

## Original Research Article

# Nonimmune hydrops foetalis: value of perinatal autopsy and placental examination in determining aetiology

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### ABSTRACT

**Background:** Authors sought to determine the possible factors in the causation of nonimmune hydrops foetalis by perinatal autopsy with placental examination and to reduce the number of cases in which the cause remains elusive.

**Methods:** Twenty five cases of nonimmune hydrops foetalis were identified in about 200 consecutive perinatal autopsies (including placental examination) performed during a 11 year period. The results were correlated with clinical, laboratory and imaging characteristics in an attempt to establish the aetiology.

**Results:** Perinatal autopsy and placental examination confirmed the following aetiologies: cardiovascular causes (8) [isolated (4), syndromic (3) and associated chromosomal (1)], placental causes (5), chromosomal (4) [isolated(3) and associated cardiovascular disease (1)], intrathoracic (3), genitourinary causes (3), infections(1),gastrointestinal lesions (1) and idiopathic causes (1). Placental mesenchymal dysplasia was a unique pathology identified among the placental lesions, which constituted the second most common cause of nonimmune hydrops foetalis. Despite careful examination no cause was identified in one case. In more than 50% of studied cases, autopsy examination either refuted or altered the ultrasound diagnosis completely.

**Conclusions:** The perinatal autopsy in combination with placental study and prenatal imaging represents the most promising tool in the evaluation of aetiology of nonimmune hydrops foetalis. The identification of a cause for nonimmune hydrops foetalis will provide a better correlation with recurrence risk and parental counselling.

**Keywords:** Aetiology, Nonimmune hydrops foetalis, Perinatal/foetal autopsy, Placental mesenchymal dysplasia, Prenatal imaging

### INTRODUCTION

Foetal hydrops is a syndrome characterized by generalized skin oedema and abnormal accumulation of fluid in one or more serous cavities of foetuses. It has been broadly classified into immune mediated (materno - foetal blood group incompatibility) and non immune types. There is a steady fall in the incidence of immunologic hydrops foetalis due to the prevention of maternal isoimmunisation and treatment of affected foetuses in utero.<sup>1</sup> This has shifted the focus towards the

non immunologic causes of hydrops which now constitutes up to 90% of cases of foetal hydrops.<sup>2</sup>

There are many impressive and ever growing causes of non immune hydrops foetalis (NIHF) and its development is known to be associated with maternal, foetal and placental diseases.<sup>3</sup> The foetal hydrops can be identified anytime throughout the pregnancy. The perinatal mortality rate is generally high. The spectrum of possible causative factors of NIHF include cardiovascular diseases, chromosomal aberrations, haematologic

abnormalities, infections, intrathoracic lesions, lymphatic dysplasias and placental causes including twin-twin transfusion syndrome. The other causes are syndromes, urinary tract malformations, inborn errors of metabolism, extra thoracic tumours, gastrointestinal disorders, miscellaneous and idiopathic.<sup>4</sup>

Improvements in obstetric ultrasound (USG) and foetal echocardiography enable the early and frequent detection of hydrops, resulting in foetal interventions / termination of pregnancy and have altered the incidence of hydrops.<sup>5</sup>

Given the multiple aetiologies of NIHF, we sought to determine the presence of possible factors in its causation by analysing the autopsy with placental material and to reduce the number of cases in which the cause remains elusive.

## METHODS

Twenty five cases of NIHF were identified in about 200 consecutive perinatal autopsies (including placental examination) performed during a 11 year period from January 2007 to December 2017 at the department of pathology, PSG Institute of Medical Sciences and Research. The institutional ethical review board approval was obtained for the study.

### *Exclusion criteria*

Hydrops foetalis of immunologic origin were excluded from the study on the basis of blood typing, direct and indirect coomb's tests.

