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THE DIAGNOSIS AND TREATMENT OF THE NONIMMUNE HYDROPS FETALIS

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Fetal hydrops is associated with two distinct pathophysiologic situations. The isoimmune hydrops fetalis is a well understood disorder, and as the result of medical advances and prophylactic therapy its frequency is diminishing. The nonimmune hydrops fetalis is a poorly understood disease with a bad prognosis. The two disorders can be differentiated with the indirect Coombs test. In both cases the ultrasound examination plays an important role in the diagnosis, prognosis and management.

Examination of the fetal blood sample gives recently a possibility to approach the disease. In NIHF the examination of fetal blood sample would give a relatively quick and effective diagnosis but its value for the treatment is limited.

Although with the present technology it is impossible to diagnose all cases of NIHF, the early recognizing, the careful and step by step investigation, the active perinatologic management mostly can show the etiology and can help the perinatal team at the treatment of the disease.

Abbreviations
NIHF = nonimmune hydrops fetalis
IIHF = isoimmune hydrops fetalis
TORCH = toxoplasma, rubeola, cytomegalis herpes

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INTRODUCTION

The latin term "hydrops fetalis" means an excessive fluid accumulation into the extravascular compartment and the body cavities, leading to the development of anasarca, ascites, pleural or pericardial effusion. The hydrops is called "nonimmune" if there is no feto-maternal blood group incompatibility, therefore the haemolysis of fetal red blood cells and the anaemia of the fetus are not the result of a maternal IgG antibody response.

Though Ballantyne wrote about the heterogeneity of the conditions of fetal hydrops about 100 years ago /2/, Potter was the first who made acquainted in details with the nonimmune hydrops fetalis (NIHF) disease /30/.

Because in Hungary the description of this disease has not been described until now - probably because of the rare occurrence - we aimed to survey the material of the Department and review the experiences with the NIHF.

PATIENTS AND METHOD

In the Department of Prenatal Diagnostic and Therapy of the University Bonn 402 cases were diagnosed prenatally in the last 9 years. After the ultrasound examination the first step was to determine the maternal anti-D titers (indirect Coombs antibody screen) to exclude the diagnosis of the isoimmune hydrops fetalis (IIHF). After this step in a logical sequence (later detailed) from the noninvasive methods to the use of the invasive techniques, it would be possible to reach the correct diagnosis in most of the cases.

Frequency

Until recently the disease was very rare. However, with the introduction of the anti-D IgG gamma globulin the cases of

isoimmunization decrease parallel with an increasing percentage of hydropic patients from other causes /1/. With the general use of the ultrasound examinations a lot of NIHF cases were diagnosed earlier registered as unexplainable intrauterine death. In Norfolk (USA) the ratio of the NIHF to IIHF was 9 to 1 in 1986 /36/. In the Australian population the incidence of NIHF is one out of 3538 newborns /24/, while one newborn out of 2566 deliveries in the Los Angeles area /25/.

By the examination of the etiology of the nonimmune hydrops fetal cases, Holzgreve et al classified as idiopathic 50 percentage /16/, while others classified 80-85 percentage as idiopathic /15, 16, 18/.

DISCUSSION

Etiology

Numerous causes of NIHF have been described /16/. The possible causes of NIHF in the literature data as well as in our own experiences are summarized in Table.

Diagnosis

The usual presentation of the NIHF is polyhydramnion or a decreased fetal body movement leading to an ultrasound examination and discovery of NIHF. Most frequently the diagnosis is made by ultrasound requested for routine or another cause.

The most striking sign is the ascites. The most characteristic picture of the ascites is a large amount of intraabdominal fluid and the free floating or compressed bowel (Figure 1). With a good equipment it is possible to detect the fetal ascites as little as 100 ml /8/. The judgement of the punction of the ascites is ambiguos. According to the general opinion the punction of ascites during pregnancy is unlucky, because of a rapid reaccumulation. However, just before the

TABLE

Diseases playing role in the developing of nonimmune hydrops fetalis

A./ Maternal disease
- diabetes mellitus
- EPH gestosis
- severe anaemia

B./ Placental causes
- umbilical vein thrombosis
- chorionangioma
- true cord knots

