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REVIEW ARTICLE

A Review on Pathophysiology, Clinical Manifestations, and Therapeutic Management of Non-Immune Hydrops Fetalis

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Abstract: Non-immune hydrops fetalis (NIHF) is a fetal condition characterized by abnormal fluid accumulation in two or more anatomical compartments, including the peritoneal cavity, pleural space, pericardial sac, and subcutaneous tissues. While immune hydrops fetalis historically dominated cases due to maternal-fetal Rh incompatibility, the widespread implementation of anti-D immunoglobulin prophylaxis has led to NIHF becoming the predominant form, accounting for 85-95% of cases. The etiology of NIHF encompasses a broad spectrum of pathological conditions, including cardiovascular anomalies, chromosomal disorders, metabolic diseases, infections, and lymphatic malformations. Recent literature on prenatal diagnostic techniques, particularly genetic testing and high-resolution ultrasonography, have enhanced our ability to identify underlying causes and initiate appropriate interventions. The condition presents significant challenges in prenatal management and is associated with considerable perinatal morbidity and mortality rates. Treatment strategies vary based on the underlying etiology and may include intrauterine interventions, medical management, or early delivery in severe cases. Despite improved prenatal care and intervention options, the prognosis remains guarded, with survival rates varying significantly based on the underlying cause, gestational age at diagnosis, and severity of presentation. Long-term follow-up studies indicate that survivors may face various complications, emphasizing the need for comprehensive multidisciplinary care.

Keywords: Non-immune hydrops fetalis; Fetal edema; Prenatal diagnosis; Perinatal outcome; Rh Factor.

1. Introduction

Non-immune hydrops fetalis is a severe fetal condition defined by pathological fluid accumulation in multiple fetal compartments [1]. The diagnostic criteria specifically require the presence of abnormal fluid collections in a minimum of two anatomical spaces, which may include the peritoneal cavity, pleural space, pericardial sac, or subcutaneous tissues [2]. While additional findings such as placentomegaly and polyhydramnios frequently accompany this condition, they are not considered primary diagnostic markers [3]. Prior to the 1970s, immune-mediated causes, particularly those related to Rh alloimmunization, predominated. However, with the advent of Rh(D) immune globulin prophylaxis, non-immune causes now constitute the vast majority of cases, accounting for approximately 90% of all presentations [4]. Current epidemiological data suggests an incidence of 1 in 1,500 to 1 in 4,000 births [5]. This shift in etiology has necessitated a comprehensive reevaluation of diagnostic approaches and management strategies. Non-immune hydrops fetalis (NIHF) represents a heterogeneous condition with over 100 potential underlying causes, encompassing cardiovascular, chromosomal, metabolic, infectious, and structural abnormalities. The pathophysiology involves various mechanisms that ultimately lead to fluid accumulation, including altered fluid dynamics, impaired lymphatic drainage, cardiovascular dysfunction, or decreased oncotic pressure.

Early detection and accurate diagnosis are crucial for optimal outcomes, as the condition carries significant mortality and morbidity rates. Modern prenatal care has incorporated advanced imaging techniques, including detailed ultrasonography and fetal echocardiography, alongside sophisticated genetic testing methods to identify underlying etiologies. This evolving diagnostic capability has enhanced our understanding of the condition's natural history and improved our ability to provide targeted interventions. The prognosis of NIHF varies considerably depending on the underlying cause, gestational age at onset, and severity of presentation. While some cases may resolve spontaneously or respond well to specific treatments, others present significant challenges in both prenatal and postnatal management. This variability underscores the importance of a systematic diagnostic approach and individualized treatment planning.

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The impact of NIHF extends beyond immediate fetal health concerns, affecting maternal well-being and requiring careful obstetric monitoring. The condition may be associated with maternal complications such as preeclampsia, mirror syndrome, and increased risks during delivery. Therefore, management typically requires a multidisciplinary approach involving maternal-fetal medicine specialists, neonatologists, geneticists, and other subspecialists based on the specific underlying etiology. The main aim of this review is to describe the current literature on pathophysiology, clinical manifestations, and therapeutic management of Non-Immune Hydrops Fetailis.

2. Pathophysiology

Hydrops fetalis occurs when the equilibrium between fluid extravasation and lymphatic drainage becomes disrupted, leading to fluid accumulation in various tissue compartments [6]. This disruption can lead to alterations in capillary permeability, changes in plasma protein concentrations, and impairment of lymphatic drainage systems. These disturbances can occur at multiple physiological levels, affecting both local tissue environments and systemic circulation.