The detailed maternal history, antenatal ultrasounds and genetic tests if any were collected. The autopsy was performed after getting informed consent. Photograph of the foetus was routinely taken with special attention to sites where abnormalities were suspected. A thorough systematic examination of foetuses and placenta was done, which included foetogram, foetal weight, anthropometric measurements (head circumference, chest circumference, abdominal circumference, crown rump length, crown heel length, foot length), external and internal examination.

After opening the body cavities, serous fluid collections were measured, and the thoracic and abdominal organs were removed en bloc. All the visceral organs were examined, and the bits were given for microscopic analysis. The brain was removed, inspected, weighed and suspended in a formalin fixative. After fixation, the brain was sliced; examined and relevant bits were taken. Examination of bone, including marrow and spinal cord were performed in selected cases. The placenta and cord were also examined thoroughly, photographed (maternal / foetal surfaces, parenchyma, umbilical cord), cut at 1cm intervals and the parenchyma was assessed for specific lesions. Relevant lesional sections were taken along with 2 sections of membrane roll, 2 sections from the

umbilical cord and 3 full thickness sections of the normal parenchyma.

All the histologic sections were stained with haematoxylin and eosin. Special stains such as Grocott-Gomori's methenamine silver (GMS), Giemsa stains for toxoplasma gondii, warthin starry stain for spirochetes and reticulin stain for vascular network were done, when required. Immunohistochemical marker for cytomegalovirus was available, hence done for suspected infectious cases. After the microscopic study, the results were correlated with clinical, laboratory and imaging characteristics and the final results were drawn.

## RESULTS

Out of 200 perinatal autopsies performed during the 10-year period, 25 cases met the criteria for NIHF, representing 12.5%. The gestational age ranged from 13 weeks to 35 weeks. All were dead-born foetuses except two. The two liveborn foetuses were delivered at 35 weeks and survived only a few hours postnatally. There were no cases of multiple gestation.

### *Clinical findings*

Maternal age ranged from 19 to 35 years, of whom 9 were primigravidas. Five cases each of polyhydramnios and oligohydramnios were present. Maternal medical diseases included 2 cases each of preeclampsia and autoimmune diseases and 1 case each of hypothyroidism and rheumatic heart disease. None of the mothers had diabetes. Recurrence of hydrops was found on 5 occasions. Previous history of hydrops was documented in 2 cases of cardiac (complete heart block and transposition of great arteries with ventricular septal defect), one case each of intra thoracic lesion (Congenital pulmonary airway malformation), chromosomal (Down syndrome) and placental mesenchymal dysplasia.

### *Ultrasound findings*

Hydrops foetalis is diagnosed with typical findings during prenatal imaging. The sonographic features include subcutaneous / scalp oedema, fluid accumulation in different serous cavities (Figure 1), polyhydramnios and placentomegaly. Correlation between prenatal USG and autopsy findings in elucidating the causes of hydrops were studied (Table 1). Complete agreement between prenatal USG and autopsy findings were seen in 11 cases (44%), while in 6 cases autopsy examination revealed additional findings (24%). In 8 cases, autopsy findings changed the diagnosis (32%).

### *Autopsy findings*

#### *Foetus*

There were 12 males and 13 females with an almost equal gender distribution. Hydrops was noted in <20 weeks (10

cases), 21-28 weeks (10 cases) and >28 weeks (5 cases) of gestation. Aetiological distribution of NIHF is listed in Table 2.



**Figure 1: Sagittal section of a 13 weeks foetus showing hydrops foetalis. the sonogram shows fluid collection (marked) in pleural, peritoneal and pericardial spaces.**

**Table 1: Correlation of prenatal USG with autopsy findings at different gestational ages.**

| Gestational age (N=25) | Autopsy confirmed the USG findings | Autopsy confirmed the USG findings with additional findings | Autopsy changed the USG findings |
|------------------------|------------------------------------|---|----------------------------------|
| <20 weeks (10)         | 4                                  | 3   | 3                                |
| 21-28 weeks (10)       | 3                                  | 3   | 4                                |
| >28 weeks (5)          | 4                                  | 0   | 1                                |

