INTRODUCTION

Hydrops fetalis is a serious, life-threatening condition caused by excessive and abnormal fluid accumulation in the foetus. It is commonly diagnosed based on the demonstration of abnormal fluid collection in at least two foetal compartments. Historically, hydrops fetalis was primarily observed in association with Rhesus incompatibility. This aetiology is now rare owing to routine immunisation of Rhesus-negative mothers, and today most cases of foetal hydrops can be described as non-immune hydrops fetalis (NIHF). The survival of...
neonates born with NIHF has been reported to be poor, with several authors citing overall first-year survival for live-born infants affected by NIHF of slightly over 50%. However, there remains uncertainty about the true incidence of NIHF, as well as the underlying aetiologies and outcomes associated with the condition.

A commonly quoted incidence of NIHF is one per 1700 to 3000 pregnancies corresponding to 3.3-5.9 per 10 000 pregnancies. These values are based partly on studies conducted prior to the introduction of routine antenatal ultrasonography. More recent studies suggest a much higher incidence of NIHF during pregnancy. Published data on the incidence of NIHF at birth are also variable, and interpretation is complicated by differences between the populations studied, live births vs all births, and clinical settings, general vs specialist or intensive care (Table S1). In an extensive population-based epidemiological study published in 2017 including more than four million live births in the United States, 1037 cases of NIHF were identified corresponding to an incidence of 2.5 per 10 000 live births. Slightly higher incidences of NIHF have been reported in local studies by two independent groups. Hutchison et al found 2.7 per 10 000 and Graves et al 3.9 per 10 000 live births. A higher incidence of NIHF among live births of 8.4 per 10 000 was reported by Czernik et al. In a 2014 study undertaken by Takci et al, the incidence of NIHF based on cases referred to neonatal intensive care was 21.0 per 10 000 live births. Other series of NIHF identified in neonatal or tertiary care units have also shown high incidences, ranging from 12.9 to 24.4 cases per 10 000 deliveries, although it is likely that the elevated incidences in such studies may be explained by referral bias. To date, no large-scale population-based study estimating the NIHF incidence at birth has included stillborn infants. Furthermore, there are limited data available on the obstetric complications in pregnancies and deliveries in which the foetus has NIHF.

Many potential causes of NIHF have been described. In two systematic and extensive reviews of the aetiology of NIHF Bellini et al found the most common cause to be disorders of the cardiovascular system. However, in many cases the aetiology remains uncertain. In a study of 65 cases of NIHF, published in 2018 the cause remained unknown in 46%. Reports of smaller series and individual cases suggest that inborn errors of metabolism, such as the mucopolysaccharidoses and other lysosomal storage disorders, could explain some cases.

The aim of the present population-based case-control study was to evaluate the incidence of NIHF at birth over a 19-year period and to study morbidity and mortality associated with NIHF. An additional objective was to identify obstetric complications in pregnancies associated with NIHF.

2 | METHODS

The data for the birth cohorts used in this case-control study were obtained from the Swedish Medical Birth Register. The register is a mandatory, nationwide repository for data on pregnancy, delivery and neonatal care in Sweden, maintained since 1973 by the National Board of Health and Welfare. It has been reported to contain data on 97%-99% of all pregnancies and deliveries in Sweden. The study cohort included all cases of NIHF recorded at birth over a 19-year period from 1997 to 2015, during which time the International Classification of Diseases, Tenth Revision (ICD-10), was used consistently. Infants with NIHF were identified based on two ICD-10 codes: O36.2, maternal care for hydrops fetalis not associated with ABO and Rhesus isoinmunisation, and P83.2, hydrops fetalis not due to haemolytic disease. All pregnancies and births not affected by NIHF served as controls. A total of 1 936 492 births were recorded in the registry during the 19-year period. For all births, data on maternal characteristics, obstetric history, pregnancy complications, and birth and infant characteristics were extracted.

Births associated with NIHF were compared with those not associated with NIHF in a number of characteristics. Maternal factors were recorded including age, parity, body mass index (BMI), diabetes, smoking, birthplace of mother, within or outside Nordic countries, previous involuntary childlessness for more than two years, and previous spontaneous abortions and stillbirths. Complications related to the current pregnancy were noted including hypertension, gestational diabetes and pre-eclampsia. Birth data registered were obstetric interventions and infant characteristics including gestational age at birth, number of births, birthweight by gestational age, delivery mode and interventions, sex and survival.

