NeoReviews™

NeoQuest April 2022: Structural Fetal Anomalies

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Article type: Resources

You are consulted to provide prenatal counseling for a woman at 29 weeks' gestation. Findings of the fetal abdomen and thorax on ultrasonography are noted in Figures 1A–D. The fetal weight is estimated to be appropriate for gestational age; however, the femurs are shortened below the 5th percentile. Fetal echocardiogram demonstrates a perimembranous ventricular septal defect and a small pericardial effusion with no arrhythmia.

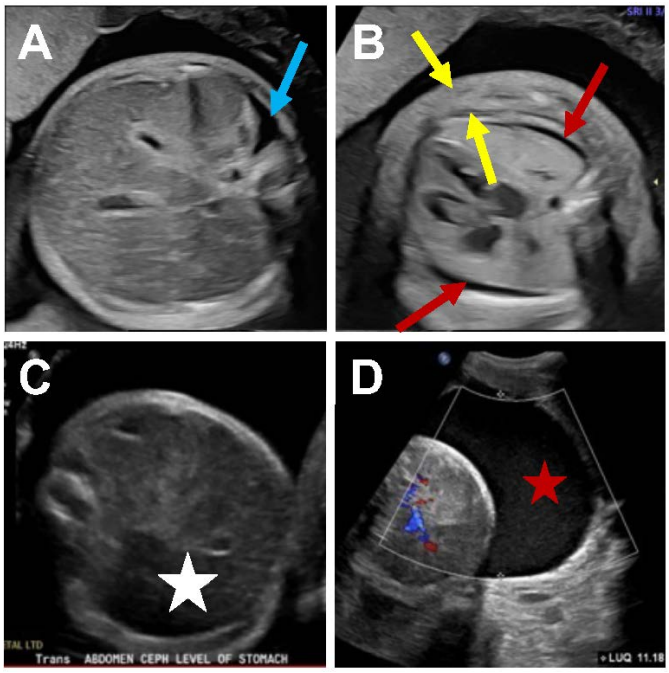

Figure 1. Ultrasound of the fetus in the vignette demonstrating fluid collections (blue, yellow, and red arrows and red star) and an absent stomach (white star in the usual location of the stomach). Adapted from Layoun V, Kim A, Edwards E, Feist C, Dukhovny S. *Neoreviews*. 2022;23(4):e284–e290. 10.1542/neo.23-4-e284 [1]

Which of the following is most likely to provide an antenatal diagnosis?

A. Amniotic fluid polymerase chain reaction
B. Fetal karyotype analysis
C. Fetal magnetic resonance imaging
D. Fetal middle cerebral artery assessment
E. Maternal blood type and Rh(D) antigen status

Answer: B. Fetal karyotype analysis

Explanation:

The fetus in the vignette has hydrops fetalis (HF) with a constellation of features most consistent with trisomy 21, which can be diagnosed with a prenatal genetic screening of the fetal karyotype **(Answer B)**.[2] In this case, ultrasonography revealed ascites **(Figure 1A, blue arrows)** moderate bilateral pleural effusions **(Figure 1B, red arrows)**, and edema of the head **(Figure 1B, yellow arrows)**. Ultrasound further revealed an absent stomach **(Figure 1C, white asterisk)** with concern for esophageal atresia and signs of polyhydramnios **(Figure 1D, red asterisk)**. HF is characterized by pathologic fluid accumulation within fetal soft tissues and body cavities. HF is defined by the presence of two or more abnormal fluid collections, which include ascites, pleural effusions, pericardial effusion, skin edema, as well as placental edema or polyhydramnios.[3,4] The systemic evaluation of HF is driven by the underlying etiology, differentiated as immune or nonimmune.[5] Immune HF occurs commonly in the setting of red cell alloimmunization and has decreased in incidence due to the use of Rhesus (Rh) D immune globulin, whereas non-immune hydrops fetalis (NIHF) accounts for up to 90% of cases of fetal hydrops.[3]

