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LONG TERM FOLLOW-UP IN FETAL THORACO-AMNIOTIC SHUNTING

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ABSTRACT

Background: Fetal hydrothorax is an abnormal accumulation of fluid in the pleural cavity. The course of untreated disease is highly variable and may resolve spontaneously, remain stable, or worsen.

The identification of long-term predictors may have prognostic implications that may be useful to the pregnant woman and her family.

Purpose: The main objective of the study is to describe the survival rate and the presence or absence of neurodevelopmental delay at 3, 5 and 10 years of age in children who underwent prenatal thoraco-amniotic shunting.

Methods: This is a single cohort retrospective observational study conducted at Vall d'Hebron University Hospital between January 2009 and March 2022.

All fetuses that underwent intrauterine thoraco-amniotic shunt and were followed up were included.

From the database, a descriptive study will be performed to assess long-term outcomes (3, 5 and 10 years).

Results: The fetus was hydropic at diagnosis in 13/25 (52%) of cases, 8/25 (32%) had bilateral shunts inserted, and 10/22 (45%) had shunt displacement. Additional diagnoses were present in 8/25 (32%) of cases. There were two intrauterine and six neonatal deaths, with an overall survival rate of 17/21 (81%) at birth. The survival rate at 12 months was 47.4%, at 3 and 5 years 44.4% and at 10 years 41.2%. Overall, 7/8 (87.5%) of survivors had abnormal development at 10 years and survival rate were higher from 12 months onwards in non-hydropic fetuses.

Conclusions: Fetal shunt therapy is associated with significant perinatal mortality and morbidity, and a pathological neurodevelopmental outcome in the majority (87.5%) of survivors. Those with isolated hydrops are more likely to survive at 12 months and up to 10 years of age.

RESUMEN

Antecedentes: El hidrotórax fetal es una acumulación anormal de líquido en la cavidad pleural. El curso de la enfermedad no tratada es muy variable y puede resolverse espontáneamente, permanecer estable o empeorar.

La identificación de predictores a largo plazo puede tener implicaciones pronósticas útiles para la gestante y su familia.

Propósito: El objetivo principal del estudio es describir la tasa de supervivencia y la presencia o ausencia de retraso en el neurodesarrollo a los 3, 5 y 10 años de edad en niños sometidos a derivación toracoamniótica prenatal.

Métodos: Se trata de un estudio observacional retrospectivo de cohorte única realizado en el Hospital Universitario Vall d'Hebron entre enero de 2009 y marzo de 2022.

Se incluyeron todos los fetos sometidos a derivación toraco-amniótica intrauterina y con seguimiento.

A partir de la base de datos, se realizará un estudio descriptivo para evaluar los resultados a largo plazo (3, 5 y 10 años).

Resultados: El feto era hidrópico en el momento del diagnóstico en 13/25 (52%) de los casos, 8/25 (32%) tenían derivaciones bilaterales insertadas y 10/22 (45%) tuvieron un desplazamiento de la derivación. Hubo diagnósticos adicionales en 8/25 (32%) de los casos. Hubo dos muertes intrauterinas y seis neonatales, con una tasa de supervivencia global de 17/21 (81%) al nacimiento. La tasa de supervivencia a los 12 meses fue del 47,4%, a los 3 y 5 años del 44,4% y a los 10 años del 41,2%. En conjunto, 7/8 (87,5%) de los supervivientes presentaban un desarrollo anormal a los 10 años y la tasa de supervivencia fue mayor a partir de los 12 meses en los fetos no hidrópicos.

Conclusiones: La terapia de derivación fetal se asocia a una importante mortalidad y morbilidad perinatal, y a un resultado patológico del neurodesarrollo en la mayoría (87,5%) de los supervivientes. Los fetos con hidropesía aislada tienen más probabilidades de sobrevivir a los 12 meses y hasta los 10 años de edad.

RESUM

Antecedents: L'hidrotòrax fetal és una acumulació anormal de líquid a la cavitat pleural. El curs de la malaltia no tractada és molt variable i es pot resoldre espontàniament, romandre estable o empitjorar.

La identificació de predictors a llarg termini pot tenir implicacions pronòstiques útils per a la gestant i la família.

Propòsit: L'objectiu principal de l'estudi és descriure la taxa de supervivència i la presència o absència de retard al neurodesenvolupament als 3, 5 i 10 anys en nens sotmesos a derivació toracoamniòtica prenatal.

Mètodes: Es tracta d'un estudi observacional retrospectiu de cohort única realitzat a l'Hospital Universitari Vall d'Hebron entre el gener del 2009 i el març del 2022.

S'hi van incloure tots els fetus sotmesos a derivació toracoamniòtica intrauterina i amb seguiment.

A partir de la base de dades, es farà un estudi descriptiu per avaluar els resultats a llarg termini (3, 5 i 10 anys).

Resultats: El fetus era hidròpic en el moment del diagnòstic a 13/25 (52%) dels casos, 8/25 (32%) tenien derivacions bilaterals inserides i 10/22 (45%) van tenir un desplaçament de la derivació. Hi va haver diagnòstics addicionals a 8/25 (32%) dels casos. Hi va haver dues morts intrauterines i sis neonatals, amb una taxa de supervivència global de 17/21 (81%) al naixement. La taxa de supervivència als 12 mesos va ser del 47,4%, als 3 i 5 anys del 44,4% i als 10 anys del 41,2%. En conjunt, 7/8 (87,5%) dels supervivents presentaven un desenvolupament anormal als 10 anys i la taxa de supervivència va ser més gran a partir dels 12 mesos en els fetus no hidròpics.