Preterm births were grouped into three categories based on weeks of gestation: extremely preterm birth less than 28 weeks; very preterm birth, 28-31 weeks; and moderately preterm birth, 32-36 weeks. Infants were defined as small for gestational age (SGA), or large for gestational age (LGA) when weighing more than two standard deviations below or above, respectively, the expected birthweight for gestational age and sex according to Swedish intratuberine growth curves. Foetal death was recorded as stillbirth from gestational week 28+0 onwards until 2007 and thereafter from gestational week 22+0 onwards. Early neonatal death was defined as up to two weeks, late neonatal death 2-4 weeks, infant death 1-12 months and long-term survival after 12 months.

All births associated with NIHF in the Swedish Birth Register were linked to the Swedish National Patient Register and Swedish Cause of Death Register through each child’s unique identification.
number in order to explore morbidity and death, respectively. Causes of death were grouped into 12 categories using the ICD-10 codes listed in Table S2. Initial analysis included all causes of death allowing multiple causes to be entered for each infant. In a subsequent analysis, causes of death were organised in a hierarchical order so that an individual case was counted only once. Two different hierarchical orders were used. The first was constructed based on the reports by Bellini et al.\textsuperscript{15,16} This order included the following diagnostic categories in descending order: cardiovascular, haematological, lymphatic, genetic, syndrome or birth defect, inborn errors of metabolism or endocrine disorder, gastrointestinal, urogenital, maternal or placental problem including twin-to-twin transfusion, congenital infection, thoracic abnormality and miscellaneous causes.

The second order was constructed as considered relevant for neonatologists and genetic counsellors. This order included the following categories in descending order: genetic, syndrome or birth defect, inborn errors of metabolism or endocrine disorder, cardiovascular, lymphatic, congenital infection, haematologic, thoracic abnormality, urogenital, maternal or placental problem, gastrointestinal and miscellaneous causes.

Morbidity among the subset of children with NIHF surviving after 12 months of age was analysed based on records associated with hospitalisation. The presence of inborn errors of metabolism and endocrine disorders was searched for specifically in this cohort.

Statistical analyses were performed by analysis of crude odds ratios (OR) with 95% confidence intervals (CI) using the method proposed by Miettinen.\textsuperscript{24} Data completeness was assessed. Complete data (>95%) were available for all variables except maternal BMI (78.0% and 89.2% in the NIHF and control groups, respectively) and smoking (80.6% and 94.2% in the NIHF and control groups, respectively).

The study protocol was approved by the Regional Ethics Committee in Stockholm (approval number 2017/2311-31/2).

3 | RESULTS

A total of 1 936 492 births were available for analysis. NIHF was reported in 309 cases corresponding to an incidence of 1.6 per 10 000 births. Stillbirth was recorded in 45 (14.6%) cases in the NIHF group compared with 7051 (0.4%) stillbirths in the control group (OR 81.2, 95% CI 58.2-113.4), resulting in an incidence of NIHF among live births of 1.4 per 10 000.

Annual variation in the proportion of births affected by NIHF over the 19-year period was small, mean ± SD 1.6 ± 0.05 per 10 000. The sex distribution was similar in the NIHF and control cohorts, with males making up 53.1% and 51.4% of the groups, respectively.