**Table 2: Aetiological distribution of hydrops foetalis.**

| Aetiology                      | No. of cases (N=25) |
|--------------------------------|---------------------|
| Intrathoracic lesions          | 3                   |
| <b>GI lesions</b>              |                     |
| Hypertrophic pyloric stenosis  | 1                   |
| Cardiac defects                | 4                   |
| Genitourinary lesions          | 3                   |
| <b>Chromosomal abnormality</b> |                     |
| Down syndrome                  | 3 (1*)              |
| Turner syndrome                | 1                   |
| <b>Infections</b>              |                     |
| Parvo virus                    | 1                   |
| Placental causes               | 5                   |
| <b>Syndromic *</b>             |                     |
| Ellis van creveld syndrome     | 1                   |
| Zellweger syndrome             | 1                   |
| Vacterl                        | 1                   |
| Idiopathic                     | 1                   |

\*Coexistent with congenital heart disease

**Cardiovascular diseases (n=8)**

Congenital cardiac defects represented the largest aetiological group and were seen in 8 fetuses (32.0%). Among these 8 cases, 7 fetuses had structural malformations and 1 had functional defect. 2 cases of isolated cardiac defects, 3 cases of syndromic association and one case of chromosomal abnormalities were identified (Table 3). Cystic hygroma was noted in 2 instances.

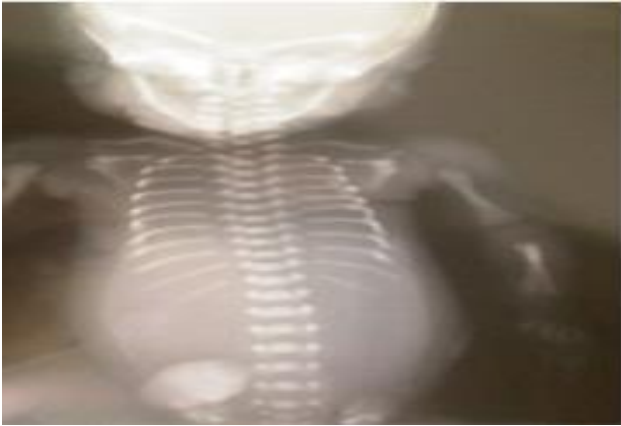
**Table 3: Isolated and associated cardiac defects in fetuses with NIHF.**

| Type of congenital cardiac defects   | Associated abnormalities  |
|--|---|
| Premature closure of ductus  |   |
| Complete heart block secondary to fibrosis of cardiac conduction system, immune mediated       |   |
| TGA with hypoplastic pulmonary arterial trunk  |   |
| Subaortic VSD  |   |
| TOF with right aortic arch and left sided PDA  | VACTERL association   |
| Secundum ASD   | Multiple congenital anomaly syndrome -?<br>Zellweger syndrome-?<br>Smith Lemli Opitz syndrome |
| Common atrium with complete common AVSD  | Ellis- Van Creveld syndrome   |
| Common AVSD with persistent left superior vena cava and mild tubular hypoplasia of aortic arch | Down syndrome   |
| TGA and VSD  | Partial urorectal septum malformation sequence (Cloacal dysgenesis sequence)                  |

TGA-transposition of great arteries; VSD-ventricular septal defect; TOF-tetralogy of fallot; PDA-patent ductus arteriosus; VACTERL-vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities; ASD-atrial septal defect; AVSD- atrioventricular septal defect.