Conclusions: La teràpia de derivació fetal s'associa a una mortalitat i morbiditat perinatal important, ia un resultat patològic del neurodesenvolupament en la majoria (87,5%) dels supervivents. Els fetus amb hidropesia aïllada tenen més probabilitats de sobreviure als 12 mesos i fins als 10 anys.

1. INTRODUCTION

Fetal hydrothorax is an abnormal accumulation of fluid in the pleural cavity that was first described by Carroll 1977(1). It is a rare condition with an incidence of approximately 1:10,000-1:15,000 pregnancies(2).

It can be subdivided according to etiology into primary hydrothorax (also known as isolated pleural effusion) and secondary hydrothorax.

Primary hydrothorax is most often caused by abnormalities in the development of the lymphatic system and is usually a diagnosis of exclusion. Secondary hydrothorax may be part of non-immune fetal hydrops fetalis and is caused by abnormalities such as chromosomal abnormalities (mainly trisomy 21 and monosomy X), fetal anaemias, viral infections (adenovirus, parvovirus B19, herpes simplex), heart disease and genetic syndromes (mainly Noonan syndrome). (3,4)

The course of the disease without treatment is variable and may resolve spontaneously, remain stable or worsen. Spontaneous resolution in cases of mild primary hydrothorax (without hydrops or hydramnios, unilateral and diagnosed in the 2nd trimester) has been reported in up to 22% of 204 cases(5). However, since many cases of spontaneous regression are not reported, this may be underestimated(4). Although in most cases, it will worsen to a progressive course with hydrops fetalis, polyhydramnios and intrauterine death in up to 53% of cases(2).

Prenatal management options include thoracentesis, thoraco-amniotic shunting, pleurodesis with OK-432 and early termination of pregnancy. Thoraco-amniotic shunting was first described by Seeds and Bowes in 1986 (6) and involves continuous drainage of the pleural effusion into the amniotic cavity.

Although thoracoamniotic drainage has been shown to improve survival (2,4,7,8), there are few studies reporting on the long-term outcomes of babies with fetal hydrothorax treated with thoracoamniotic shunting. So far, it has been described in a Canadian study that 84% had normal neurological development at 18 months (being up to 92% in isolated hydrops) and pulmonary outcomes were excellent (9).

The main hypothesis is that the main predictors of adverse long-term outcomes are gestational age at diagnosis of hydrothorax or thoracic anomaly, association with hydrops, and association with other concomitant anomalies (non-isolated cases).

The primary objective of the study is to describe survival rate and presence or absence of neurodevelopmental delay at 3, 5 and 10 years of age in children that underwent thoraco-amniotic shunting prenatally.

The secondary objectives are:

- To describe the perinatal outcomes: livebirth, stillbirth, termination of pregnancy (TOP); gestational age at delivery.
- To describe the survival at 6, 12 and 24 months of life.
- Describe the complications and need for surgery at 6, 12 and 24 months, 3, 5 and 10 years of life
- Describe the additional findings or diagnoses at 6, 12 and 24 months, 3, 5 and 10 years of life
- Stratify previous outcomes according to the presence or absence of hydrops

2. METHODS

Setting

This is a single cohort retrospective observational study conducted at Vall d'Hebron University Hospital between January 2009 and March 2022, where we evaluated the short-term and long-term outcomes of fetuses undergoing thoraco-amniotic shunting.

Ethics statement

The study was conducted in accordance with the Declaration of Helsinki, in line with the standards of Good Clinical Practice ICH E6(R2) and in compliance with national (RD 957/2020) and European (Commission Directive 2005/28/EC) legislation in force. Personal data were processed in accordance with current national (Organic Law 3/2018 of 5 December on the Protection of Personal Data and Guarantee of Digital Rights) and European (Regulation (EU) 2016/679 on Data

Protection) Personal Data Protection. The local Ethics Committee, *Comité de Ética de Investigación con Medicamentos y comisión de proyectos de investigación del Hospital Universitari Vall d'Hebron* (CEIm-VHIR), approved the study (PR(AMI)458/2022) on the 16th of December 2022. As this was a retrospective study, a waiver of written informed consent was obtained.

Clinical protocol

Before selecting the fetuses suitable for shunting, a prenatal examination was performed detailing: gestational age at diagnosis, genetic study (karyotype, array, whole exome sequencing (WES)), study of infections in amniotic fluid (cytomegalovirus, Parvovirus B19, toxoplasmosis, Herpes virus, Chicken pox), the presence of hydrops or not and whether it was associated with other malformations.

Study population

The study population were women attending the Fetal Medicine Unit at Vall d'Hebron Hospital for fetal hydrothorax. Inclusion criteria were women whose fetuses were diagnosed with unilateral or bilateral hydrothorax with or without hydrops and fetuses treated with unilateral or bilateral thoracoamniotic shunt. Exclusion criteria were loss to follow-up and other indications for thoracoamniotic shunt without the presence of hydrothorax.

The search has been carried out in Viewpoint^{Ô} to identify pregnant patients undergoing thoracoamniotic shunt placement. A research electronic data capture (EDC) has been created in REDCap^{Ò} with restricted access to researchers in which no identifying data of the women or children has been collected (medical record number, name, surname, date of birth, address or telephone number were excluded). The correlation between the medical record number and the REDCap code was collected in an encrypted Excel file with a password only known by researchers involved in the data collection. Once the database was completed, it was exported to R software for data analysis.