C./ Fetal causes

1. Cardiovascular
   - severe congenital heart disease (atrial septal defect, interventricular septal defect, hypoplastic left heart, pulmonary valve insufficiency, Ebstein's anomaly, aortic stenosis)
   - premature closer of foramen ovale
   - myocarditis
   - large atrioventricular malformation
   - tachyarrythmias: atrial flutter, supraventricular tachycardia
   - bradyarrythmias
   - tumor of the heart
2. Haematologic
   - homozygous alpha thalassaemia
   - chronic feto-maternal transfusion
   - twin-to-twin transfusion
   - multiple gestation with parasitic fetus
3. Chromosomal
   - trisomy 21
   - Turner's syndrome
   - triploidy
   - mosaicism

Table continued

4. Pulmonary
   - cystic adenomatoid malformation of the lung
   - pulmonary lymphangiectasia
   - pulmonary hypoplasia
   - congenital chylothorax
5. Renal
   - congenital nephrosis
   - renal vein thrombosis
   - spontaneous bladder perforation
6. Intrauterine infections
   - syphilis
   - toxoplasmosis
   - leptospirosis
   - Chagas disease
   - congenital hepatitis
   - herpes simplex
7. Congenital anomalies
   - achondroplasia
   - thanatophic dwarfism
   - sacrococcygeal teratoma
   - Francois's syndrome (Tip.III.)
   - artogryposis multiplex congenita
   - McKusik-Kaufmann's syndrome
   - Smith-Lemli-Opitz's syndrome
8. Miscellaneous
   - meconium peritonitis
   - fetal neuroblastomatosis
   - tuberous sclerosis
   - small-bowel volvulus

D./ Idiopathic cause

delivery it would be useful to decompress the fetal abdomen and to allow vaginal delivery. This procedure would be useful for

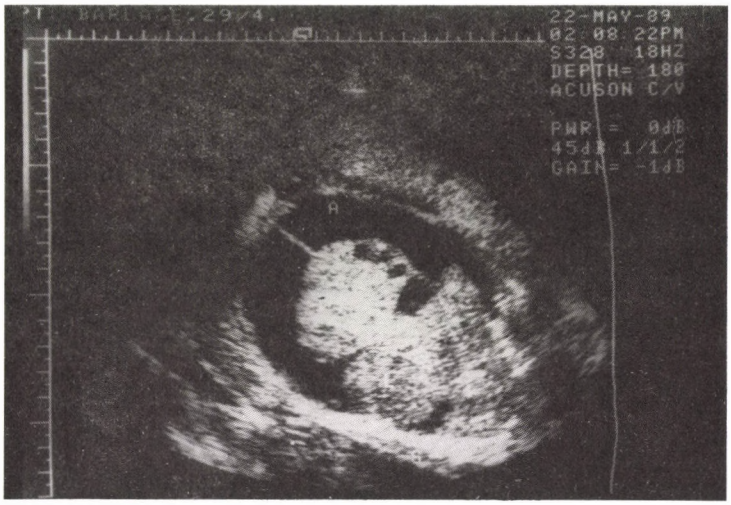

Fig. 1. Ascites in the 29th week of pregnancy.
A cross section of fetal abdomen can be seen on the picture. Under the liver (L) the compressed bowels (I) can be observed. Abdominal cavity is filled up with ascites (A) (S=spine)

the newborn after the delivery, too, as to impair diaphragmatic motion and lung compression, and to achieve spontaneous respiration in the newborn. Ascites and hydrothorax are frequently a common symptom of NIHF (Figure 2).

The pericardial effusions (Figure 3) and the hydrothorax (Figure 4) can also be easily visualized, and can occur isolated or as a part of the generalized hydrops.

With a fetus with generalized hydrops, the outer margins of the edematous tissue over the fetal head, neck, thorax and abdomen are thick, sometimes giving a halo in sonographic cross sections (Figure 5). Sometimes it is possible to diagnose the skin edema in the first trimester of pregnancy (Figure 6).

By experience the increasing ascites and the generalized edema are very bad signs, the fetal outcome is very bad. When at the examination of the fetal anasarca the generalized skin thickness is 5 mm or more, it is in most cases an ante finem stage.