Maternal characteristics for NIHF and control cohorts are presented in Figure 1. A greater proportion of mothers expecting NIHF infants were ≥35 years (27.5% vs 20.2%, respectively; OR 1.5, 95% CI 1.2-1.9) and had a BMI ≥ 30 (13.3% vs 10.4%, respectively; OR 1.6, 95% CI 1.1-2.2) compared with mothers of infants in the control cohort. Parity, smoking, country of origin and history of involuntary childlessness were similar between the groups. A history of previous stillbirth was more common in the NIHF cohort compared with controls (3.9% vs 1.3%, respectively; OR 3.1, 95% CI 1.7-5.5), but there was no difference between groups in terms of history of spontaneous abortion. Pre-existing diabetes was slightly more common among NIHF than control mothers (OR 2.9, 95% CI 1.1-7.8). The presence of essential hypertension did not differ between mothers in the NIHF and control groups (OR 2.6, 95% CI 0.84-8.21). There were marked differences in obstetric complications depending on whether or not the pregnancy was affected by NIHF (Figure 1). Pre-eclampsia occurred more often in the NIHF group than in controls, affecting 9.7% vs 3.1% of pregnancies, respectively (OR 3.4, 95% CI 2.3-4.9). Development of gestational diabetes did not differ between NIHF and control groups, affecting 0.6% and 1.0% of pregnancies, respectively.
There was a marked difference in gestational duration between NIHF pregnancies and controls (Figure 2). The majority, 77.7%, of the NIHF children were delivered at 36 weeks of gestation or earlier compared with 6.2% of controls. Delivery was extremely preterm in 9.4% vs 0.3% (OR 113.6, 95% CI 73.6-175.5), very preterm in 22.3% vs 0.7% (OR 143.6, 95% CI 102.8-200.6) and late preterm in 46.0% vs 5.2% (OR 37.4, 95% CI 31.4-44.5) of NIHF and control births, respectively. Multiple births were more common in the NIHF group than in controls, being observed in 12.3% vs 2.9% of deliveries, respectively (OR 4.6, 95% CI 3.3-6.5). As expected, more neonates were born LGA in the NIHF group than in the control group: 31.1% vs 3.5%, respectively (OR 13.6, 95% CI 10.6-17.4). Being born SGA was also more common in the NIHF compared with the control group: 8.4% vs 2.7%, respectively (OR 4.8, 95% CI 3.2-7.3).

Obstetric interventions were common in the NIHF group. In the NIHF group, 68.9% of infants were delivered by Caesarean section compared with 17.0% in the control group. The Caesarean sections were elective in 23.3% vs 7.3% of cases, respectively (OR 8.5, 95% CI 6.2-11.6), and emergency in 45.6% vs 9.7% of cases, respectively (OR 12.6, 95% CI 9.6-16.4) (Figure 2). There was no difference between groups in the proportion of babies delivered by forceps. Induction of labour was more frequent in the NIHF group than in the control group: 19.7% vs 12.5%, respectively (OR 1.7, 95% CI 1.3-2.3).

Overall survival at 12 months for children with NIHF was 50.2% compared with 99.3% in the control group. Of the 309 cases diagnosed with NIHF at birth, 45 (14.6%) were stillborn; hence, overall survival at 12 months for live-born infants with NIHF was 58.7%.

Among the 264 live-born infants with NIHF, 93 (35.2%) died during the neonatal period (29.9% within 2 weeks after birth; 5.3% between 2 and 4 weeks) and another 16 (6.1%) died between 4 weeks and 12 months. The risk of death during these time periods was higher in the NIHF vs the control group; mortality in the control group was 0.19% during the neonatal period (0.14% within 2 weeks [OR 375.5, 95% CI 285.3-494.3]; 0.05% between 2 and 4 weeks [OR 198.0, 95% CI 114.1-343.7]) and another 0.09% died between 4 weeks and 12 months (OR 114.9, 95% CI 68.5-192.7) (Figure 2). In addition to the 154 deaths reported in the first year of life in the NIHF group, four further deaths were reported after 12 months of age.

Causes of death reported for the NIHF group are given in Table 1. Multiple reasons for death were cited in many cases, and a total of 295 causes were reported in association with the 158 deaths. The most common causes of death were cardiovascular disorders and thoracic abnormalities. Cause of death was not specified in two-thirds of cases of stillbirth. The two hierarchical analyses of causes of death are shown in Table 2. According to first hierarchical system (Table 2a), the two most common causes of death during the first four weeks after birth were cardiovascular disorders (47.3%) and thoracic abnormalities (18.3%). The predominant cause of death occurring after four weeks of age was cardiovascular disorders (70.0%). Using the second hierarchical system (Table 2b), the predominant causes of death recorded in the neonatal period were again cardiovascular disorders (35.5%) and thoracic abnormalities (18.3%). Cardiovascular disorders remained
the predominant cause of death in the post-neonatal period, being associated with 55.0% of deaths.