Statistical analysis

For descriptive analysis: numerical variables were described as mean and standard deviation (SD) or median and interquartile range depending on whether the distribution was parametric or not. Categorical variables were described as absolute and relative frequencies (percentage). For the comparison of quantitative variables between two groups, they were compared by t-test or Mann-Whitney test depending on whether the variable follows a normal distribution or not. For the comparison of categorical variables between groups, the Chi-square test or Fisher's test was used, as appropriate.

The R software (R Foundation for Statistical Computing, Vienna, Austria) was used for statistical analysis. The significance level was set at 0.05.

3. RESULTS

In 27 fetuses an intervention for shunt placement was scheduled, in two fetuses shunt placement was not possible for technical reasons and therefore they were excluded from the study. Finally, 25 cases were included in the analysis.

Demographic characteristics

Of the 25 that were finally analyzed, their demographics, shunting and pregnancy outcome are reported in Table 2 and Supplementary Table 1. No women reported alcohol consumption, 3 out of 20 (15%) were smokers, 8 out of 24 (33%) had a medical condition (1 with obesity, 2 with polycystic ovary syndrome, 1 with asthma, 1 with epilepsy and untreated hyperthyroidism, 1 with migraine and the last one with uterine myoma) and 1 had a history of tracheal malformation in a previous pregnancy.

Perinatal outcomes

Of the 25, 24 (96%) underwent invasive testing (20 QF-PCR, 14 Karyotype, 11 Array and two exome) of which all were normal except for three (one was diagnosed with Klinefelter's syndrome, the other with trisomy 21 and the last with duplication of 22q11.23). The detection of infections in

amniotic fluid was negative in all those who underwent the test, although most of them were not asked for syphilis.

During ultrasound screening four out of 25 (16%) were diagnosed with another thoracic malformation (two with pulmonary sequestration, one with a bronchogenic cyst and one with a diaphragmatic hernia) and eight out of 25 (32%) with other anomalies (choroid plexus cyst, abdominal cyst, macrocystic CPAM). In total 13 of 24 (54%) developed hydrops.

The indication for shunt placement was hydrothorax without hydrops in 54% and hydrothorax with hydrops in 46% out of 24 patients. In 8 patients a bilateral shunt was placed (32%) and in the majority (72%) only one attempt was required for placement. In 10 patients out of 22 (45%) the shunt was displaced at a mean of 29.6 weeks of gestation (SD, 5.7), and shunt placement was repeated in seven patients.

Of the 25 fetuses, two opted for legal termination of pregnancy (8%), two resulted in intrauterine deaths (8%) and four were lost to follow up (16%). During the neonatal period (N=17), eight required respiratory support (47%), two of them (11.7%) needed surgery (diaphragmatic hernia surgery and for pulmonary sequestration). Six out of 17 (35.3%) had an additional morbidity: two had a right pneumothorax, one of them with left pleural effusion that required drainage, one required double thoracic drainage, another was found leukopenia and thrombocytopenia and two were born with a short neck phenotype with low-set ears.

Finally, six of those requiring ventilatory support were neonatal deaths (35%), which meant that the study could only continue with 11 neonates.

Figure 1 shows the flow chart with the cases followed up until 10 years of age. Supplementary Figure 1 shows the additional findings through the follow up.

Short term follow-up

At **three months,** we followed 11 infants, without any death in this period. During this time, no additional diagnoses were found, although one of them had pneumothorax, and required respiratory support due to pulmonary lymphangiectasia at two months of life.

At **six months**, one case was lost due to lack of follow up, so the subsequent follow-up was up to 10 patients. At five months, the one who had pulmonary lymphangiectasia at two months was diagnosed with Noonan syndrome (mutation in the PTPN11 axon) and at six months required nasogastric tube placement due to gastrointestinal (GI) reflux. In another one, at six months, the shunt was extracted and although neurodevelopment was normal due to corrected age, he was sent to Early Childhood Development and Care Centres (CDIAP) and the one with thrombocytopenia at birth had a bone barrow aspirate.

At **12 months,** one infant required oxygen therapy in the context of an episode of bronchiolitis and one of those who had short neck phenotype with low-set ears was diagnosed with left pulmonary hypoplasia without repercussions at eight months of age and was lost to follow-up from then on.

At **24 months**, we lost 2 patients because of lack of follow up, so we just have eight patients. The one with Noonan syndrome has a percutaneous gastrostomy, one was diagnosed with spina bifida at L5, the one that had the bronchiolitis episode was diagnosed with asthma and egg allergy at 18 months, and the one that was in follow-up with CDIAP was diagnosed with language delay (no speech at 19 months).

Long term follow-up

Figure 2 shows the neurodevelopmental outcome at 3, 5 and 10 years.

At **three years** of follow-up, the eight children were alive. Apart from the previous case, in this period two have developed neurodevelopmental disorders: the one with Noonan syndrome had an expressive language delayed and the one with thrombocytopenia does not speak, just communicates by gestures.

At **five years** of age, there were not any deaths in this period but, two go to the speech therapist (one is the one with diaphragmatic hernia). The one that was in in follow-up with CDIAP had to undergo myringotomy with bilateral drainage at the age of four years. In addition, the one with thrombocytopenia was diagnosed with linear leukoma and superior irregularity with hyperopia (14 diopters in the right eye) corrected with glasses.