2.1. Fluid Dynamics

The maintenance of normal fluid distribution depends on a delicate balance between hydrostatic and oncotic pressures across capillary membranes. The endothelial glycocalyx layer plays a crucial role in regulating this fluid movement, working along with the lymphatic system to maintain appropriate fluid homeostasis [7]. This process involves Starling forces governing fluid movement across capillary membranes, coupled with sophisticated endothelial barrier function and its regulation. The interstitial fluid pressure dynamics work in conjunction with active and passive lymphatic transport mechanisms, while plasma protein concentrations and their distribution play vital roles in maintaining appropriate fluid balance. These components form an interconnected system where disruption of any single element can lead to pathological fluid accumulation.

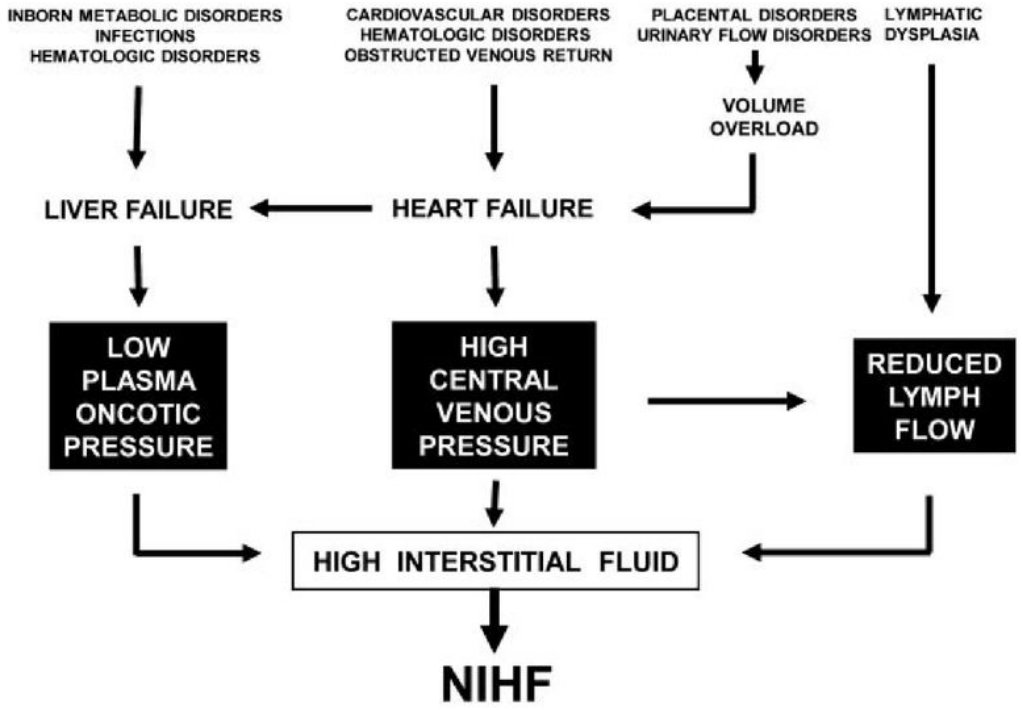

Figure 1. Pathophysiology of NIHF

2.2. Cellular and Molecular Mechanisms

The pathogenesis may also involve interactions between various physiological systems. Disruptions can occur at multiple levels, including:

2.2.1. Cardiovascular Dysfunction

Cardiac anomalies or dysfunction can lead to altered hemodynamics, resulting in increased systemic venous pressure and subsequent fluid extravasation [8]. The cardiovascular manifestations can present through structural heart defects affecting chamber development or function, or through rhythm disturbances impacting cardiac output. Myocardial dysfunction affecting contractility

often compounds these issues, while vascular anomalies can significantly affect blood flow distribution. Furthermore, alterations in peripheral vascular resistance contribute to the complex cardiovascular pathophysiology observed in hydrops fetalis.

2.2.2. Abnormalities in Lymphatic System

Developmental or functional lymphatic disorders can impair fluid drainage, contributing to tissue edema and fluid accumulation in body cavities [9]. The spectrum of lymphatic dysfunction encompasses primary lymphatic developmental defects and secondary lymphatic dysfunction due to increased lymph production. Abnormalities in lymphatic vessel formation can significantly impact fluid homeostasis, while disorders affecting lymphatic transport proteins further compromise normal function. The dysfunction of lymphatic valves and pumping mechanisms represents another critical aspect of lymphatic system involvement in hydrops fetalis.