The incidence of NIHF is estimated as 1 per 1,700–3,000 pregnancies and 1 per 4,000 live-born infants.[3] The presence of malformations on prenatal ultrasonography should suggest concern for a syndrome or chromosomal anomaly. The most common genetic cause of NIHF is aneuploidy, particularly monosomy X, trisomy 21, and trisomy 18.[3,5] NIHF has been described in fetuses with trisomy 21 in the absence of structural cardiac defects due to transient abnormal myelopoiesis (TAM), a preleukemic syndrome. TAM involves abnormal fetal hematopoiesis, mutations in the *GATA1* gene in fetal liver hematopoietic cells, and monoclonal expansion with blast cell sequestration, resulting in hepatomegaly and development of NIHF **(Figure 2)**.[1,6] As the prenatal findings of TAM are not specific, a high index of suspicion for TAM should be indicated in a fetus with hepatomegaly, hydrops, and ultrasonographic markers that raise concern for trisomy 21.[1,6]

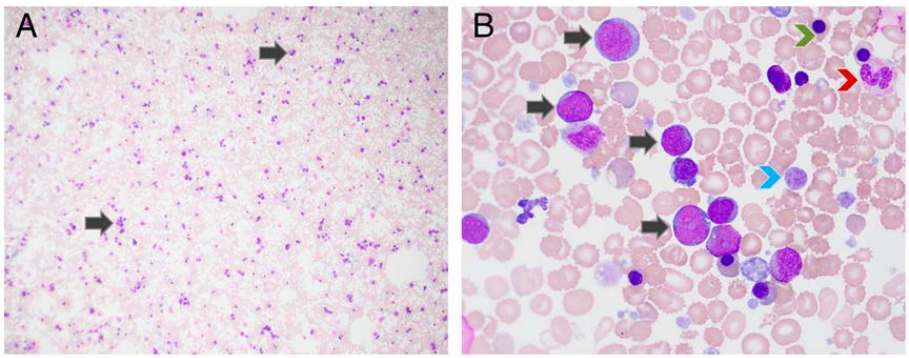

Figure 2. Peripheral blood smear in transient abnormal myelopoiesis (TAM) in an infant with trisomy 21 A. Low-power view reveals an increased number of blasts (black arrows). B. High-power view demonstrates large blasts with a high nuclear-to-cytoplasmic ratio (black arrows), erythrocyte precursors (green arrowhead), neutrophils (red arrowhead), and giant platelets (blue arrowhead). Adapted from O'Connell et al. Perinatal transient myeloproliferative disorder in trisomy 21. *Neoreviews*. 2016;17(11):e636–e644 [6]

The Society for Maternal–Fetal Medicine provides the current recommendations for the evaluation of suspected NIHF **(Figure 3)**.[4] Pregnant women with a concern for NIHF are advised to receive detailed ultrasonography and fetal echocardiogram. If these assessments reveal the presence of structural abnormalities, further diagnostic evaluation is warranted. **(Figure 3)**.[4]