At **10 years**, we just have information about seven cases because they are not yet of that age. The one who had a pulmonary sequestration has maintained normal development so far and the two who at five years old went to the speech therapist, continue to go without new incidents. The one with spinal bifida diagnosed with another with attention deficit hyperactivity disorder, dyslexia, and speech disorder. The one that was in follow-up with CDIAP had diagnosed with attention deficit hyperactivity disorder and autism spectrum disorder; and the one with Noonan Syndrome at the age of six, his gastrostomy was closed and at the age of 10, he was granted a degree of dependency two, disability of 55%, and he goes to a speech therapist and has anxiety. Finally, the one with thrombocytopenia and leukopenia was diagnosed at nine years of age ok congenital cataract and finally diagnosed with a heterozygous mutation of the SRP71 gene which causes medullar failure syndrome type 1, although for the moment he is being monitored and everything seems normal.

Outcome according to the presence or absence of hydrops

Figure 3 shows the survival flowcharts of fetuses with and without hydrops.

Table 1 summarizes the survival rates and neurodevelopmental outcomes in fetuses with and without hydrops. The survival rate at 12 months, 3, 5 and 10 years was higher in fetuses who didn't develop hydrops.

Table 1. Summary of survival rates at different stages, and neurodevelopmental delay at 10 years of age.

	All	Hydrops	No hydrops	p
Survival at birth	17/21 (81.0%)	7/10 (70%)	10/11 (90.9%)	0.311
Survival at 12 months	9/19 (47.4%)	2/10 **(20%)**	8/10 **(80.0%)**	**0.023**
Survival at 3 years	8/18 (44.4%)	1/9 (**11.1%)**	7/9 (**77.8%)**	**0.015**
Survival at 5 years	8/18 (44.4%)	1/9 (**11.1%)**	7/9 (**77.8%)**	**0.015**
Survival at 10 years	7/17 (41.2%)	1/9 (**11.1%)**	6/8 (**75.0%)**	**0.015**
Neurodevelopmental delay	7/8 (87.5%)	1/1= 100%	5/6 (83.3%)	1

Comparisons between the hydrops group and the non-hydrops group by Fisher's test

4. DISCUSSION

In this study we have observed that if hydrothorax is treated with shunt the overall survival at birth is 81% (17/21) and at 10 years 41.2% (7/17). 1/7 (14.3%) of the survivors have normal neurological development and 6/7 (85.7%) a pathological development at 10 years. It should be noted that mortality in these patients remains high (10.53% intrauterine mortality, 35.29% perinatal) with considerable morbidity (of the 25 shunts placed, 8/ 15 [42%] died).

Our study confirms the difference in behaviour between a fetus that develops hydrops and one that does not, the survival rate in the first ones being 11.1% with neonatal comorbidities at 6/7 (85.7%) and neurodevelopmental problems in 100% over 10 years versus the latter with a survival rate of 80% with neonatal comorbidities at 3/10 (30%) and neurodevelopmental problems in 5/6 (83.3%) over 10 years of age.

In the neonatal period many require a prolonged stay in the hospital (9–14), like these studies, of the 17 that were born alive in our center 47% required ventilatory support, 11.7% required surgery and therefore neonatal mortality was 35.29%.

In our study, additional findings were detected both prenatally and postnatally in 6/25 (24%) of cases.

Long-term neurodevelopmental outcomes have not been described in many series. In our cohort, only one case of 7 had a normal neurodevelopmental outcome. Here, we could not compare fetuses with and without hydrops, as only one of the fetuses with hydrops arrived alive to 10 years of age.

In our analysis, hydrops was associated with the adverse outcome of death and pathological neurodevelopment.

The strength of this study is the long-term follow-up of the survivors as there is not much literature on them. One possible limitation is the difficulty in follow-up, as many were from abroad and we could not access their medical records. Another limitation is that the sample size is small and therefore it is difficult to extrapolate results and make associations.

In conclusion, fetal shunt therapy is associated with significant perinatal mortality and morbidity, and a pathological neurodevelopmental outcome in the majority (87.5%) of survivors. Those with isolated hydrops are more likely to survive at 12 months and up to 10 years of age.

These data are important for prenatal counselling, because in counselling not only the short-term but also the long-term results have to be discussed.

However, there is still a lack of research in this field, and we encourage further studies of the long-term outcomes of these patients.

5. ACKNOWLEDGEMENTS

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Table 2. Demographic characteristics of the study population

	N=25	***Value***
Age		32.9 ± 4.9
Conception		
Spontaneous		20 / 21 (95%)
IVF		1 / 21 (4.8%)
Unknown		4
Weight		65 ± 16
Unknown		6
Height		166 ± 8
Unknown		6
Smoke		
Smoker		3 / 20 (15%)
Non-smoker		17 / 20 (85%)
Unknown		5
Alcohol		
Yes		0/20 (0%)
No		20 / 20 (100%)
Unknown		5
Gravida:		
1		9 / 25 (36%)
2		10 / 25 (40%)
3		4 / 25 (16%)
4		1 / 25 (4.0%)
6		1 / 25 (4.0%)
Para		
0		12 / 25 (48%)
1		11 / 25 (44%)
2		1 / 25 (4.0%)
3		1 / 25 (4.0%)

	N=25	***Value***
Medical condition:		
Yes		8 / 24 (33.3%)
No		17 / 24 (70.8%)
Unknown		1
Diabetes Mellitus type 1		
Yes		0 / 24 (0%)
No		24 / 24 (100%)
Unknown		1
Diabetes Mellitus type 2		
Yes		0 / 24 (0%)
No		24 / 24 (100%)
Unknown		1
Hypothyroidism		
Yes		0 / 24 (0%)
No		24 / 24 (100%)
Unknown		1
Chronic hypertension		
Yes		0 / 24 (0%)
No		24 / 24 (100%)
Unknown		1
Asthma		
Yes		0 / 24 (0%)
No		24 / 24 (100%)
Unknown		1
Other medical condition:		
Yes		7 / 24 (29%)
No		17 / 24 (71%)
Unknown		1
Gestational age at diagnosis (weeks)		24.6 (5.6)