The most common causes of NIHF in our series were cardiovascular diseases, of which structural anomalies predominate. The most frequently found structural heart lesion with hydrops is atrio ventricular septal defects, and transposition of great vessels. Less common structural cardiac abnormalities observed were premature closure of ductus, tetralogy of Fallot and secundum atrial septal defect. There were 2 cases of isolated heart defects. One fetus had premature closure of ductus and the other was a neonate with complete heart block. In the second instance, an association with maternal connective tissue disease was identified. This newborn female with complete heart block also had a sibling delivered at same gestational age with similar hydropic features and died within a few hours of birth. Autopsy was not performed

for the sibling. Our newborn was delivered preterm at 34 weeks of gestational age due to severe bradyarrhythmia. The neonate was hydropic, hypertonic and had intractable bradycardia at birth. Pace maker insertion was not acceptable to the parents. Child expired within 3 hours of birth. Autopsy examination revealed biventricular hypertrophy, dysplasia of atrioventricular valves, fibrosis of sinoatrial and atrioventricular nodes and patchy endocardial fibroelastosis.



**Figure 2: Foetogram: shows short long bones.**



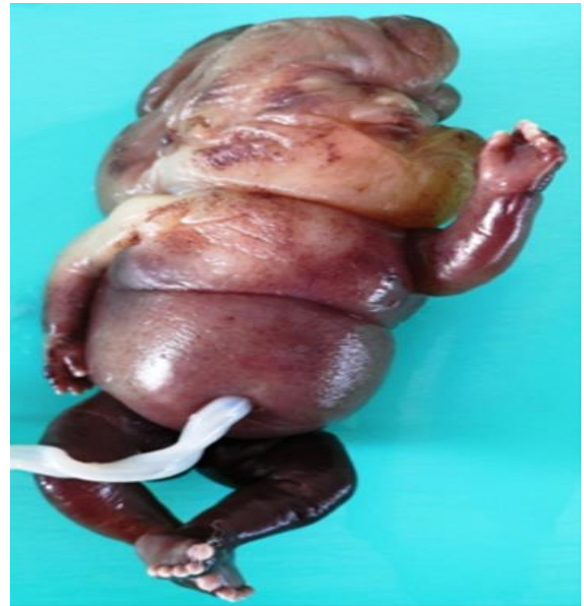
**Figure 3: Post axial polydactyly of feet.**



**Figure 4: Common atrium with complete common atrioventricular canal defect.**

In present series, cardiac defects were also seen in association with Ellis-Van Creveld Syndrome (Figure 2), Multiple congenital anomaly syndrome and VACTERL association.

There were 3 cases of Down syndrome, all with typical phenotypic manifestations and one with atrioventricular septal defect (Figure 5). The other significant associated anomaly noted was partial urorectal septum malformation sequence (Cloacal dysgenesis sequence).



**Figure 5: Grossly oedematous foetus of 17 weeks of gestation with generalized subcutaneous oedema.**

#### *Other disorders associated with NIHF*

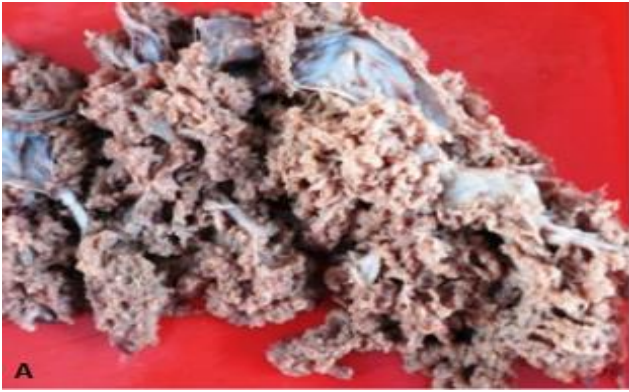
Placental, intrathoracic and genitourinary lesions are summarized in (Table 4).

#### *Placental lesions (n=5)*

The placenta was examined in all the cases and showed villous edema, prominent Hofbauer cells and villous capillary erythropoiesis.

Placental causes of hydrops were found in 5 cases. Two cases each of maternal vascular malperfusion and placental mesenchymal dysplasia. The underlying pathology in the fifth case was foetal vascular malperfusion (organising and recanalizing thrombi with avascular villi), villitis of unknown aetiology and acute chorioamnionitis.