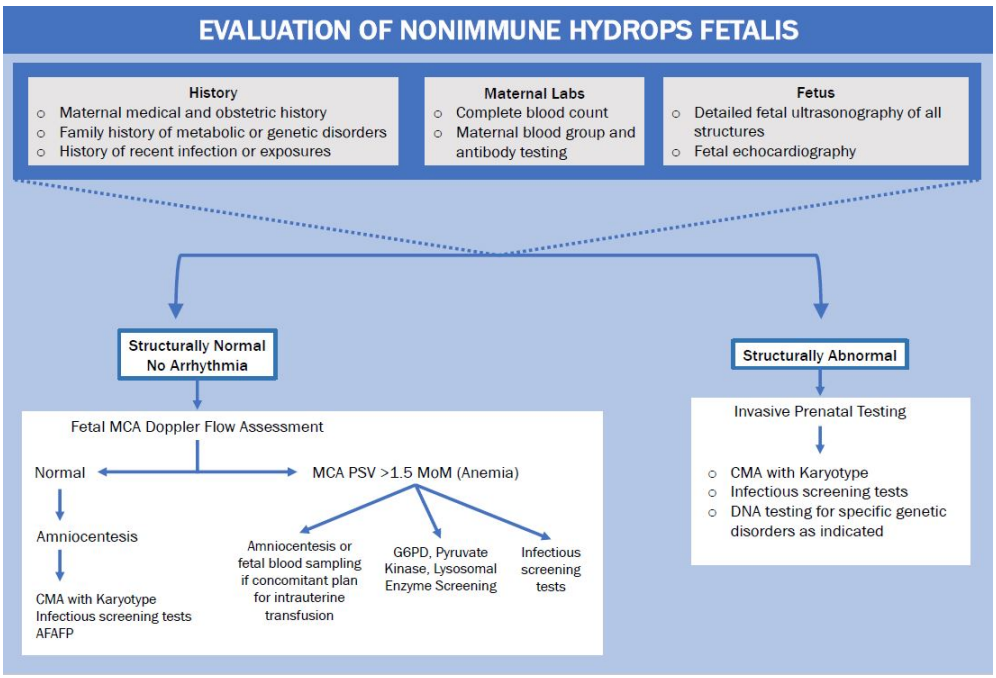

Figure 3. The recommended approach for the evaluation of nonimmune hydrops fetalis. Adapted from Norton et al. Society for maternal-fetal medicine (SMFM) clinical guideline #7: nonimmune hydrops fetalis. *Am J Obstet Gynecol.* 2015;212(2):127–139. [4] Abbreviations: AFAFP; amniotic fluid alpha-fetoprotein; CMA, chromosomal microarray; G6PD, glucose-6-phosphate dehydrogenase deficiency; MCA PSV, middle cerebral artery peak systolic velocity; MoM, multiples of the median; PCR, polymerase chain reaction.

Polymerase chain reaction DNA amplification is a useful method to investigate infectious causes of NIHF, such as human parvovirus B19, cytomegalovirus, and toxoplasmosis **(Option A)**.[7] These intrauterine infections account for up to 10% of cases of NIHF.[4] However, the fetus in this vignette demonstrated features that are not consistent with an infectious etiology, such as the absence of maternal illness and the presence of structural anomalies such as a nuchal fold and absent fetal stomach.

Though additional imaging, such as fetal magnetic resonance imaging, may be helpful to further delineate the structural abnormalities identified on the prenatal ultrasound, it is not specific for identifying the primary cause for NIHF in this vignette **(Option B)**.

Doppler assessment of the middle cerebral artery **(Option C)** is recommended to screen for fetal anemia in fetuses without structural anomalies with probable NIHF **(Figure 3)**. For example, human parvovirus B19 infection of fetal erythrocyte precursors causes cell destruction and arrest of red blood cell production resulting in anemia-induced heart failure and nonimmune hydrops.[7] The multiple structural anomalies in the fetus in this case, such as long bone shortening and esophageal atresia, makes fetal anemia an unlikely primary cause for NIHF.

Determining the presence of Rh(D) alloimmunization using maternal blood type and Rh(D) antigen status is useful for screening for isoimmune hydrops fetalis **(Option D)**.[4] However, the presence of a structurally abnormal fetus in this vignette makes alloimmunization an unlikely cause of hydrops.[1,4]

Did you know?

- The presence of NIHF in the setting of trisomy 21, hepatomegaly, and TAM is associated with an estimated 92% mortality rate.[8]

What is the most common fetal tachyarrhythmia associated with the development of NIHF? To learn more about fetal supraventricular tachycardia and treatment with transplacental medical therapy, refer to Watson et al. Abnormal fetal echocardiogram at 33 weeks' gestation. *Neoreviews*. 2020;21(5):e367–e369 [9]

What is the differential diagnosis of persistent neonatal bradycardia and hydrops? To learn more, refer to: Sharma et al. Neonate with persistent hydrops. *Neoreviews.* 2015;16(6):e380–e383 [10]

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