	N=25	***Value***
Invasive test		24
Normal		21/24
Abnormal		3/24
Unknown		1
Infections		20
CMV		
Positive		0/20
Negative		14/20
Parvovirus B19		
Positive		0/20
Negative		14/20
Toxoplasmosis		
Positive		0/20
Negative		14/20
Herpes		
Positive		0/20
Negative		7/20
Chickenpox		
Positive		0/20
Negative		13/20
Syphilis		
Positive		0/20
Negative		2/20
Other thoracic anomalies		
Pulmonary sequestration		2 / 25 (8.0%)
Bronchogenic cyst		1 / 25 (4.0%)
Diaphragmatic hernia		1 / 25 (4.0%)
Additional ultrasound anomalies (*Choroid plexus cyst, abdominal cyst, macrocystic CPAM***)**		8 / 25 (32%)

	N=25	***Value***
Hydrops		13 / 25 (52%)
Shunt indication		
Hydrothorax without hydrops		12 / 25 (48%)
Hydrothorax with hydrops		13 / 25 (52%)
Shunt laterality		
Unilateral left		7 / 25 (28%)
Unilateral right		10 / 25 (40%)
Bilateral		8 / 25 (32%)
Shunt displacement		10 / 22 (45%)
Unknown		3
Shunt repeated		7 / 22 (32%)
Unknown		3

Data are represented as mean +/- standard deviation (SD), n (%). CMV= Cytomegalovirus; CPAM= congenital malformation of the pulmonary airway.

Figure 1. Flow chart with the cases followed until 10 years of age.