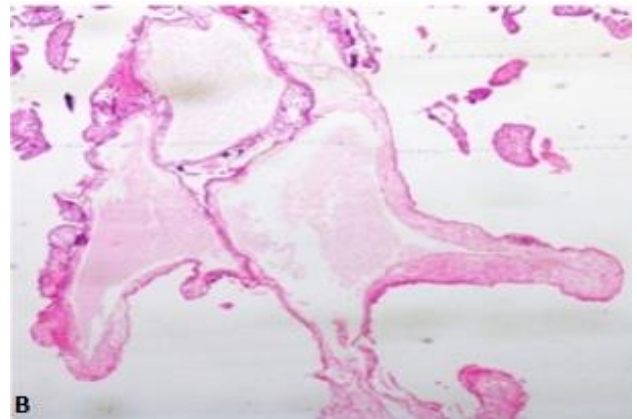
Histologically, the cases with maternal vascular malperfusion had multiple parenchymal infarcts, increased syncytial knotting and distal villous hypoplasia. Preeclampsia was noted in both the mothers.



**Figure 6: Small vesicles in the parenchyma, thick ropy stem villi that have been shorn off the villous parenchyma.**

The placentas with mesenchymal dysplasia grossly showed hypercoiled cord, parenchymal disruption with thick, oedematous villi and small vesicles (Figure 6). Histologically, all villi showed collapsed vesicle with

central cystic degeneration with absent trophoblastic proliferation and markedly dilated vascular channels (Figure 7).



**Figure 7: Collapsed vesicle with central cystic degeneration, greatly dilated vascular channels and no trophoblastic proliferation.**

**Table 4: Other disorders (Placental/intrathoracic/ genitourinary lesions) associated with NIHF.**

| Aetiologic distribution           | Major pathologic findings and diagnosis   |
|-----------------------------------|---|
| Placental causes (N=5)            | Case 1: Preeclampsia, Multiple parenchymal infarcts, increased syncytial knotting: MVM  |
|                                   | Case 2: Preeclampsia, infarcts, Distal villous hypoplasia: MVM  |
|                                   | Case 3: The Placental parenchyma is disrupted, fleshy, pulled apart and the villi appear thick. The stem villi oedematous, hypercoiled cord : Placental mesenchymal dysplasia |
|                                   | Case 4: Small vesicles in the parenchyma, thick stem villi: Placental mesenchymal dysplasia   |
|                                   | Case 5: placenta with FVM.VUE and A/C CAM   |
| Intra thoracic lesions (n=3)      | Case 1: Both lungs: dilated airways and lymphatics : CPAM   |
|                                   | Case 2: The right lung appears large and occupies almost the entire thoracic cavity: CPAM   |
|                                   | Case 3: Laryngeal (Glottic) atresia : CHAOS   |
| Genitourinary abnormalities (n=3) | Case 1: BOO due to posterior urethral valve causing dilated posterior urethra, bladder, ureters and bilateral hydronephrosis. Ventriculomegaly, absent corpus callosum        |
|                                   | Case 2: Distal urethral stenosis with dilatation and hypertrophy of the urinary bladder: BOO. Pulmonary hypoplasia  |
|                                   | Case 3: BOO due to posterior urethral valves. Mild dilatation of both ureters and pelvis  |

CPAM- congenital pulmonary airway malformation; CHAOS- congenital high airway obstruction syndrome; BOO- bladder outlet obstruction; MVM-maternal vascular malperfusion; FVM- foetal vascular malperfusion; VUE- villitis of unknown aetiology; A/C CAM- acute chorioamnionitis

Authors did not find any chorangioma as a cause of NIHF.

**Intrathoracic lesions (n=3)**

There were 3 instances of intrathoracic lesions causing NIHF. Two cases of congenital pulmonary airway malformation (CPAM) (Figure 8) and one case of congenital high airway obstruction Syndrome (CHAOS)

were identified in our series. Mediastinal deviation was noted in all foetuses.

