

# Nonimmune Hydrops Fetalis

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## DEFINITION

Hydrops fetalis is generally classified either immune or nonimmune hydrops. Nonimmune hydrops fetalis implies an excess of total body water, which is usually evident as extracellular accumulation of fluid in soft tissues and serous cavities of the fetus without any identifiable circulating antibody against red blood cell antigen.

## INCIDENCE

Many earlier papers have been reported Rh incompatibility as a reason of hydrops fetalis in 80 percent of all cases but with the decreasing frequency of Rh isoimmunization (the introduction of Rh D immune globulin prophylaxis), nonimmune hydrops fetalis becomes a relatively more frequent kind of hydrops. Nonimmune hydrops fetalis has been reported with an incidence of 1 in 2 500 to 1 in 4 000 deliveries.<sup>1-4</sup>

## ETIOLOGY

Although the list of disturbances which can cause nonimmune hydrops fetalis is not short, in about 30 to 60 percent of fetuses nonimmune hydrops fetalis is an idiopathic condition, and cause can be elicited.<sup>5,6</sup> The causes of nonimmune hydrops fetalis are numerous, and are classified in three groups: maternal, fetal and placental.

According to Holzgrev 1984, the most frequent cases are: congenital heart anomalies in 23 percent, chromosomal abnormalities in 15 percent, recognized syndromes in 10 percent. Pulmonary anomalies in 8 percent, renal and gastrointestinal abnormalities in 7 percent. In 4 percent she found infectious etiology, and as a most frequent causes she quoted *Toxoplasma gondii*, rubella, cytomegalovirus<sup>7</sup> and herpes simplex type I (TORCH), and parvovirus B-19.<sup>8,9</sup> Table 1 is an outline of conditions associated with the presence of nonimmune hydrops fetalis. For some of these, a direct pathophysiologic mechanism has been postulated, whereas in others, a mere association has been reported without implying a causal relationship.

### Hematologic Causes

The common hematologic cause of nonimmune hydrops fetalis is fetal anemia which can be result of hemolysis, fetal blood

loos, hemoglobinopathies, monozygotic twins with twin-to-twin transfusion, feto-maternal transfusion, congenital xerocytosis<sup>10</sup> and alpha- and beta-thalassemia.

*Twin-to-twin transfusion:* Although the traditional concept has been that recipient infant is the one to become hydropic, hydrops fetalis has also been reported in the donor twin.<sup>11,12</sup> Twin-to-twin transfusion can be suspected antenatally in presence of a weight difference greater than 20 percent of the weight of the larger twin and with single placenta. The mechanism for development of hydrops has not been clearly established. Anemia has been suggested as the etiology of nonimmune hydrops fetalis in the donor, although the extent of the hydrops is greater than that observed in isoimmunized infants with comparable hemoglobin levels. Volume overload may be the explanation of hydrops in the recipient.<sup>13</sup>

*Alpha-thalassemia* is due to the absence of one or more of the genes controlling the synthesis of alpha-chains. Consequently, no hemoglobin F or A can be produced with formation of tetramers which have a higher affinity for oxygen than hemoglobin F- so high that it does not release its oxygen to fetal tissues sufficiently. Fetal tissue hypoxia leads to a high output cardiac failure state and hydrops fetalis.<sup>14</sup>

### Cardiovascular Causes

Cardiovascular problems are relatively common causes of nonimmune hydrops fetalis, accounting about 40 percent of all cases.<sup>15</sup> The most common causes are: congenital cardiac abnormalities (tetralogy of Fallot, ASD, VSD, hypoplasia of cordis, subaortal stenosis), dysrhythmia, vascular tumors, arteriovenous malformations, thrombosis of the inferior vena cava, cardiac fibroelastosis calcifications in the pericardial sac (caused by intrauterine coxsackie B<sub>3</sub> infection).