3. Clinical Classification

3.1. Immune Hydrops Fetalis

Although now less common, immune-mediated hydrops continues to occur in specific circumstances, primarily related to maternal alloimmunization against fetal red cell antigens [10]. Red cell alloimmunization, most commonly involving Rh(D), remains the predominant cause in this category. Platelet antigen incompatibility and other blood group incompatibilities can also trigger immune hydrops. These conditions significantly impact fetal hematopoiesis and circulation, often accompanied by complex inflammatory responses that exacerbate the condition.

Table 1. Classification and Etiology of Non-immune Hydrops Fetalis (NIHF)

Category	Specific Causes
Cardiovascular	Structural heart defects (septal defects, outflow obstruction); Arrhythmias (supraventricular tachycardia, heart block); Cardiomyopathies; High-output cardiac failure
Chromosomal	Turner syndrome (45,X); Trisomy 21, 18, 13; Other aneuploidies
Hematologic	Alpha thalassemia major; Fetomaternal hemorrhage; Parvovirus B19 infection
Lymphatic Dysplasia	Generalized lymphatic dysplasia; Cystic hygromas; Turner syndrome-associated lymphedema
Genetic Syndromes	Noonan syndrome; CHARGE syndrome; Skeletal dysplasias
Metabolic Disorders	Lysosomal storage diseases; Glycogen storage diseases; Peroxisomal disorders
Infectious	Parvovirus B19; CMV; Toxoplasmosis
Miscellaneous	Twin-twin transfusion syndrome; Sacrococcygeal teratoma; Placental causes
Idiopathic	Unknown etiology despite investigation

3.2. Non-immune Hydrops Fetalis

NIHF encompasses a heterogeneous group of disorders affecting multiple organ systems. The condition may arise from cardiovascular, chromosomal, infectious, or metabolic abnormalities [11]. Cardiovascular causes include structural heart defects, arrhythmias, and cardiomyopathies. Chromosomal abnormalities such as aneuploidies, microdeletion syndromes, and various genetic disorders form another significant category. Infectious etiologies span viral, bacterial, and parasitic diseases, while metabolic disorders include storage diseases, mitochondrial disorders, and transport protein defects. Each of these categories presents unique challenges in diagnosis and management.

3.3. Maternal Complications

While NIHF primarily affects the fetus, maternal complications can develop, particularly in cases complicated by mirror syndrome. This condition presents with maternal edema, hypertension, and proteinuria, mimicking preeclampsia [12]. The maternal response involves systemic inflammatory changes and significant alterations in placental function. Hormonal adaptations and cardiovascular modifications occur as the maternal system responds to the fetal condition. These changes can result in significant metabolic adjustments and potential complications for both mother and fetus.

4. Diagnosis

4.1. Prenatal Detection

Modern prenatal diagnosis of hydrops fetalis relies primarily on detailed ultrasonographic examination. The visualization of fluid collections in multiple fetal compartments, along with associated findings such as scalp edema exceeding 5mm, serves as the

cornerstone of diagnosis [13]. Early detection is crucial for optimal management and outcomes. The systematic evaluation includes assessment of all potential fluid collection sites, including the pleural space, pericardial cavity, peritoneal cavity, and subcutaneous tissues. The timing of detection often correlates with prognosis, making regular prenatal screening essential in high-risk cases. Serial examinations allow monitoring of disease progression and response to therapeutic interventions when applicable [13].

4.1.1. Imaging Techniques

Advanced imaging techniques, including fetal echocardiography and magnetic resonance imaging, provide detailed anatomical information and assist in identifying underlying structural abnormalities. These modalities offer superior tissue definition and can reveal subtle anatomical defects that may be missed on routine ultrasonography. Fetal echocardiography plays a particularly crucial role in evaluating cardiac structure and function, as cardiovascular abnormalities represent a significant proportion of underlying causes. Three-dimensional ultrasonography has enhanced our ability to assess complex anatomical relationships and provide detailed evaluation of fetal structures. Magnetic resonance imaging offers complementary information, particularly valuable in cases where ultrasound findings are limited by maternal body habitus or fetal position. This modality excels in soft tissue characterization and can provide superior visualization of the central nervous system and thoracic structures [14].