**Genitourinary abnormalities (n=3)**

Three foetuses with NIHF were complicated by genitourinary causes. Two of them had bladder outlet obstruction (BOO) due to posterior urethral valves, and the third one had distal urethral stenosis with dilatation and hypertrophy of the urinary bladder. However, one

subject with posterior urethral valve also had ventriculomegaly, absent corpus callosum, deep posterior fossa, hypoplastic ductus and pulmonary arteries.



**Figure 8: The right lung appears large and occupies almost the entire thoracic cavity. Left lung appears small; inset: in situ view (before evisceration).**

#### **Chromosomal abnormalities (n=4)**

Among cases with chromosomal abnormalities, we found one foetus with Turner syndrome, in which cytogenetic study revealed partial deletion of short arm of X chromosome. There were 3 cases of Down syndrome, all with typical phenotypic features and one foetus additionally had cardiac defect.

#### **Miscellaneous causes**

Congenital parvovirus B 19 infection was suspected in one instance. The foetus had marked subcutaneous oedema, serous effusions, enlarged liver and spleen. Lymphocytic infiltration of all viscera, predominantly myocardium with no identifiable inclusions were seen. The placenta had no lesion.

One of the foetus had hypertrophic pyloric stenosis which is a relatively uncommon cause of NIHF. The mother had polyhydramnios and autopsy revealed thickened and narrowed pylorus.

The cause of the hydrops foetalis could not be determined in only one case (4%) and it was classified as idiopathic. Subcutaneous oedema, serous effusions, micrognathia, high arched palate and dysmorphic villi were identified, and chromosomal abnormality was suspected. However, the karyotype was normal.

## **DISCUSSION**

Nonimmune hydrops foetalis is a clinical sequel of wide range of pathology and is not a diagnosis in itself. It is known to be associated with maternal, foetal and

placental diseases. In the past, the causes of hydrops were not identified in significant number of cases, even after extensive investigations. Postmortem examination including clinical assessments and targeted investigations can identify the underlying cause in majority of cases.

#### **Cardiovascular diseases**

Cardiovascular causes of NIHF accounts for about 20% of cases and includes both structural and functional defects.<sup>6</sup> In the present study cardiac defects represented the largest group and were found in 32% of foetuses.

Association of cardiac lesions with well-defined syndromes, chromosomal aberrations such as Down syndrome, cystic hygroma and additional major congenital anomalies were also noted in some of our cases.

The lone functional cardiac cause for hydrops identified in our study was complete heart block, which had serological evidence of maternal connective tissue disease. Even though sectioning is difficult, and time consuming, microscopic examination is critical in identifying fibrosis of the conduction system.

The cardiogenic hydrops would result from increase in right atrial pressure, reduced preload reserve and congestive cardiac failure.<sup>7</sup>

The immaturity of foetal myocardium (both structural and functional) with reduced relaxation is more vulnerable to any in utero insult leading to decrease in cardiac output.<sup>1</sup>

Hydrops associated with cardiac malformations generally have poor prognosis with high mortality. Recent developments in diagnostic capabilities of prenatal ultrasound along with in utero interventions will probably improve the outcome of foetuses with congenital cardiac lesions.<sup>8</sup>

#### **Placental lesions**

Interestingly, in present study group, placental lesions constituted the second most common cause of NIHF. Five of our patients demonstrated exclusive placental lesions significant enough to explain the aetiology of hydrops. Rodriguez et al, demonstrated placental pathology as the cause of hydrops in 10 patients (19.6%). In agreement with their study we too observed a similar incidence.<sup>9</sup>

Notwithstanding its rarity, we found placental mesenchymal dysplasia (PMD) as a unique pathology in two of our cases. PMD is an underreported and under recognized placental vascular anomaly causing hydrops.

It is characterized by placentomegaly (>90<sup>th</sup> percentile) with hydropic villi and absent trophoblastic proliferation.