### Infectious Causes

Nonimmune hydrops fetalis is associated with a big number of viral, bacterial and spirochetal organisms without any clear pathophysiologic mechanisms. With good documentation are available care reports of toxoplasmosis,<sup>16</sup> parvovirus,<sup>17</sup> cytomegalovirus,<sup>18</sup> coxsackievirus,<sup>19</sup> and syphilis.<sup>20</sup>

**Table 1:** Causes and conditions associated with nonimmune hydrops fetalis**MATERNAL**

- Anemia (due to blood loss or pure red cell aplasia)
- Pre-eclampsia
- Hypoalbuminemia
- Diabetes mellitus

**PLACENTAL**

- Chorioangioma
- Umbilical vein
- Compression, torsion of umbilical cord

**FETAL**• **Hematologic causes**

- Twin-to-twin transfusion
- Chronic fetomaternal transfusion
- Homozygous alpha- thalassemia

• **Cardiovascular causes**

- Congenital cardiac abnormalities (tetralogy of Fallot, ASD, VSD, hypoplasia cordis, subaortal stenosis), dysrhythmia
- Vascular tumors
- Arteriovenous malformations
- Vena cava inferior thrombosis
- Endocardial fibroelastosis calcifications in the pericardial sac
- Myocarditis (Coxsackie, CMV, parvovirus B-19)

• **Infectious causes**

- Toxoplasmosis
- Parvovirus B-19
- Cytomegalovirus hepatitis, myocarditis
- Coxsackievirus
- Syphilis
- HSV
- Leptospirosis.

• **Renal disorders**

- Congenital nephrotic syndrome with hypoproteinemia
- Obstructive uropathy
- Polycystic kidney disease
- Hydrometrocolpos
- Hypoplastic kidney
- Prune-belly syndrome

• **Gastrointestinal disorders**

- Diaphragmatic hernia
- Midgut volvulus
- Gastrointestinal obstructions
- Meconium peritonitis
- Hepatic disorders such as cirrhosis and necrosis.

• **Chromosomal abnormalities**

- Trisomies 21,18,13
- Mosaicisms

*Contd...*

- Unbalanced translocation and triploidy
- Turner's syndrome
- **Metabolic disorders**
  - Cerebrosidosis (Gaucher's disease)
  - Gangliosidosis GM1 type I
  - Mucopolysaccharidosis
  - Mucopolipidosis
- **Pulmonary causes**
  - Congenital adenomatoid malformation
  - Pulmonary lymphangiectasia
  - Pulmonary leiomyosarcoma
  - Diaphragmatic hernia
  - Alveolar cell adenoma of the lung

**Renal Disorders**

Congenital nephrotic syndrome with hypoproteinemia is a cause of nonimmune hydrops fetalis as another abnormalities of the urinary tract, such as obstructive uropathy, polycystic kidney disease with hydrometrocolpos, hypoplastic kidney.<sup>5,11,21</sup>

**Gastrointestinal Disorders**

A big number of gastrointestinal disorders are associated with hydrops fetalis: diaphragmatic hernia, midgut volvulus, gastrointestinal obstructions, meconium peritonitis, hepatic disorders such as cirrhosis and necrosis.<sup>5</sup> The common mechanism in developing of hydrops can be hypoproteinemia.

**Chromosomal Abnormalities**

Nonimmune hydrops fetalis is reported in association with many genetic abnormalities such as trisomy 21, trisomy 18, trisomy 13, mosaicisms, unbalanced translocation and triploidy. Turner's syndrome is one of the most common causes of nonimmune among chromosomal abnormalities associated with hydrops.<sup>22</sup> In this syndrome there is a lack of communication between the lymphatic system and venous drainage in the neck. Infants have also lymphoedema of the hands and feet as well as chylothorax, giving a picture resembling hydrops fetalis.

**Metabolic Disorders**

The metabolic derangements associated with nonimmune hydrops fetalis involves either synthesis or storage disorders. The storage diseases that have been reported could be cerebrosidosis (Gaucher's disease), gangliosidosis GM1 type I, mucopolysaccharidosis and mucopolipidosis. But it is unclear if these metabolic diseases are associated with nonimmune fetal hydrops or simply with soft tissue excess that leads to gross appearance resembling hydrops.

*Contd...*

**Table 2:** Nonimmunologic hydrops fetalis—sonographic characteristics

*Sonographic signs of nonimmune hydrops fetalis*

1. Polyhydramnios
2. Placental edema—more than 4.5 cm
3. Dilatation of fetal umbilical vein
4. Edema of the head, neck, thorax and abdomen
5. Fetal ascites
6. Pericardial effusion
7. Pleural effusion
8. Anasarca (more than 5 mm)

**Pulmonary Causes**

Many pulmonary lesions can cause nonimmune fetal hydrops, and the most frequent are congenital adenomatoid malformation,<sup>23</sup> pulmonary lymphangiectasia, pulmonary leiomyosarcoma,<sup>24</sup> diaphragmatic hernia, alveolar cell adenoma of the lung.