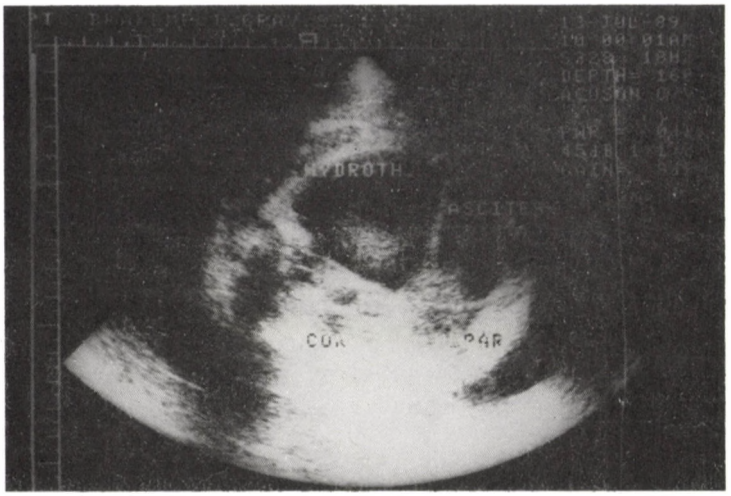

Fig. 2. Hydrothorax and ascites in the 31st week of pregnancy. Excessive fluid can be observed both in the thorax and in the abdominal cavity (hydroth., ascites). The compressed lung and the fetal heart (cor) can be observed beside the hydrothorax and the liver (hepar) can be observed beside the ascites

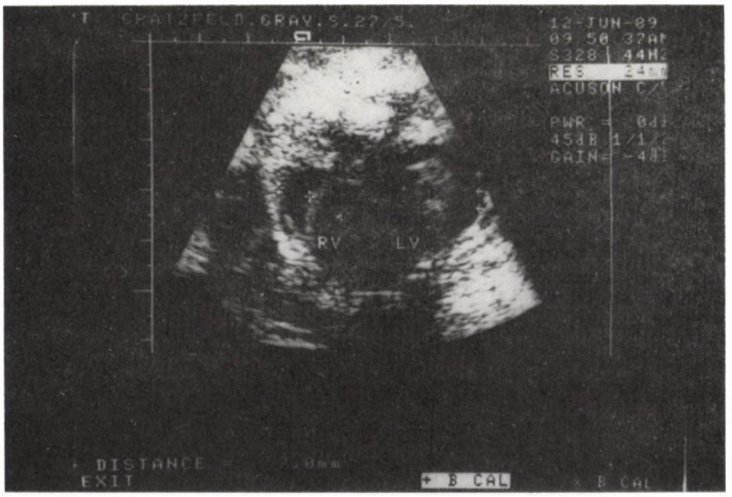

Fig. 3. Pericardial effusion in the 27th week of pregnancy. The right ventricule (RV) and the left ventricule (LV) can be observed on the picture. The crosses indicate 7 mms thick fluid on the right side and on the left side marked by arrow there is a thicker effusion

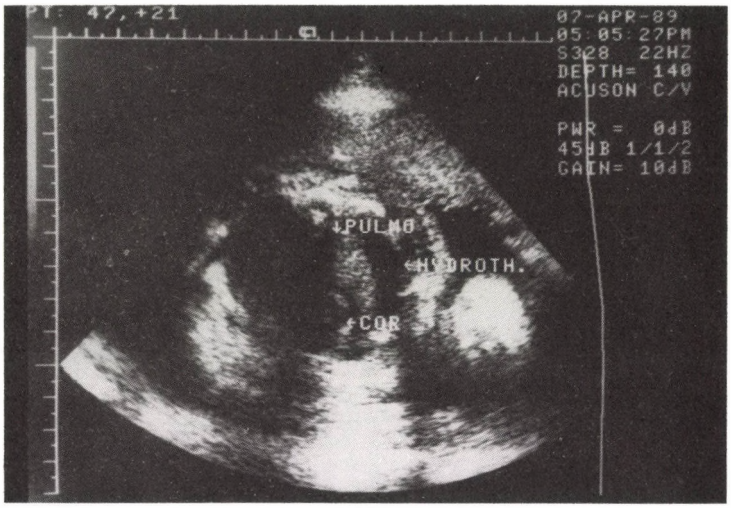

Fig. 4. Two sides hydrothorax in the 25th week of pregnancy. The compressed lung (pulmo) on both sides of the cross section of the thorax and on the left side the fetal heart (cor) can be seen. The pathological fluid volume (hydroth.) can be seen very well on the both sides