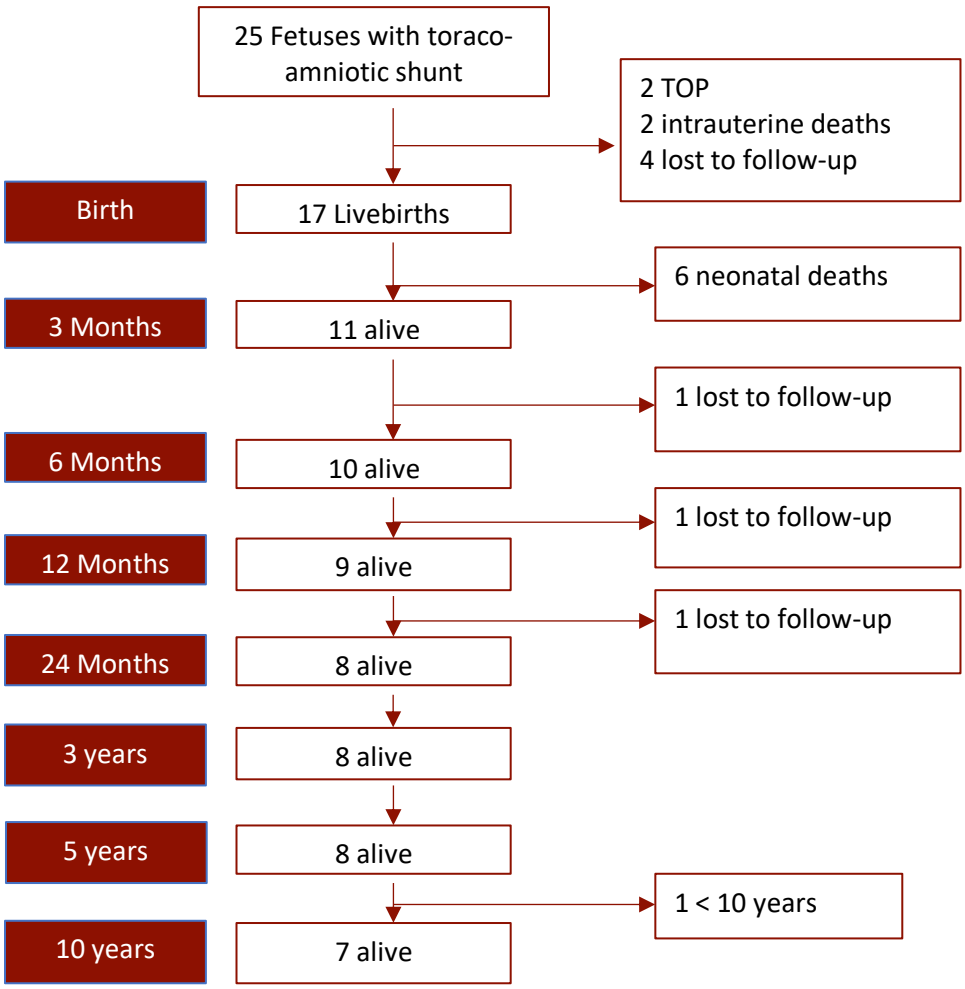
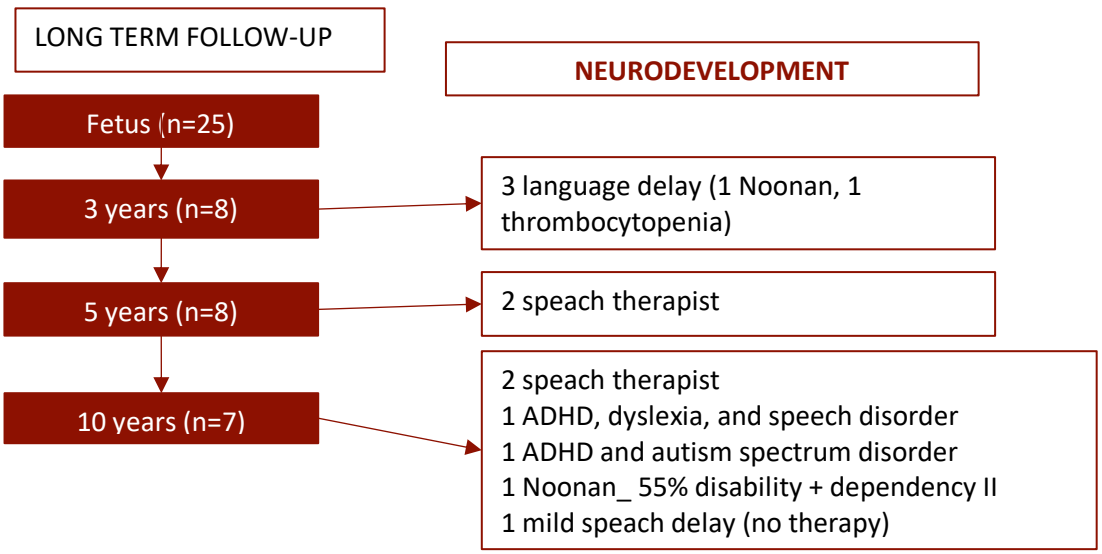
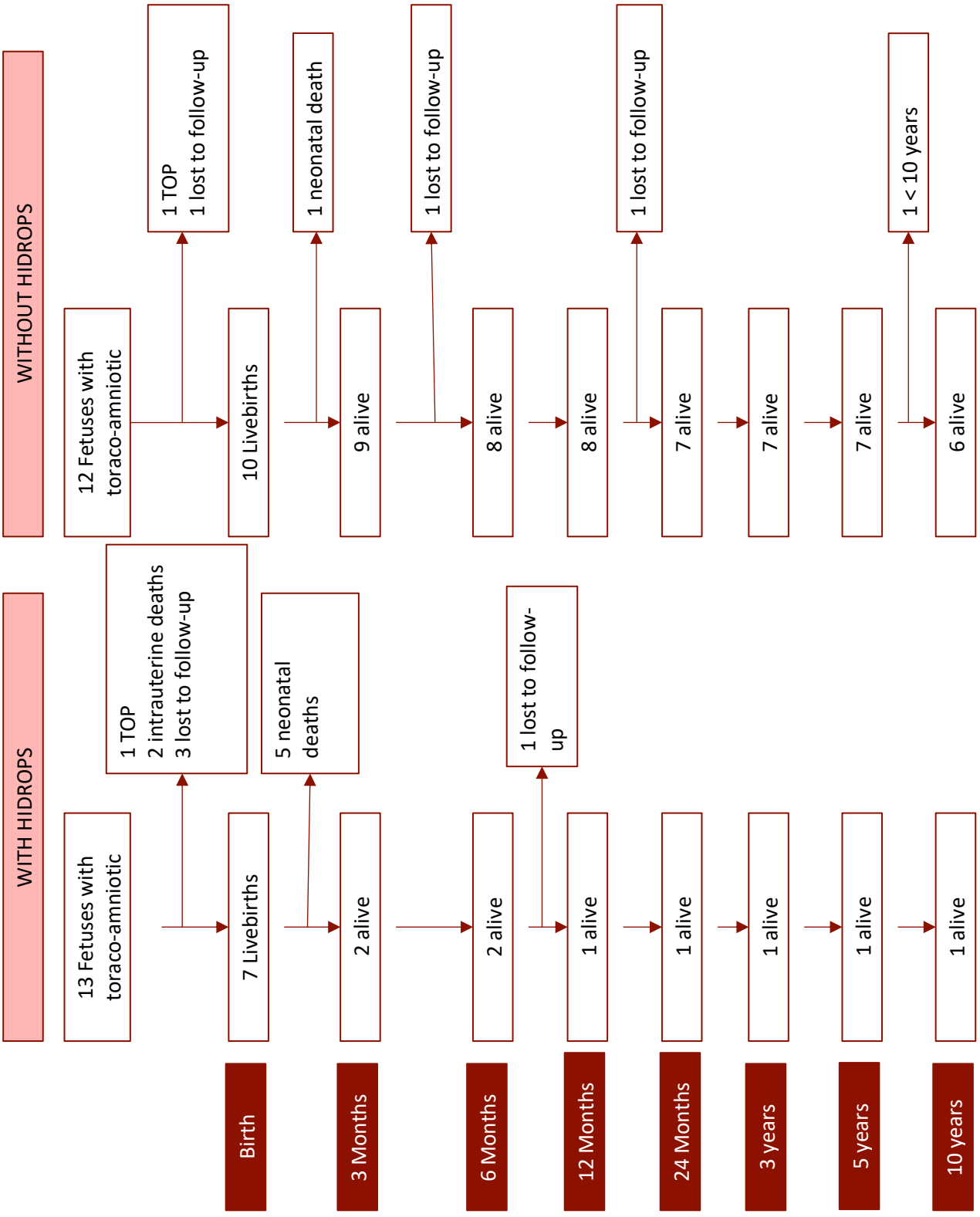