**DIAGNOSIS**

The diagnosis of hydrops is easy. The method of the choice, the best and the easiest way to diagnose nonimmune fetal hydrops is the sonographic examination. Advances in ultrasonography (pulsed Doppler, color Doppler, power Doppler) have made the diagnosis of these defects possible early in gestation. For this reason, in all cases of fetal hydrops, an ultrasound study is necessary (Table 2).

Excessive body fluid accumulation can be seen as subcutaneous edema (skin thickness > 5 mm), pleural or pericardial effusion, ascites, polyhydramnios, or placental enlargement (more than 6 cm) and hemodynamics features. Pericardial



**Fig. 1:** Cross-section of the fetal trunk shows subcutaneous edema



**Fig. 2:** Hydrops fetalis. Edema of the fetal upper leg



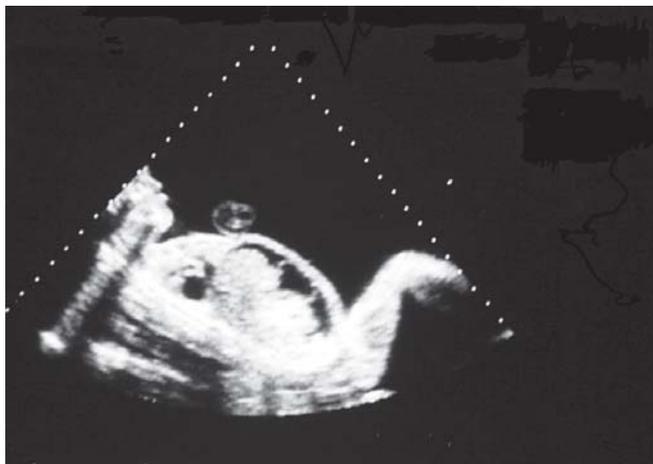
**Fig. 3:** Ascites in the area of the liver. Ascites (A), spine (SP)

effusion and pleural effusion are easy noticeable by ultrasound examination, and can appear with general hydrops or as an isolated finding<sup>24</sup> (Figs 1 and 2).

Subcutaneous edema is defined as skin thickness more than 5 mm and is sign of final stage of hydrops.

Fluid accumulation must involve more than one site before the diagnosis of hydrops be stated. When the fluid accumulation is limited to only one place, the situation should be described in terms of involved site. The first place to show excessive fluid accumulation may vary with the cause of the hydrops as in case of cystic adenomatoid tumor of the lung.<sup>25,26</sup> Therefore, depending on when the fetus is examined, it may be possible to detect excessive fluid accumulation in a single site before it becomes generalized (Fig. 3).

Pericardial effusion may be also the first sign of fluid overload. This is probably due to the volume limitation of



**Fig. 4:** Ascites. Sagittal section of the fetal trunk



**Fig. 6:** Fetal hydrops. Anechoic area surrounds the fetal liver



**Fig. 5:** Edema of the fetal skull



**Fig. 7:** Hydrothorax

pericardial cavity in contrast to ease of fluid distribution within the pleural or abdominal cavity (Fig. 4).

In systematic conditions (e.g. anemia), fluid accumulation tends to be more evenly distributed and can be detected simultaneously in multiple sites. Many important factors as lymphatic drainage, venous return, surface area and potential volume of serous cavities, and accessibility to ultrasound evaluation, effect the detection of fluid accumulation with ultrasound (Fig. 5).

Many cases of isolated ascites have been described and caused in most cases by meconium peritonitis and viral infections (Cytomegalovirus).

Polyhydramnios is defined as quantity as more than 1500 to 2000 ml of amniotic fluid in third part of pregnancy. Polyhydramnios is associated with hydrops fetalis in about 75

percent of cases.<sup>12</sup> When polyhydramnios is detected, incipient hydrops fetalis should be excluded by careful examination of the fetal serous cavities. In some cases, the amount of fluid can be so massive as to preclude appropriate visualization of the fetus with real-time ultrasound because the fetus is beyond the depth field of the transducer.

In the cases with generalized hydrops fetus we examine outer borders of head tissue, region of the neck, thorax and abdomen (Figs 6 to 10).

The moderate quantity of fetal ascites can be easily visible at the border of the liver, and a huge quantity between bowels.