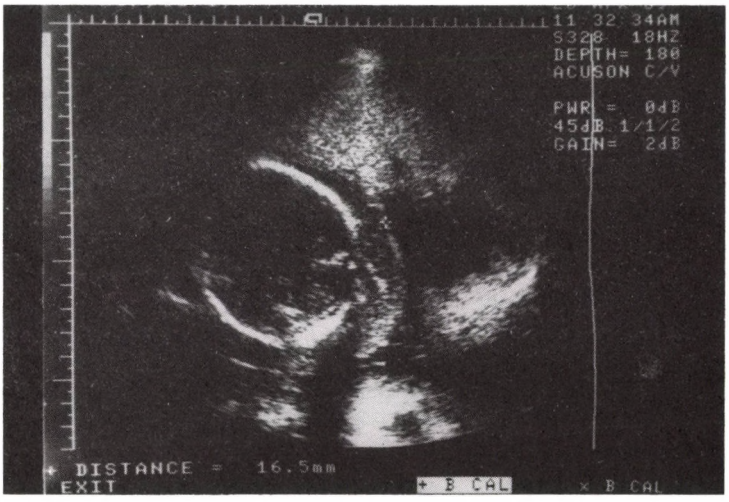

Fig. 5. Skin edema in the 30th week of pregnancy. Around the fetal head like a "halo", about 1.5 cm thick edema would be seen (sign with +)

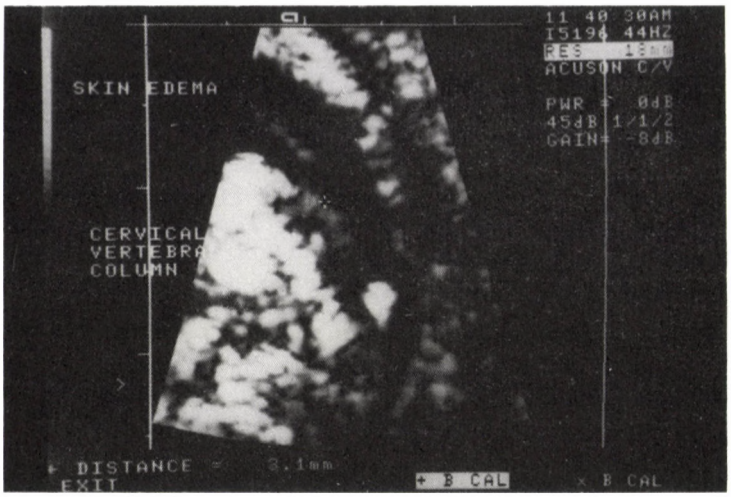

Fig. 6. Skin edema in the 13th week of pregnancy.
3 mm edema can be observed at the cervical cerebral column of the fetus (sign with +)

Though it is impossible to differentiate between NIHF and IIHF by ultrasound alone, the cardinal symptoms of NIHF in the second trimester are the anasarca, ascites, hydrothorax. These symptoms occur by an IIHF only in the final stadium of the fetus.

If the hydrops is recognized, the first step is to clear up if the diagnosis is IIHF or NIHF. For this question the indirect antibody screening will immediately give answer. If it is negative, the possible causes must systematically be examined in a logical order. It is very important to go on from the less invasive methods to the more invasive ones emphasized also in the literature by the authors /14, 15, 39/.

The first step is the examination of the maternal blood sample. A complete blood count, haemoglobin electrophoresis, blood chemistry (serum glucose level for the exclusion of diabetes mellitus), Kleihauer-Betke test (exclude the fetomaternal transfusion), VDRL (because of the maternal disease can cause a fetal infection and this can be a cause of the NIHF), Torch titer examination (Toxoplasma, Rubeola,

Cytomegalia, Herpes), excluding the paravirus infection, specific enzyme deficiencies in the fetus can be suggested by determination of the glucose-6-phosphate dehydrogenase and pyruvat kinase levels of maternal erythrocytes. The examination of maternal serum AFP level is suggested, too.

A complete blood count with red blood cell indices should be obtained on both parents, to search for heterozygous alpha-thalassemia.

At those patients, where the NIHF is reccurent or it was impossible to detect the cause, parental HLA typing must be done. Warsof et al have written two cases of idiopathic NIHF in which the parents have similar HLA alleles /37, 38/. The idea is that in these cases the common fetal and maternal HLA haplotypes derange the normal immunologic responses and the NIHF devepoled secondary to an abnormal maternal immunologic response against her fetus.