Figure 2. Neurodevelopmental outcome at 3, 5 and 10 years



ADHD = Attention-Deficit/Hyperactivity Disorder

Figure 3. Survival flowcharts of fetuses with and without hydrops



TOP = Termination of pregnancy

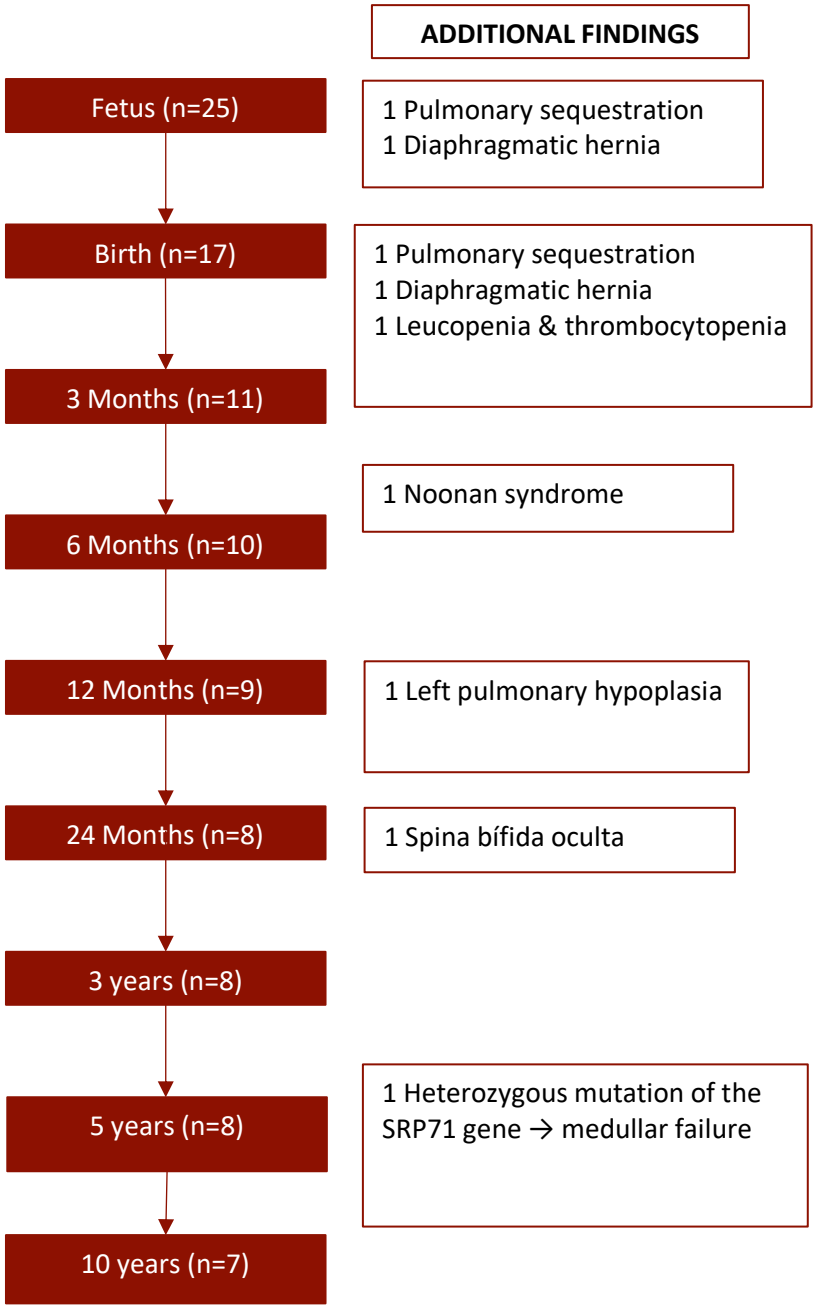
SUPPLEMENTARY TABLES

SUPPLEMENTARY TABLE 1. Pregnancy and perinatal outcomes

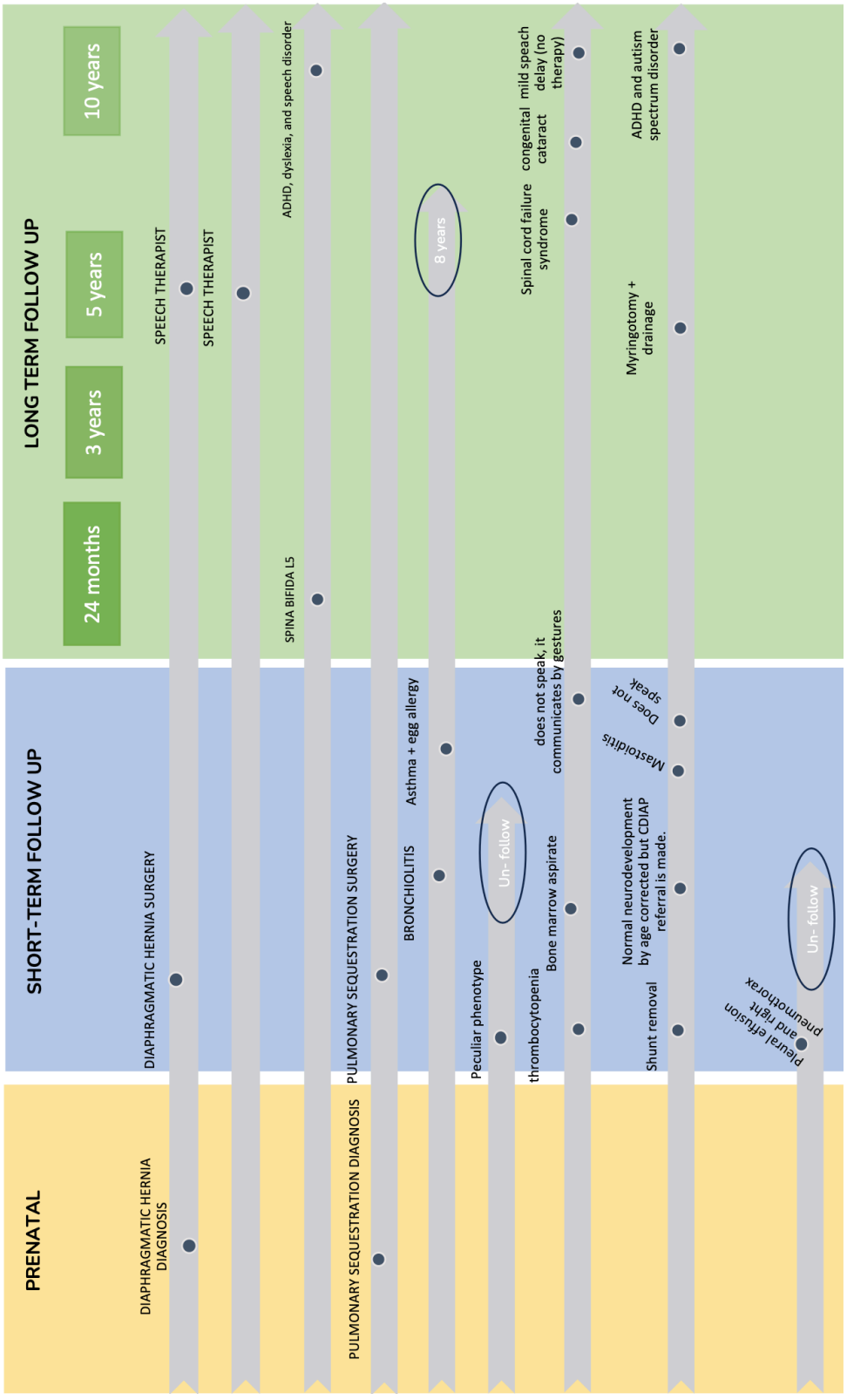
Variable		***Value***
Survival	*N= 25*	
TOP		2 / 25 (8.0%)
Neonatal death		6 / 25 (24%)
Unfollow		4 / 25 (16%)
Survival after neonatal period		11 / 25 (44%)
IUD		2 / 25 (8.0%)
GA at birth		34.2 $\pm$ 5.3
Unknown		4
Weight at birth (kg)		2.416 $\pm$ 0.771
Unknown		9
Apgar 1 minute		5.25 $\pm$ 3.75
Unknown		5
Apgar 5 minutes		6.2 $\pm$4.3
Unknown		5
Apgar 10 minutes		5.0 $\pm$4.7
Unknown		13
Additional diagnosis		