## PROGNOSIS

Although some cases of spontaneous intrauterine remission of nonimmune hydrops fetalis are described in the literature,<sup>27-32</sup>



Fig. 8: The example of the severe fetal ascites



Fig. 9: Sagittal section of the fetus—severe ascites

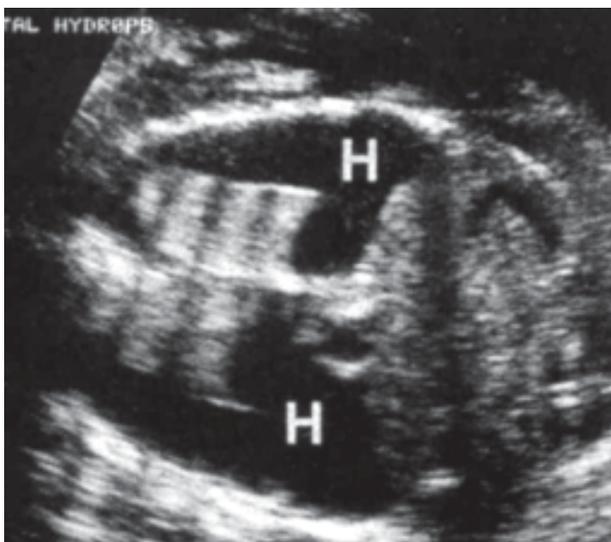


Fig. 10: Hydrops fetus—hydrothorax with hypoplasia pulmonum (H)

the prognosis for the majority of these infants is very bad. Perinatal mortality in cases of nonimmune fetal hydrops rises to 50 to 98 percent,<sup>33-35</sup> so only early recognition and perinatal approach can improve already bad prognosis.<sup>5</sup> However, prognosis of hydrops fetus is improved in selected group.<sup>36,37</sup> Cardiac dysrhythmias amenable to transplacental medical therapy usually carry a good prognosis, provided they are not associated with a serious congenital anomaly. The same situation is in cases in cases with fetomaternal hemorrhage, which may be treated with intrauterine transfusion.<sup>38</sup>

## REFERENCES

1. Maidman JE, Yeager C, Anderson V. Prenatal diagnosis and management of nonimmunologic hydrops fetalis. *Obstet Gynecol* 1980;56:571.
2. Schwartz SM, Visekul C, Laxova R. Idiopathic hydrops fetalis report of 4 patients including 2 affected sibs. *Am J Med Gen* 1981;8:59.
3. Mostoufi-Zadeh M, weiss LM, Driscoll SG. Nonimmune hydrops fetalis: a challenge in prenatal pathology. *Hum Pathol* 1985;16:785.
4. Platt LD, DeVore GR. *In utero* diagnosis of hydrops fetalis:ultrasound methods. *Clin Perinatol* 1982;9(3):627.
5. Hutchinson AA, drew JH, Yu VYH. Nonimmunologic hydrop fetalis: a review of 61 cases. *Obstet Gynec* 1982;59:347.
6. Latin V, Miškoviæ B. Neimunološki hidrops. U: Kurjak A i sar. (ur). *Ultrazvuk u ginekologiji i porodništvu*. Zagreb: Art studio Azinoviæ, 2000;359-66.
7. Inoue T, Matsumara N, Fukuoka M, Sagawa N, Fujii S. Severe congenital cytomegalovirus infection with hydrops in a cytomegalovirus—seropositive healthy women. *Eu J Obstet Gynecol, Reprod Biol* 2001;95(2):184-6.
8. Holzgrewe W. Management of the fetus with nonimmune hydrops fetalis. In: Harrison MR, Golbus MS, Filly RA, (Eds): *The Unborn Patient: Prenatal Diagnosis and Treatment*. New York: Grune-Straton 1984;193-216.
9. Bhal PS, Davies NJ, Westmoreland D, Jones A. Spontaneous resolution of nonimmune hydrops fetalis secondary to transplacental parvovirus B-19 infection. *Ultrasound Obstet Gynecol* 1996;7:55-7.
10. Vicente-Gutierrez MP, Castello-Almazan I, Salvia-Roiges MD et al. Nonimmune hydrops fetalis due to congenital xerocytosis. *Journal of Perinatology* 2005;25:63-5.
11. Lubinsky M, Rapport T. Transient fetal hydrops and “prune-belly” in one identical female twin. *N Engl J Med* 1983;308: 256.
12. Macafee CAJ, Fortune DW, Beischer NA. Nonimmunological hydrops fetalis. *J Obstet Gynaecol Br Commonw* 1970;77:226.
13. Turkel SB. Conditions associated with nonimmune hydrops fetalis. *Clin Perinatol* 1982;9:613.
14. Chan V, Chan TK, Liang ST. Hydrops fetalis due to an unusual form of Hb H disease. *Blood* 1985;66:224.
15. Allan LD, Crawford DC, Sheridan R. Etiology of nonimmune hydrops: the value of echocardiography. *Br J Obstet Gynecol* 1986;93:223.

