIH was the most frequent accounting for 95.5% of our cases. This is largely due to the prevention of the majority of allo-immune disease that has resulted from the introduction of the routine administration of Anti-D to rhesus negative mothers. A definite cause for the hydrops was established in 84.1% of cases. In 7 cases (15.9%) no cause was identified, which is consistent with a systematic review of non-immune hydrops by Bellini who reported 17.8 % of cases as idiopathic (6).

The single most common anomaly in our series was congenital chylothorax, identified in 6 cases (13.6%) of which only 2 (33%) survived to discharge from the NICU. Congenital chylothorax is mostly an isolated finding but has been associated with chromosomal anomalies or congenital heart disease (7). There were no associated cardiac anomalies in our 6 cases and all those tested had a normal karyotype (4 out of 6).

Chromosomal abnormalities were found in 3 out of the 42 cases of the NIH (7%). In our population, karyotype was available in 81% of the cases with NIH as well as in all the idiopathic cases. Comparative genomic hybridization (CGH) was only performed in one case and identified a deletion of then undetermined significance. CGH was not readily available in our institutions during the majority of the period under study.

9.5% of the NIH cases in our study were attributed to cardiovascular abnormalities, which is in concordance with the 10-20% reported in the literature (8). Similarly, the mortality rate in our study, excluding the terminations but including IUFD, END, LND and infant death was 69%,; the survival rate of 30.7% is similar to that previously reported. Noteworthy is the fact that 25% (3 out of 12) of survivors were discharged from the NICU with complications of prematurity including chronic lung disease, periventricular leukomalacia, seizure disorder, and retinopathy of prematurity. .

Three intrauterine transfusions were performed with one fetal loss during the procedure. This loss occurred during intra-cardiac fetal transfusion following failure of the intravascular umbilical approach in a 21 week fetus with Pavovirus B19 infection. In the literature survival of fetuses with severe Parvovirus infection even with fetal blood transfusion is less than in those with Rhesus isoimmunisation, this may be secondary to the severity of the anemia, impairment of myocardial contractility and thrombocytopenia (9, 10). In one series of 8 cases of intra-cardiac transfusion prior to 24 weeks there were 2 IUFD and the perinatal survival was 75% (11).

We had one case of neonatal alloimmune thrombocytopenia with severe intracranial hemorrhage and anemia leading to hydrops and IUFD at 23 weeks gestation. Hydrops secondary to NAIT has been previously reported (12-15). NAIT should be kept in mind in cases with hydrops and the fetal platelet count should be requested in addition to hemoglobin and hematocrit if a cordocentesis is performed.

Recurrent hydrops raises the possibility of a genetic condition that may not yet have been identified. In one of our two recurrent cases, the first fetal hydrops was attributed to a chorangioma. Although these are most often isolated findings, associations with gene mutations have been observed, including the Beckwith-Wiedemann syndrome (16) and deletions at 2q13 and 7p21.1. Mutations in these regions may be associated with various placental malformation including placental mesenchymal dysplasia that may also result in both fetal as well as placental hydropic changes (17).

We had 4 cases of with features suggestive of the mirror syndrome; a condition that was first documented by O'Driscoll in 1956. He reported that in cases of fetal hydrops the mother may develop edema mirroring the disease of the fetus. Hypertension and proteinuria consistent with preecalmpisa are present in half of cases of mirror syndrome. Soluble vascular endothelial growth factor 1

(sVEGFR-1), an antiangiogenic factor, has been associated with the pathogenesis of preeclampsia. It was proposed that hypoxia of the villous trophoblasts in case of villous edema leads to increased production and release of sVEGFR-1 and possibly other antiangiogenic factors into the maternal circulation. These factors may be responsible for both the maternal edema as well as the endothelial dysfunction in the cases complicated by preeclampsia (18). In 2 of our cases there was only maternal edema (pleural and ascetic) whilst in 2, preeclampsia developed.

The first case of mirror syndrome in our series occurred in the woman with the placental chorioangioma. It is postulated that in such cases underlying placental ischemia (reflected by trophoblast proliferation) and subsequent increased placental vascular resistance may account for the mirror syndrome through the mechanisms outlined above (19).

It is evident that hydrops fetalis remains a heterogeneous condition with many varied etiologies. The rate of immune hydrops, previously most frequently due to Rhesus iso-immunisation, has declined principally due to the prophylactic use of Anti-D in rhesus negative women, and subsequently non-immune hydrops now accounts for the vast majority of cases. Despite advances in sonography, genetic diagnosis and the more widespread use of interventions, hydrops continues to be associated with a poor overall prognosis with a survival rate of just over 30% in our series, with 25% of survivors suffering complications related to prematurity. The latter is unsurprising given that cases generally delivered within a short interval following the diagnosis.

The impact that screening for fetal chromosomal abnormalities has had on the rate of hydrops cannot be determined from our population in part due to its referred nature but also due to the inconsistency in screening approaches within Quebec at the time of this study. Given the etiologies we identified in this series and the lack of universal serum or ultrasound screening during much of the study period, it might be expected that earlier detection of not only aneuploidies but also critical cardiac defects, the latter through the routine use of Nuchal translucency screening, may impact upon a proportion (up to 20%) of the cases that might subsequently be at risk of developing hydrops. However as is evident, many cases remain unidentified as being at risk even at the routine anatomical survey given the median presentation at 28 weeks of gestation.

A proportion of cases remain idiopathic, but the increasingly widespread availability of more detailed genetic analysis in the form of array CGH and whole exome sequencing may allow the proportion of cases of unknown cause to be further reduced and also provide some data that may identify mothers whose subsequent pregnancies may also be at risk.

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