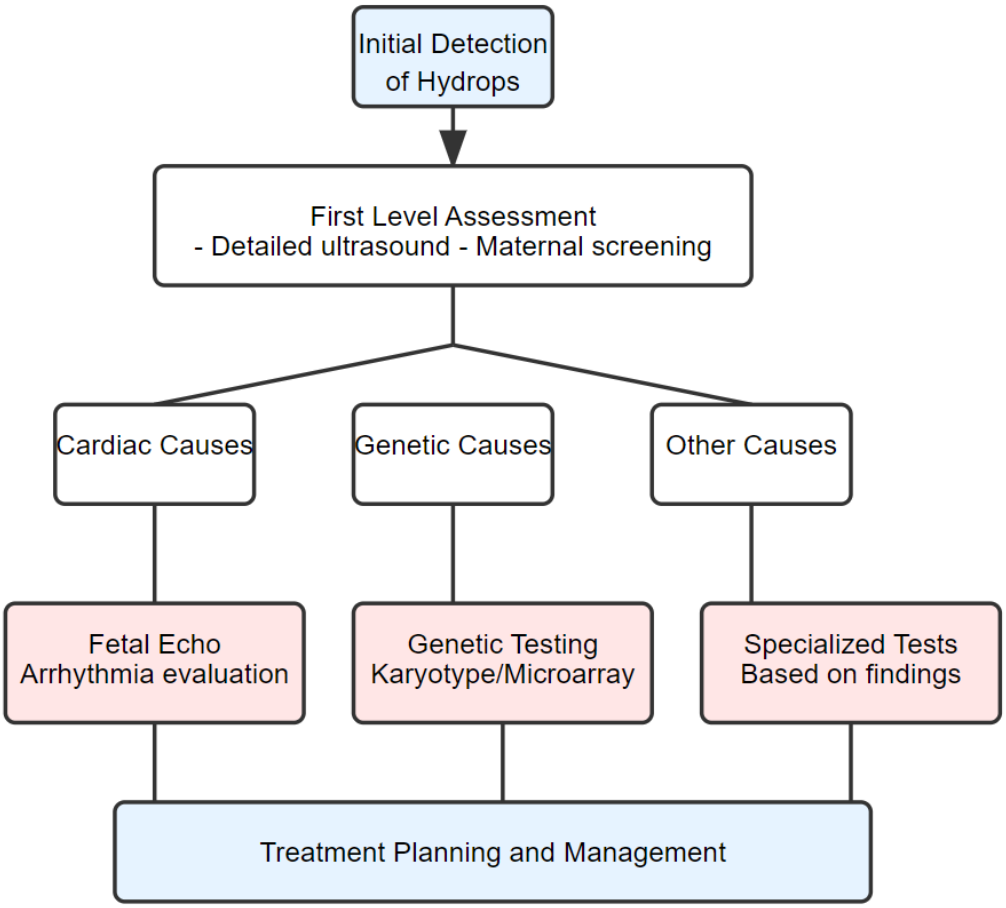

Figure 2. Diagnostic Algorithm for Non-immune Hydrops Fetalis

4.2. Laboratory Investigations

A systematic diagnostic approach incorporating maternal and fetal testing is essential for determining the underlying etiology:

4.2.1. Maternal Screening

Initial maternal evaluation includes blood type, antibody screening, complete blood count, and serological testing for infectious diseases. Specialized metabolic screening may be indicated based on family history or clinical presentation [15]. The maternal screening process begins with comprehensive blood work to evaluate for potential immune causes and infectious etiologies. Serological testing typically includes assessment for viruses known to cause fetal hydrops, including parvovirus B19, cytomegalovirus, and toxoplasmosis. Endocrine function tests may be indicated in specific cases. The evaluation of maternal autoimmune status can provide additional diagnostic information in selected cases. Careful attention to maternal symptoms and signs is essential, particularly for early detection of mirror syndrome or other pregnancy complications [15].

4.2.2. Genetic Analysis

Recent advances in genetic testing have revolutionized the diagnostic approach. Next-generation sequencing and chromosomal microarray analysis can identify genetic causes in previously undiagnosed cases [16]. The expansion of genetic testing capabilities has dramatically improved our ability to identify underlying genetic disorders. Whole exome sequencing has emerged as a powerful tool in identifying novel genetic causes of hydrops fetalis. The integration of molecular genetic testing into the diagnostic algorithm has significantly reduced the proportion of cases classified as idiopathic. Cell-free fetal DNA testing can provide additional information in specific cases, while targeted gene panels may be appropriate based on clinical presentation and family history. The interpretation of genetic findings requires careful consideration of variant pathogenicity and clinical correlation The potential for identifying variants of uncertain significance requires careful discussion (genetic counselling before and after testing) with families regarding the implications of testing [16].

