

**PERINATAL DEATHS AND LYMPHATIC SYSTEM INVOLVEMENT:
A DIAGNOSTIC FLOW-CHART
APPLYING IMMUNOHISTOCHEMICAL METHODS**

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ABSTRACT

A diagnostic flow chart is presented for use in case of perinatal death or still birth with non-immune hydrops fetalis, visceral effusions, or increased nuchal translucency. Immunohistochemical staining with CD-31, CD-34, D2-40, and smooth muscle actin is recommended.

Keywords: perinatal mortality, non-immune hydrops, lymphatic dysplasia, immunohistochemistry, flow chart

Fetal loss and perinatal deaths are frustrating clinical problems both for the physicians and healthcare team and for the families involved. Hydrops fetalis, acute asphyxia, and shock are believed to be the main mechanisms leading to fetal or perinatal death. Almost all reports describing perinatal death list nonimmune hydrops fetalis (NIHF) either as a consequence of a known and diagnosed disorder, or as “other” cause, “unexplained” cause, or the like, whenever a clear cause is unavailable (1,2).

We recently proposed a diagnostic flow-chart for NIHF that includes the use of immunohistochemical (IHC) methods (3).

We applied and validated this flow-chart by evaluating 79 fetuses with a diagnosis of NIHF (out of a total of 1,098 fetuses that underwent autopsy) (4). We concluded that specific IHC staining techniques aimed at detecting lymphatic dysplasia are needed and should be mandatory in autopsies of fetuses with non-immune hydrops fetalis.

We then applied IHC methods in the histological examination of 18 aborted fetuses that had a prenatal diagnosis of increased nuchal translucency (NT) and concluded that IHC investigations are of value to confirm that increased NT is the result of a lymphatic malformation or of delayed development of the lymphatic system (5).

Based on our experience, we now present and suggest our diagnostic flow-chart (*Fig. 1*) aimed at providing guidance in diagnosing and searching for the cause of death in fetuses or newborns who present clinically evident signs or findings of possible lymphatic dysplasia, such as hydrops itself, pleural, pericardial, or abdominal effusions, cystic hygroma or prenatal, unexplained, increased NT.

We are not suggesting that this flow-chart should be included in routine autopsy protocols, but rather that this method should

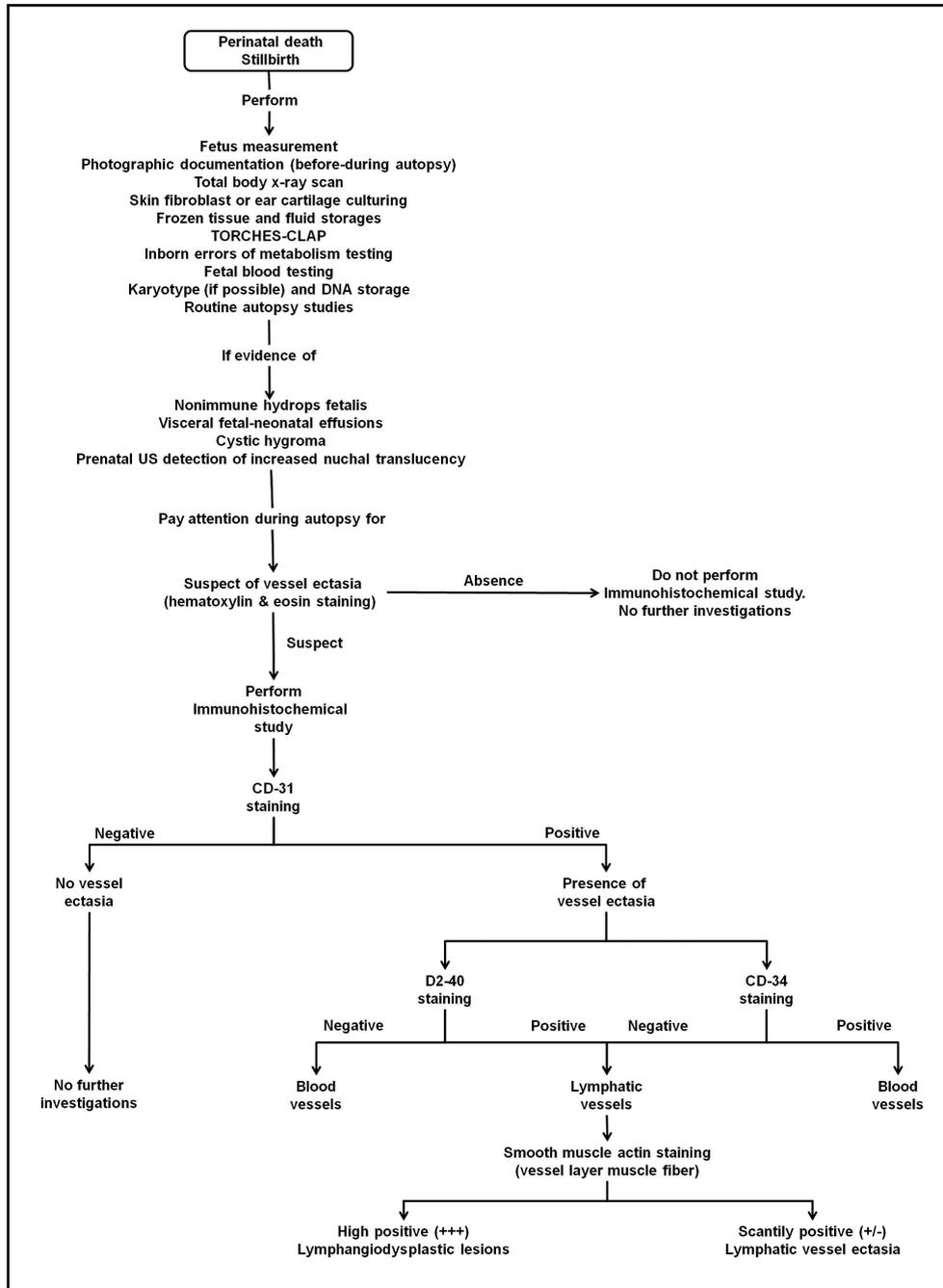


Fig. 1. Diagnostic flow-chart for perinatal death. The flow-chart is applicable to cases of perinatal death or stillbirth with the presence of nonimmune hydrops fetalis, visceral fetal or neonatal effusion, cystic hygroma or prenatal diagnosis of increased nuchal translucency. The following monoclonal antibodies are recommended: CD-31, CD-34, D2-40 (or Podoplanin), and smooth muscle actin (SMA). CD-31 is a platelet endothelial cell adhesion molecule-1 that is highly specific for lymphatic and blood endothelium. CD-34 is expressed by embryonic cells, including blood-vascular vessel endothelial cells. D2-40 (Podoplanin) is a selective marker for lymphatic endothelium. SMA is useful to identify myofibroblasts and muscle cells in the intima and media of lymph vessels.

be used in selected cases and that these ancillary investigations should be placed in the hands of a skilled pathologist with experience in the field of perinatal autopsy studies.

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