The vascular changes observed in PMD might have led to heart failure with hydrops and ultimately resulting in intrauterine foetal demise.<sup>10</sup>

The other causes identified were maternal vascular malperfusion, foetal vascular malperfusion, villitis of unknown aetiology and acute chorioamnionitis.

### ***Intrathoracic lesions***

Among the intrathoracic causes (CPAM and CHAOS), an increase in intrathoracic pressure by enlarged lungs leading to impaired venous return could have contributed to foetal hydrops.<sup>11</sup>

### ***Genitourinary abnormalities***

Bladder outlet obstruction causing hydrops foetalis have been well documented in the literature. Mechanical obstruction of great vessels due to enlarged urinary bladder with resultant reduced venous return to heart is the underlying pathology.<sup>12</sup> Early onset oligohydramnios secondary to BOO leads to pulmonary hypoplasia, further reducing the survival chances.

### ***Chromosomal abnormalities***

In previously reported series of NIHF, chromosomal abnormalities were found in 10% of cases.<sup>4,6,13</sup> In the present study, there was 1 case of Turner syndrome and 3 instances of Down syndrome accounting for 16% of cases. Except for the Turner syndrome, none were confirmed by karyotyping. Among the 4 foetuses, 3 were identified in early gestation and one was associated with cardiac defect and cystic hygroma. Chromosomal analysis should be performed in all cases of NIHF, more so when identified in earlier gestation and when associated with structural anomalies.<sup>14</sup>

### ***Miscellaneous causes***

Intrauterine infections can cause foetal hydrops. There was one case of Parvovirus B19 infection in our study which showed hepatosplenomegaly with dense lymphocytic infiltration of myocardium. The underlying mechanisms include foetal anaemia, viral myocarditis and impaired hepatic function.<sup>14,15</sup> High index of suspicion and prenatal screening for intrauterine infections will make the interpretation easier. Incidence of "idiopathic" category varies among studies.<sup>9,16,17</sup> After detailed and systematic examination of foetuses including placenta, we found only one case (4%) of NIHF in which the cause was not identified. This highlights the value of autopsy with accompanying placental examination as the most complete procedure to establish the cause of NIHF.

### ***Ultrasound correlation***

Studies comparing the utilisation of foetal autopsy with prenatal USG findings have shown correlation in 98% of

cases.<sup>18,19</sup> But these studies did not involve cases with hydrops foetalis. In more than 50% of studied cases, autopsy examination either refuted or altered the USG diagnosis completely. Though it is known that USG might miss some findings due to many reasons like equipment quality, sonographer expertise, maternal body habitus and liquor volume, this gross discrepancy is speculative. This might emphasize the need for autopsy, especially in cases of hydrops to arrive at a final aetiological diagnosis.

Also worthy of mention are the absence / rare diagnosis of inborn errors of metabolism and infective diseases in our series of cases. A better and complete laboratory work up with utilization of immunohistochemistry for lymphatic dysplasia/viral inclusions may be helpful to overcome this low diagnostic yield.

The causes of NIHF is heterogenous and the survival of the foetus depends on the underlying aetiology. The most promising tool in understanding the aetiology of NIHF is systematic evaluation of the foetuses including placenta. Multidisciplinary approach including foetal imaging, laboratory work up, postmortem bacterial / viral culture, genetic study, complete autopsy with utilization of immunohistochemistry (when necessary) will identify the potential causes in foetuses with suspected NIHF. This will determine new strategies for in utero therapy, and thus make a positive impact on perinatal outcome. Knowledge about the aetiology and pathogenesis will provide a better correlation with risk of recurrence. It may also improve parental counselling and prevent similar mishaps in subsequent pregnancies.

## **CONCLUSION**

In conclusion, the autopsy provides the final diagnosis and enables us to understand the disease process and its natural history. The decline in clinical autopsies is a matter of great concern to the clinicians and pathologists alike. State of the art imaging devices and molecular biology techniques can complement, but not replace a comprehensive autopsy.

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