Outcomes of fetal intervention for primary hydrothorax


A R T I C L E   I N F O

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A B S T R A C T

Objective: Primary hydrothorax is a rare congenital anomaly with outcomes ranging from spontaneous resolution to fetal demise. We reviewed our experience with fetuses diagnosed with primary hydrothorax to evaluate prenatal management strategies.

Methods: We reviewed the records of patients evaluated for fetal pleural effusions at our Fetal Treatment Center between 1996 and 2013. To define fetuses with primary hydrothorax, we excluded those with structural or genetic anomalies, diffuse lymphangiectasia, immune hydrops, and monochorionic diamniotic twin gestations.

Results: We identified 31 fetuses with primary hydrothorax, of whom 24 had hydrops. Hydropic fetuses were more likely to present with bilateral effusions. Of all fetuses with primary hydrothorax, 21 had fetal interventions. Survival without hydrops was 7/7 (100%), whereas survival with hydrops depended on whether or not the patient had fetal intervention: 12/19 (63%) with intervention and 1/5 (20%) without intervention. Premature delivery was common (44%) among those who had fetal intervention.

Conclusions: Fetal intervention for primary hydrothorax may lead to resolution of hydrops, but preterm birth and neonatal demise still occur. Understanding the pathophysiology of hydrops may provide insights into further prenatal management strategies, including targeted therapies to prevent preterm labor.

Fetal primary hydrothorax (PH) is a rare congenital anomaly with an incidence of 1 in 10,000–15,000 pregnancies [1]. Male fetuses are affected more frequently than females (2:1) and can present with either unilateral or bilateral effusions [2]. PH (also known as congenital chylothorax) was originally described in 1917 [3], and the embryogenesis has since been studied at length. In normal development, paired lymphatic buds migrate caudally adjacent to the internal jugular veins, forming numerous crosslinks. The superior right and inferior left lymphatic buds then obliterate, and an anastomosis between the nonobliterated ducts forms around T4–T6 [4]. This "normal" path is only evident in 65% of the population [5], and it is likely that an error in the complex process of lymphatic formation and reabsorption leads to the development of PH, resulting in accumulation of chyle in the pleural cavity.

On initial evaluation of a fetus with a pleural effusion, secondary causes such as structural anomalies, chromosomal abnormalities, or infections must be excluded. There is a wide variation in disease progression, with some fetuses having spontaneous resolution and others developing hydrops and fetal demise. The overall mortality is 22–55% [1,6,7]. Prenatal management includes serial ultrasounds, in utero thoracocentesis [8], thoracoamniotic shunt placement [9–12], and, in some centers, in utero chemical pleurodesis [13]. We practice for patients without hydrops has been to offer a thoracocentesis for PH causing mediastinal shift. For patients with hydrops or disease progression, we frequently offer a thoracoamniotic shunt. Patients with small unilateral PH can often be managed expectantly with serial ultrasounds to monitor for resolution or progression as these often resolve or remain stable. Given the heterogeneity of the disease, we reviewed our management strategies and outcomes in fetuses with PH in order to better define prognostic indicators and elucidate guidelines for best practices.

1. Materials and methods

After IRB approval (number 10-04093), we queried our Fetal Treatment Center database to identify patients evaluated between 1996 and 2013 with primary hydrothorax. Key words included chylothorax, pleural effusion, and hydrothorax. We then reviewed the prenatal records of each patient evaluated and treated at our hospital. To define fetuses with PH, we excluded those in which another etiology was identified such as structural or karyotypic anomalies,
infections, diffuse lymphangiectasia, immune hydrops, and monochorionic diamniotic twin gestations. We defined hydrops as the presence of fluid in one other compartment (pericardium, peritoneum, or integument) in addition to the thorax. Since there is a lack of consistency with the use of placentomegaly in the definition of hydrops [14], we did not use this parameter. We stratified fetuses into two groups based on the presence or absence of hydrops. Preterm birth was defined as delivery prior to 37 weeks gestation. For fetuses born at our center, detailed postnatal records were also reviewed while those born at an outside hospital (14 of 21) had telephone follow-up. Fetuses without postnatal follow-up were excluded.

2. Results

We identified 113 fetuses with pleural effusions. Those with structural anomalies (62), chromosomal abnormalities or variants (11), monochorionic diamniotic twin gestations (7), and infections (2) were excluded. The remaining 31 fetuses had primary hydrothorax. The mean gestational age (GA) at diagnosis was 24 ± 4.0 weeks (Table 1). Nineteen fetuses presented with bilateral effusions. Twelve fetuses presented with unilateral effusions, with four of these progressing to bilateral involvement during prenatal surveillance. Three patients elected termination of pregnancy and six experienced in uterofetal demise (IUFD). Twenty-two (71%) progressed to viable births, but two of these patients experienced early postnatal demise. Thus, the overall survival for patients with PH was 20/31 (65%). The mean GA at birth was 37 ± 3.9 weeks (range 30–42 weeks), with eight fetuses (26%) delivering preterm and seven delivering at ≤34 weeks. Nine of 22 born patients (41%) required postnatal pleural fluid drainage.

Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>GA at Diagnosis</td>
<td>24 ± 4.0</td>
</tr>
<tr>
<td>GA at Treatment</td>
<td>25 ± 3.5</td>
</tr>
<tr>
<td>GA at Delivery</td>
<td>37 ± 3.9</td>
</tr>
<tr>
<td>Unilateral Effusion</td>
<td>8/31 (26%)</td>
</tr>
<tr>
<td>Bilateral Effusion</td>
<td>19/31 (61%)</td>
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<tr>
<td>Progression from unilateral to bilateral</td>
<td>4/31 (13%)</td>
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<tr>
<td>Survival</td>
<td></td>
</tr>
<tr>
<td>TOP</td>
<td>3/31 (10%)</td>
</tr>
<tr>
<td>IUFD</td>
<td>6/31 (19%)</td>
</tr>
<tr>
<td>Viable birth</td>
<td>22/31 (71%)</td>
</tr>
<tr>
<td>Postnatal demise</td>
<td>2/22 (9%)</td>
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<tr>
<td>Overall survival</td>
<td>20/31 (65%)</td>
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Abbreviations: GA, Gestational Age; TOP, Termination of Pregnancy; IUFD, In Utero Fetal Demise. Data are mean ± SD or n (percent).

2.1. Hydropic fetuses

Since the presence of hydrops suggests the severity of the condition and often dictates the prenatal management, we stratified our cohort based on its presence. Fig. 1A illustrates the typical ultrasound findings in a hydropic fetus with a large pleural effusion and ascites. Fig. 1B and C demonstrate the preprocedural and postprocedural appearance of the chest in a fetus with bilateral effusions who underwent thoracoamniotic shunt placement.

Twenty patients presented with hydrops and four additional fetuses who were initially not hydropic at presentation developed hydrops during prenatal follow-up scans, giving the overall rate of hydrops 24/31 (77%). Hydropic fetuses were more likely to present with bilateral effusions compared to nonhydropic fetuses (17/20 (85%) hydropic vs. 1/11 (9%) nonhydropic, Fisher’s exact p < 0.0001). Among the four patients who developed hydrops while being monitored, three presented with unilateral effusions, which progressed to bilateral effusions, then hydrops, suggesting that progression from unilateral to bilateral involvement is a harbinger of worsening disease. Hydrops developed 2.8 ± 1.8 weeks after initial evaluation in this cohort, highlighting the importance of frequent evaluations.

2.2. The impact of fetal intervention for hydrops

Nineteen fetuses with hydrops underwent fetal intervention (Fig. 2). Fourteen fetuses initially underwent fetal thoracentesis, 79% of whom subsequently required thoracoamniotic shunt placement for reaccumulation of pleural fluid or worsening hydrops. Fetal intervention resulted in resolution of hydrops in 10/19 (53%) fetuses. Among 19 hydropic fetuses who underwent fetal interventions, three (16%) had in uterofetal demise (IUFD), two (11%) underwent pregnancy termination, and 14 (74%) were born alive, although two experienced early postnatal demise. The overall survival for hydropic patients who underwent fetal intervention was 12/19 (63%) (Fig. 2).

Five fetuses with hydrops did not undergo intervention because of patient preference, and none had resolution of hydrops. Three had IUFD, one underwent pregnancy termination, and one was born alive. The overall survival rate for hydropic patients who did not have fetal intervention was therefore 20% (1/5) (Fig. 2). This surviving fetus had a prolonged hospital course but was eventually discharged home at 1.5 months of life.

2.3. Nonhydropic fetuses

Seven fetuses in our cohort did not have hydrops (Fig. 2). Two of these fetuses underwent intervention (one thoracentesis and one thoracoamniotic shunt) because of the severity of mediastinal shift in

![Fig. 1. Ultrasound images of fetuses with primary hydrothoraces. A. Sagittal view of a large right primary hydrothorax with associated hydrops. * indicates the large pleural effusion. Thin arrow points to the everted diaphragm and thick arrow points to the ascites. B. Coronal view of a fetus with bilateral primary hydrothoraces. * indicates the large right pleural effusion and the arrow points to the small left pleural effusion. C. Coronal view with a thoracoamniotic shunt in place. * indicates the amniotic cavity. Thin arrow points to the thoracoamniotic shunt and thick arrow points to the small residual right pleural effusion.](image-url)
one and progression from a unilateral to bilateral effusions in the other. In this cohort, all seven fetuses survived, giving a survival rate 100%. The survival rate of fetuses with hydrops who underwent fetal intervention (63%) is not significantly different from those without hydrops (100%, p = 0.22 by Chi square test), underscoring the efficacy of fetal intervention for PH with hydrops.