Among the examinations the ultrasound can be counted as the most important noninvasive method. The fetal anatomical developing status must be determined very precisely. The congenital anomalies must be recognised. The fetal skin thickness has to be measured. Very important is the real-time echocardiography (2-DE examination, M-mode examination, Doppler colour-examination), to exclude arrhythmias, anatomical disorders of the heart and of the great vessels. The diagnosis of lethal (uncorrectable) anatomic heart lesions, or complete heart block gives the possibility of interruption of the pregnancy in the second trimester.

The placental thickness must be measured. Polyhydramnion may cause a thinning of the placenta which means, if in the third trimester of the pregnancy a normal thickness of the placenta could be measured (3.0 to 4.5 cm), the placenta is likely edematous /36/.

Invasive methods are the examination of amniotic fluid by amniocentesis, the examination of fetal blood sample by chordocentesis and the transabdominal placental biopsy.

By the examination of the amniotic fluid it is possible to do a chromosomal analysis (duration 2-4 weeks), clear up the aneuploidia, it is possible to exclude the specific enzyme

deficiency of amniotic fluid cells or the cytomegaly viral infection, respectively.

From the fetal blood sample the total blood count, the blood chemistry (albumin, total protein, enzymes and so on), the Torch specific IgM could be determined /17, 20, 24, 26, 28, 39/. Karyotyping can also be done in 2-4 days from fetal lymphocytes.

The fastest method for rapid karyotyping which can reveal cytogenetic results on the day of the sampling procedure is the transabdominal placenta biopsy with direct cytogenetic preparation /16, 17/.

According to the literature /16/ a general perinatal examination (maternal serological, ultrasound, echocardiography, amniocentesis, fetal blood sampling) and examination after delivery (genetics, X-ray examination of the skeletal system, to recognise an achondrogenesis, serologic and metabolic examination) lead in most of the cases (85 %) to a diagnosis /15, 16/. According to Hutchinson et al /18/ with a very profound examination, 80 % of the NHF cases could be diagnosed at about the 28th week of pregnancy.

Prognosis

Despite of the recent advances the fetal prognosis in the NIHF is generally poor, especially when we do not know the cause. In a recent study of the King's College Hospital (London) in 30 pregnancies, where fetal arrythmias were excluded, the survival was only 10 % /28/. Other reports have written 75-90 % perinatal loss /16/. The survival was more frequent in cases where it was possible to convert the cardiac arrythmia and the hydrops disappeared.

After 21 examinations Castillo et al found that the prognosis of the NIHF is especially poor when fetal malformation and/or pleural effusion can be detected with ultrasound /7/.

In the literature the perinatal mortality rate is between 50 % /10/ and 98 % /18/, which depends on the distribution of the etiologies in the different groups.

Recurrence of NIHF is fortunately very rare /10, 22, 23/. In

those cases in which a cause is determined, the recurrence risk is that of the disease. In the further pregnancies the survival has a good chance, in one case there were three /10, 32/ survivors.

Treatment

Management must be individualized. The most important point in the control of the treatment's efficiency is the repeated ultrasound examination. So, it is possible to check the progress or regress of the disease. Furthermore, it is very important to check the number of fetal body movements and to make cardiotocography. Medical and surgical treatment must be considered individually.

The arrythmia must be identified and treated. Digoxin, quanidin, and procainamid have been used frequently. Arrhythmias must be treated with digoxin, mostly, when the cause of the NIHF is unknown and the delivery is impossible because of the prematurity.

Furosemid would be helpful in the mobilization of excessive fetal fluid.

Ultrasound-guided para- or thoracocentesis would be justified, though the benefit of the procedure is unclear.

If the examination of fetal blood sample showed a hypalbuminaemia of the fetus it is possible to give an albumin infusion into the umbilical vein, though it would be also successful to inject albumin intraabdominally for the fetus /34/.

Preterm delivery may be indicated in some cases, though the treatment of the hydropic newborn has a lot of problems. In most cases, the death of premature infants is caused by pulmonal edema or pulmonal hypoplasy, so peritoneal dialysis can be used to eliminate the excessive fluid from the intravascular and third space caused by a congestive heart failure /6/.