Congenital chylothorax		2 / 17 (11.7%)
Need for respiratory support		8 / 17 (47.05%)
Need for surgery		2 / 17 (11.76%)
Type of surgery		
Diaphragmatic hernia		1 / 2 (50%)
Pulmonary sequestration		1 / 2 (50%)
Additional morbidity		6 / 17 (35.29%)

Data are represented as mean +/- SD, n (%). IUD = Intrauterine death. TOP = Termination of pregnancy. GA= gestational age

SUPPLEMENTARY FIGURE 1. Additional findings through the follow up.

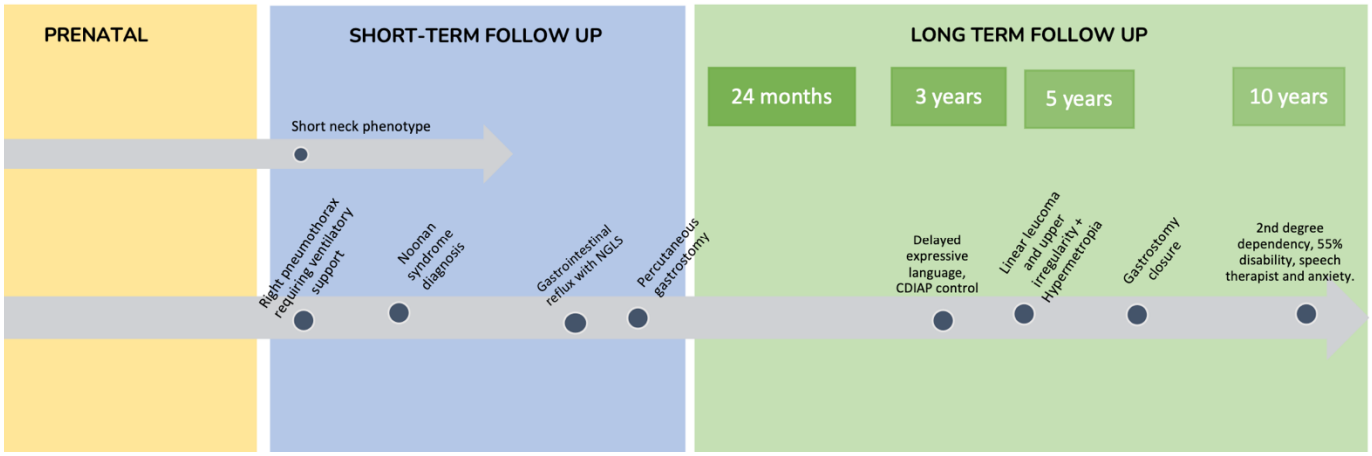


SUPPLEMENTARY FIGURE 2. Non hydropic fetuses follow-up



CDIAP= Early Childhood Development and Care Centers. ADHD = Attention-Deficit/Hyperactivity Disorder

SUPPLEMENTARY FIGURE 3. Hydropic fetuses follow-up.



NGLS: nasogastric tube. CDIAP= Early Childhood Development and Care Center