2.4. Fetal interventions

Overall, 21 fetuses with PH underwent fetal intervention with a mean GA at treatment of 25 ± 3.5 weeks. Fifteen fetuses underwent thoracentesis, with 73% subsequently requiring thoracoamniotic shunt placement for reaccumulation of pleural fluid or worsening hydrops. The mean latency period between the two interventions was 3.5 days (range = 1–17 days). Seventeen fetuses underwent thoracoamniotic shunt placement, with follow-up ultrasound demonstrating shunt dislodgement in 11/17 (65%) fetuses. Shunts were replaced in four severe cases with only one survivor, who required bilateral chest tubes at birth. Among seven fetuses who did not require repeat shunt placement, six progressed to viable births (three were asymptomatic at birth and three required chest tubes), and one resulted in an IUFD. One thoracentesis and one thoracoamniotic shunt were complicated by a subpleural hematoma.

The number of procedures also affected outcomes. Survival among fetuses who underwent 1 or 2 procedures was 8/10 (80%) and 6/6 (100%), respectively, compared to 1/5 (20%) among those who underwent 3 procedures. Additionally, preterm births were more frequent in those undergoing multiple procedures—3/8 (38%) of those who underwent 1 procedure, 3/6 (50%) of those who underwent 2 procedures, and 2/2 (100%) of those who underwent 3 procedures were born preterm. The observation that mortality and preterm delivery increased in those undergoing 3 procedures likely reflects a persistent disease processes not ameliorated by fetal intervention combined with the insult of fetal intervention.

2.5. Preterm birth

Eight patients had spontaneous preterm labor, giving an overall rate of 29%. All patients who had preterm births carried hydropic fetuses and 88% (7/8) had fetal intervention, with six of these born ≤34 weeks gestation. Among all patients who underwent fetal interventions, the rate of preterm birth was 44% (7/16). The average latency period between intervention and birth was 11 weeks. In contrast, there were no preterm births in fetuses who were not hydropic, although two fetuses in this group had intervention. This data suggests that hydrops with fetal intervention is a significant risk factor for preterm birth in these fetuses.

2.6. Pleural fluid evaluation

Fetal pleural fluid was analyzed in 14 fetuses with PH and the analysis revealed high (≥85%) lymphocyte fraction in 13 of the 14 samples, supporting the presumed diagnosis of chylothorax. Pleural lymphocyte fractions were not significantly different between hydropic and nonhydropic groups (90 ± 5.6% and 93 ± 4.1%, p = 0.39), suggesting that both groups share the same underlying disease, albeit with a different severity. In four fetuses, both prenatal and postnatal pleural fluid were obtained and compared. Three of these samples demonstrated a persistent lymphocytosis postnatailly while one had a spontaneous decrease in the lymphocyte fraction (88% intrapartum vs. 44% postnatally). Although the percentage of lymphocytes dropped, the effusions did not resolve spontaneously and he required two thoracenteses within the first week of life.

3. Discussion

We report a 17-year experience with the prenatal management of fetal primary hydrothoraces. Our data indicate that intervention among fetuses with PH has the potential to improve survival for hydropic fetuses, but there is still a significant risk of mortality and preterm birth. Our survival data following shunt placement is consistent with previously reported series [10,11,15,16]. Overall, nonhydropic fetuses with a primary hydrothorax can be monitored closely. The survival rate after hydrops with fetal intervention in our series is better than what would be expected knowing the natural history of this condition. The progression from unilateral to bilateral effusions is a sign of impending hydrops and should prompt appropriate patient counseling and, possibly, fetal intervention. However, the risks of the procedure and of preterm labor should be considered.

One weakness to our study is that our series likely underrepresents fetuses with simple unilateral effusions who are not referred to our
tertiary care center. Thus, the rate of small unilateral PH that resolves spontaneously may be higher in this disease. We found that fetuses who present with bilateral effusions tend to have hydrops on presentation, and that progression from unilateral to bilateral can precede the development of hydrops. This observation suggests that bilateral primary hydrothoraces may be a more fulminant form of the disease with a worse prognosis. For example, it is possible that fetuses with unilateral effusions initially have maldevelopment of lymphatics on only one side, with the contralateral side developing a reactive effusion rather than a true chyle leak.

We were able to analyze pleural fluid both prenatally and postnatally in several cases to understand the natural history of the prenatal chyle leak. We found one hydropic fetus whose pleural lymphocyte fraction decreased to normal levels postnatally and one hydropic fetus who survived without any prenatal intervention. These observations support previous reports of spontaneous resolution of PH [17]. The biological reasons behind the initiation and resolution of the thoracic chyle leak are not currently known, although there are reports of increased inflammatory mediators in the pleural fluid in this disease [18,19]. Several hereditary lymphedema-associated gene loci (VEGFR3, ITGA9, PTPN11) have been detected in human fetuses with this condition and had a worse prognosis because of defective lymphangiogenesis [20]. A more thorough analysis of relevant biomarkers in pleural fluid may improve our understanding of the pathophysiology and prognostic indicators in this disease.