16. Bain AD, Bowie JH, Flint WF. Congenital toxoplasmosis simulating hemolytic disease of the newborn. *J Obstet gynecol Br Commonw* 1956;63:826.
17. Brown T, Anand A, Ritchie LD. Intrauterine parvovirus infection associated with hydrops fetalis. *Lancet* 1984;2:1033.
18. Filloux F, Kesley DK, Bose CL. Hydrops fetalis with supraventricular tachycardia and cytomegalovirus infection. *Clin Pediatr* 1985;24:534.
19. Bates HR. Coxsackie virus B3 calcific pancarditis and hydrops fetalis. *Am J Obstet Gynecol* 1970;106:629.
20. Bulova SI, Schwartz E, Harrer WV. Hydrops fetalis and congenital syphilis. *Pediatrics* 1972;49:285.
21. Fleischer AC, Killam AP, Boehm FH. Hydrops fetalis: sonographic evaluation and clinical implications. *Radiology* 1981;141:163.
22. Perlín BM, Pomerance JJ, Schifrin BS. Nonimmunologic hydrops fetalis. *Obstet Gynecol* 1971;57:584.
23. Beischer NA, Fortune DW, Macafee. Nonimmunologic fetal hydrops and congenital abnormalities. *Obstet Gynecol* 1971;38:86.
24. Jones DC. Nonimmune fetal hydrops: diagnosis and obstetrical management. *Am J Obstet Gynecol* 1999;180:148-50.
25. Jimenez JF, Uthman EO, Townsend JW. Primary bronchopulmonary leiomyosarcoma in childhood. *Arch Pathol Lab Med* 1986;110:348.
26. Kurjak A, Marton U. Anomalije dišnog sustava. U: Kurjak A i sur (ur). *Ultrazvuk u ginekologiji i porodništvu*. Zagreb: Art studio Azinoviæ 2000;506-14.
27. Leppert PC, Pahlka BS, Stark RI. Spontaneous regression of fetal ascites *in utero* in an adolescent. *J Adolescent Health Care* 1984;5:286.
28. Ramzin MS, Napflin S. Transient intrauterine supraventricular tachycardia associated with transient hydrops fetalis. *Br J Obstet Gynaecol* 1982;89:965.
29. Robertson L, Ott A, Mack L. Sonographically documented disappearance of nonimmune hydrops fetalis associated with maternal hypertension. *West J Med* 1985;143:382.
30. Shapiro I, Sharf M. Spontaneous intrauterine remission of hydrops fetalis in one identical twin: sonographic diagnosis. *J Clin Ultrasound* 1985;13:427.
31. Treadwell MC, Sherer DM, Sacks AJ, Ghessi F, Romero R. Successful treatment of recurrent nonimmune hydrops secondary to fetal hypothyroidism. *Obstet Gynecol* 1996;87(5):838-40.
32. Megory E, Weiner E, Shalev E, et al. Stuck twin with cotwin nonimmune hydrops: successful treatment by amniocentesis. *Fetal Diagn Ther* 1991;6:126-31.
33. Etches PC, Lemons JA. Nonimmune hydrops fetalis: Report of 22 cases including three siblings. *Pediatrics* 1979;64:326.
34. Gough JD, Keeling JW, Castle B, et al. The obstetric management of non-immunological hydrops. *Br J Obstet gynaecol* 1986;93:226.
35. Im SS, Rizos N, Joutsu P, et al. Nonimmunologic hydrops fetalis. *Am J Obstet Gynecol* 1984;148:566.
36. Stephenson T, Zuccollo J, Mohajar M. Diagnosis and management of non-immune hydrops in the newborn. *Arch Dis Child* 1994;70:151-4.
37. Mc Mahan MJ, Donovan EF. The delivery room resuscitation of the hydropic neonate. *Semin Perinatol* 1995;19:474-82.
38. Romero R, Pihu G, Jeanty P, Ghidini A, Hobbins JC. Prenatal diagnosis of congenital anomalies. Norwalk, Connecticut, San Mateo, California. Appleton and Lange 1988;414-6.