Fetal conditions

According to Phibbs et al /29/ the decreased albumin syntesis and the low colloid osmotic pressure could play a role

in the mechanism of hydrops formation in erythroblastosis fetalis, but it is still uncertain whether the hypoproteinemia due to liver dysfunction or the congestive heart failure is the prime pathophysiologic process for the development of NIHF /19, 33/. Nikolaides and Rodeck found hypoproteinaemia in all 40 cases at the examination of fetal blood samples /27/. By the survivors of NIHF the total protein and albumin were in the normal range /21/.

One of the causes of NIHF could be the obstruction of venous return /12/ but also the obstruction of the lymph flow (e.g Turner's syndrome, congenital lymphedema).

In twin pregnancies as a result of the pathological blood flow situation between the fetuses (twin-transfusion syndrome), NIHF developed in the donor twin, because of the secondary anaemia that causes a congestive heart failure /3, 9/.

Maternal conditions

Holzgreve et al /16/ found after the examination of 103 cases the following maternal complications associated with NIHF: EPH gestosis (12 cases), severe anaemia (4 cases), hypalbuminaemia (7 cases), postpartum haemorrhage with difficult delivery of the placenta (6 cases).

According to one paper /13/, which overviews 26 cases, hypalbuminaemia was found in 67 % and pregnancy induced hypertension was found in 46 %.

The presence of polyhydramnion is very frequent /31/, it can be observed in 50 % of the cases /16/, but in one case oligohydramnion was found.

According to Holzgreve et al /16/ there was no teratogenic exposure in the examined groups.

Feto-maternal haemorrhage /35/, or a massive haemorrhage in the in utero closed space (e.g.premature placental abruption) could be the cause of the NIHF /4/.

Differential diagnosis

The diagnosis of fetal ascites and of the generalized edema with ultrasound is usually not difficult, but sometimes there are some differential diagnostic problems, e.g.hygroma colli or

a big intraabdominal cystic structure.

Cystic hygroma colli is easy to diagnose with ultrasound /11/, it is also described in Turner'syndrome, trisomy 21 and other chromosome aberrations. By Brock et al /5/ the mistakenly punctured cystic hygromas fluid can be distinguished from the amniotic fluid by the measurement of alkaline phosphatase (ALP) isoenzymes.

The persistent cloaca syndrome is an important differential diagnostic problem. The typical ultrasound picture of this disease is the multiple thin-walled cysts of different size which have to be differentiated from the ascites by visualising the free floating bowels. The most cases of fetal common cloaca are associated with other serious congenital anomalies.

RESULTS

On the basis of the analyses of 402 cases - similar to the literature data - extremely great number of possible causes of NIHF were found:

1./ Cardiovascular disease was the most frequent cause of NIHF (90 of 402 - 22.8 %). The survival in this group was generally poor (17 of 90), except where tachyarrhytmia was diagnosed and where it was possible to treat it (12 of 21).

2./ Chromosomal disorder was the cause of NIHF in 54 cases (11.7 %). In this group only 3 newborns survived, their diagnosis was set up after the 24th week of pregnancy. In 36 cases, in which pathological karyotypes were recognized before the 24th week of pregnancy, all of the pregnancies have been interrupted.

When the NIHF joined to hygroma colli (11.7 %) the survival was very poor, even when the karyotype was normal. 1 of 48 survived with a little hygroma colli and minimal ascites with a normal karyotype.

3./ If the cause of the NIHF was haematologic (either feto-maternal of feto-fetal transfusion) the survival rates were only 9.7 % (10 out of 39). The possible treatment is the

intrauterine transfusion and the transplacental digitalisation.

4./ In 11 cases (2.7 %) it was possible to identify the intrauterine infection with the examination of fetal blood sample. There were only 2 survivors.

5./ In 23 fetuses the diagnosis was hydro-, chylothorax. If there was no chromosomal disorder the survival rate was very high (13 of 16 newborns). In 7 cases the diagnosis was 21 trisomy (survival rate was 1 out 7). For facilitating the postnatal resuscitation it was in all these cases necessary to make a therapeutic thoracocentesies before the delivery.

6./ All of the 18 fetuses with isolated ascites (4.5 %) survived. In 15 cases the ascites spontaneously disappeared in utero.

7./ There were different etiologies in 98 cases (24.3 %). In this group the diagnoses were gastrointestinal, urogenital disorder or malformation syndromes. The survival rate was very poor, 12 out of 98.

8./ In 47 cases the diagnosis was idiopathic NIHF (11.7 %), and only 1 newborn has survived.

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