Table 2. Diagnostic Work up for NIHF

Investigation Level	Tests	Purpose
First-Line Maternal Studies	Blood type and antibody screen; Complete blood count; Infections screening (TORCH); Kleihauer-Betke test	Initial screening and risk assessment
Detailed Fetal Imaging	Detailed anatomic ultrasound; Fetal echocardiogram; MRI (if indicated)	Structural evaluation
Genetic Testing	Karyotype; Microarray analysis; Whole exome sequencing	Genetic diagnosis
Invasive Testing	Amniocentesis; Cordocentesis; Pleural fluid analysis	Specific diagnosis

5. Clinical Manifestations

5.1. Fetal Presentations

The spectrum of fetal manifestations extends beyond fluid accumulation. Cardiac dysfunction often manifests as cardiomegaly and altered blood flow patterns detectable through Doppler studies. Pleural effusions may compromise lung development, while ascites can lead to abdominal distention and organ compression [17].

5.2. Perinatal Complications

The immediate postnatal period presents significant challenges. Newborns often exhibit respiratory distress, cardiovascular instability, and coagulation abnormalities. The presence of pleural effusions and ascites may necessitate immediate therapeutic intervention [18].

6. Therapeutic Interventions

6.1. Prenatal Management

Treatment strategies are tailored to the underlying etiology and severity of presentation. Interventions may include:

6.1.1. Fetal Therapy

Direct fetal interventions such as thoracentesis, paracentesis, or shunt placement may be necessary to alleviate severe fluid accumulations. These procedures require careful patient selection and expertise in fetal medicine [19].

6.1.2. Medical Management

Specific conditions may respond to targeted medical therapy. For instance, maternal administration of digoxin or other medications may benefit cases of fetal arrhythmia-induced hydrops [20].

6.2. Delivery Planning

Timing and mode of delivery require careful consideration of fetal condition, gestational age, and available neonatal support facilities. A coordinated multidisciplinary approach optimizes outcomes [21].

6.3. Prognosis

Survival rates vary significantly based on multiple factors including etiology, gestational age at diagnosis, and severity of hydrops. Early diagnosis and intervention generally correlate with improved outcomes [22]. Survivors of hydrops fetalis require long-term follow-up to monitor for potential sequelae. Neurodevelopmental outcomes, cardiovascular function, and respiratory status warrant particular attention [23].

Table 3. Treatment Options Based on Underlying Etiology

Etiology	Treatment Options	Expected Outcomes
Cardiac Arrhythmias	Maternal antiarrhythmic medication; Fetal cardiac pacing (select cases)	Good if detected early
Parvovirus B19	Intrauterine transfusion; Serial monitoring	75-85% survival with treatment
Twin-Twin Transfusion	Laser photocoagulation; Selective reduction (severe cases)	Variable based on severity
Thoracic Space-Occupying Lesions	Thoracentesis; Shunt placement	Depends on underlying lesion
Anemia	Intrauterine transfusion; Maternal treatment if applicable	>80% survival if treated
Structural Heart Disease	Medical management; In-utero intervention (select cases)	Variable based on defect
Metabolic Disorders	Enzyme replacement therapy; Supportive care	Generally poor

7. Conclusion

Non-immune hydrops fetalis remains a challenging condition that requires a systematic diagnosis and coordinated multidisciplinary care. The shift from immune to non-immune causes has necessitated more sophisticated diagnostic strategies and varied therapeutic approaches. Early detection through comprehensive prenatal screening enables timely intervention and optimizes outcomes. Despite advances in prenatal care and therapeutic options, the condition continues to carry significant mortality and morbidity risks. The integration of modern genetic technologies has enhanced our diagnostic capabilities and opened new avenues for targeted therapies.

References

[1] Santo S, Mansour S, Thilaganathan B, Homfray T, Papageorghiou A, Calvert S, et al. Prenatal diagnosis of non-immune hydrops fetalis: what do we tell the parents? Prenat Diagn. 2021;31(2):186-95.

[2] Bellini C, Donarini G, Paladini D, Calevo MG, Bellini T, Ramenghi LA, et al. Etiology of non-immune hydrops fetalis: An update. Am J Med Genet A. 2020;167A(5):1082-8.