The effectiveness of thoracentesis alone for prenatal drainage of a primary hydrothorax has been debated, as there can be rapid reaccumulation of pleural fluid [21,22]. Thoracentesis may result in complications such as hematomas, as we describe here. The risks associated with thoracoamniotic shunts include bleeding, limb constriction, hypoproteinemia, preterm premature rupture of membrane and preterm delivery [10,21]. In our series, we noted that 73% of fetuses who undergo thoracentesis eventually require thoracoamniotic shunt, suggesting it may be reasonable to proceed directly to shunting for hydropic fetuses with bilateral effusions. Two fetuses, however, were adequately treated with thoracentesis alone. In addition, although we determined that some of our shunts had migrated, similar to what has been reported [21], only 36% (4/11) were severe enough to warrant replacement. This suggests that even a short period of drainage can be beneficial in resolving the chyle leak, possibly by reversing diaphragmatic erosion and restoring normal fetal chest movement.

Although fetal intervention can lead to resolution of hydrops, our series indicates that 44% of viable deliveries following fetal intervention were preterm, which increases their morbidity. Hydrops was a significant contributor to preterm birth: Among the eight fetuses with preterm deliveries, all had hydrops. In contrast, there were no preterm births in the nonhydropic group, although two fetuses had intervention. We speculate that preterm delivery is secondary to both the intervention and the hydropic state of the fetus. Preterm birth may be a result of a Fetal Inflammatory Response Syndrome (FIRS) [23], which leads to preterm contractions in the setting of inflammation. Whether the inflammation originates from the hydropic state of the fetus or the fetal intervention is not known. However, understanding the molecular mechanisms that lead to development of hydrops in these fetuses will allow institution of targeted therapies to stop preterm labor in this group of patients.

The outcomes of fetuses with primary hydrothoraces and associated hydrops vary from survival without intervention to death, with progression from unilateral to bilateral effusions portending imminent hydrops. Fetal intervention has improved survival in these patients but continues to carry the risk of preterm labor. Developing a more refined understanding of the physiologic changes that lead to hydrops will likely improve patient prognosis in this disease.

References


Discussion

Discussant: Jim Pierce, MD, Halifax, Nova Scotia: I was wondering if you looked at the difference between those patients with Down Syndrome or congenital heart disease that may have a different pathophysiology from those babies that did not have a predisposition to chylothorax?

Response: Dr. Derderian: It’s an excellent question. We in fact excluded those patients because we were really focused on patients who just had an idiopathic primary hydrothorax with an unknown etiology. Anything with a genetic abnormality or chromosomal abnormality was excluded in this case so we did not actually look at those particularly.

Discussant: Steve Fishman, MD, Boston, MA: Very nice paper. I have a question about—idiopathic which means we don’t know, and antenataly that may be the case. After they were born, was a cause found? Was a cause ever found? The related question would be as a fetal interventionalist or a fetal center where you are looking at babies and defining survival, I assume survival was defined as the baby was born alive. Can you comment on what the survival was, 30 days, 30 months, 10 years later?

Response: Dr. Derderian: Excellent question. As far as the diagnosis as a neonate, unfortunately we treat these neonates as if they have a...
congenital chylothorax so some chyle leak, so we usually do not
feed them, we feed them fat nutrients that don’t have any fat
content on them so if we perform a thoracentesis on them we are
still looking at lymphocyte counts and not necessarily at the
production of chyle which would be like triglycerides, so we still
usually do not know the diagnosis in these instances. The ones that
did have a potential diagnosis of any other cause were excluded
from this. As far as survival, this was actually the survival to
hospital discharge. We do have some fetuses that had neonatal
deaths within 30 days. I lumped them into the non-survivors in
this. Those fetuses with severe disease progress that had shunts
placed, shunt dislodgement, re-accumulation of fluid and a second
shunt placed and didn’t do any better with that. So there is
obviously a difference between the fetuses that do better versus
those that don’t. It’s still unclear as to why that is.

**Dr. Fishman:** I would encourage you to do a follow-up study of how
these patients are doing. Just because you feed or don’t feed a child
at birth because you assume they have a chylothorax, I wish it was
the case that just treating them as chylothorax with PN or fat-free
formulas whatever would mean that they are cured, and many of
them, most of them will go to hospital discharge but many of them
have lifelong morbidity or mortality. I would encourage you to
follow this semilarge series with long-term outcome.

**Dr. Derderian:** That’s an excellent point. Thank you, sir.