[3] Sparks TN, Thao K, Norton ME. Genetic causes of non-immune hydrops fetalis: a systematic review. J Perinatol. 2019;39(12):1593-1607.

[4] Society for Maternal-Fetal Medicine, Norton ME, Chauhan SP, Dashe JS. Society for Maternal-Fetal Medicine Clinical Guideline: Nonimmune hydrops fetalis. Am J Obstet Gynecol. 2020;223(2):B28-B42.

[5] Désilets V, De Bie I, Audibert F. No. 363-Investigation and Management of Non-immune Fetal Hydrops. J Obstet Gynaecol Can. 2018;40(8):1077-90.

[6] Castanon M, Molina S, Garzon S, Berghella V. Fetal hydrops: a contemporary review. J Perinat Med. 2021;49(4):366-76.

[7] Gimovsky AC, Luzi P, Berghella V. Lysosomal storage disease as an etiology of nonimmune hydrops. Am J Obstet Gynecol. 2019;221(4):295-304.

[8] Hellmund A, Berg C, Geipel A, Müller A, Gembruch U. Prenatal diagnosis and management of fetal hydrops due to various causes: a retrospective analysis of 156 cases. Arch Gynecol Obstet. 2020;301(2):325-35.

[9] Laterre M, Bernard P, Charrier A, Capron C, Ville Y. Prognostic factors in non-immune hydrops fetalis: a systematic review. Prenat Diagn. 2021;41(9):1073-83.

[10] Jung E, Won HS, Lee PR, Kim A. The progression of non-immune hydrops fetalis to anemia: a systematic review. J Perinat Med. 2019;47(2):176-81.

[11] Mackie FL, Hall MJ, Morris RK, Kilby MD. Early prognostic factors of outcomes in monochorionic twin pregnancy: systematic review and meta-analysis. Am J Obstet Gynecol. 2018;219(5):436-46.

[12] Randenberg AL. Nonimmune hydrops fetalis part I: etiology and pathophysiology. Neonatal Netw. 2020;29(5):281-95.

[13] Bellini C, Donarini G, Paladini D, Calevo MG, Bellini T, Ramenghi LA. Diagnostic Flow-Chart for Non-Immune Hydrops Fetalis: An Update. Am J Perinatol. 2021;38(4):366-74.

[14] Suksai M, Thanaboonyawat I, Sirichotiyakul S, Wanapirak C, Tongprasert F, Srisupundit K, et al. Fetal hemodynamic patterns in nonimmune hydrops fetalis. J Matern Fetal Neonatal Med. 2019;32(10):1654-9.

[15] Rodriguez MM, Bruce JH, Jimenez XF, Romaguera RL, Bancalari E, Garcia OL, et al. Nonimmune hydrops fetalis in the liveborn: series of 32 autopsies. Pediatr Dev Pathol. 2018;21(1):4-14.

[16] Yuan SM. Nonimmune hydrops fetalis: an update. Pediatr Med. 2021;4:40-52.

[17] Yeom W, Paik ES, An JJ, Oh SY, Choi SJ, Roh CR, et al. Clinical characteristics and perinatal outcome of fetal hydrops. Obstet Gynecol Sci. 2020;63(1):64-73.

[18] Bebbington M. Nonimmune hydrops fetalis: a practical guide to management. Obstet Gynecol Clin North Am. 2020;47(1):201-13.

[19] Yinon Y, Kelly E, Ryan G. Fetal pleural effusions. Best Pract Res Clin Obstet Gynaecol. 2019;58:66-77.

[20] Datkhaeva I, Arboleda VA, Senaratne TN, Nikita ME, Stadler A, Stiller RJ, et al. Identification of novel genetic causes of non-immune hydrops fetalis: a systematic review. J Perinatol. 2020;40(12):1832-41.

[21] Apkon M. Pathophysiology of hydrops fetalis. Semin Perinatol. 2019;19(6):437-46.

[22] Lallemand AV, Doco-Fenzy M, Gaillard DA. Investigation of nonimmune hydrops fetalis: multidisciplinary studies are necessary for diagnosis. Pediatr Dev Pathol. 2019;22(5):403-12.

[23] Sinkey RG, Habli MA, Cleary JP, Livingston JC, Lim FY, Crombleholme TM. Outcome of prenatally diagnosed solid fetal tumors. Am J Obstet Gynecol. 2019;220(3):278.e1-278.e8.

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