Morbidity among the 151 long-term survivors born with NIHF, based on diagnoses recorded on hospitalisation, is presented in Table 3. The most common problems were cardiovascular disorders, haematological disorders and thoracic abnormalities. Twelve children had a diagnosis in the category inborn errors of metabolism or endocrine disorder, but no lysosomal storage disorders were reported. The endocrine and metabolic disorders involving hospitalisation included diabetes mellitus, hypopituitarism, thyrotoxicosis, hypothyroidism, endocrine short stature, hypoglycaemia, disorder of bilirubin metabolism, inappropriate anti-diuretic hormone secretion, hyponatraemia and alkalosis related to intense vomiting.

## 4 | DISCUSSION

The incidence of NIHF observed in this population-based case-control study including almost two million births recorded in a national register over a 19-year period was 1.6 per 10 000 births. When only live births were considered, the observed incidence fell to 1.4 per 10 000 live births. These results suggest the incidence of NIHF at birth to be lower than estimated in previous regional or single-centre epidemiological studies, as well as in the only large-scale population-based study to date of NIHF in live-born infants.

A potential explanation for the low incidence of NIHF at birth in the present study is that a high proportion of NIHF pregnancies ended early owing to late miscarriage or legal termination. The incidence of NIHF at birth is known to represent only a fraction of all cases of NIHF. In a study including ultrasound examination during pregnancy over an 8-year period, for example, 103 cases of NIHF were identified in 25 200 women, corresponding to an incidence of 40.9 per 10 000 pregnancies compared with the 1.6 per 10 000 at birth reported in the present study. Other large patient series suggest that the incidence during pregnancy may be even higher. Thus, many pregnancies affected by NIHF are ending prematurely. Although data on miscarriages were not captured within the Swedish Birth Register, the number of stillbirths is likely to have been greater than was reported in the current study owing to the use of a more conservative definition of stillbirth within the database during the first 10 years of the study, namely 28 weeks of gestation or later vs the more recent definition of 22 weeks of gestation or later. Furthermore, antenatal care is well developed in Sweden and free to all expectant mothers, most cases of NIHF during the study period will have been identified by routine ultrasound at an early stage of pregnancy, giving parents time to consider the option of a legal termination. Published data suggest that rates of legal termination may be high following detection of NIHF during pregnancy. In the recent study by He et al, 459 (95.2%) out of 482 cases of NIHF detected by ultrasonography during pregnancy ended in spontaneous or legal termination, with only 23 (4.8%) cases continuing to birth. Thus, legal terminations and late miscarriages may contribute to the lower incidence reported here compared with other studies.

A second explanation, but less likely explanation for the low incidence of NIHF, is that the ICD codes used to identify NIHF pregnancies did not capture all cases. However, as NIHF is an obvious condition at birth, it is reasonable to assume that reporting obstetricians and midwives would use the appropriate codes. Furthermore, ICD codes were used successfully to identify cases of NIHF in the only other population-based study by Steurer et al that found an
incidence of 2.5 per 10,000 live births. The low incidence reported in the present study was likely to be related to factors arising owing to the provision of free antenatal care throughout Sweden during the 19-year period studied. In fact, the homogeneous nature of antenatal and obstetric care in Sweden and extended time period of this population-wide study were key strengths of this investigation.

Understanding the challenges associated with NIHF in pregnancy and after birth is important so that appropriate antenatal care and genetic counselling can be given. Pregnancies affected by NIHF were associated with many obstetric complications. Most notably, there was a marked over-representation of preterm deliveries. Furthermore, 68.9% of NIHF babies were delivered by Caesarean section compared with only 17.0% of controls. A similar difference, with even higher rates of Caesarean section in both NIHF pregnancies and controls, 76.7% vs 33.4%, respectively, was previously reported by Steurer et al in the United States for the period 2005 to 2012. Pre-existing maternal diabetes mellitus was also found to be slightly more common, and multiplex pregnancies to be several-fold more common, among mothers in the NIHF group, observations in accordance with the findings of Steurer et al. As also seen by Steurer et al, maternal ethnicity did not seem to play a role in NIHF. At birth, NIHF infants in our study were more likely than controls to be born either LGA or SGA, again, mirroring previous findings. Rates of stillbirth in NIHF pregnancies were high.

The overall outcome for children born with NIHF is poor. In addition to a high rate of stillbirth, mortality during the first year, particularly during the first month, has been recognised to be high. We found 58.7% survival among live-born NIHF infants at 12 months. This is in line with reports by other investigators. In the study by Fukushima et al, 91 out of 145 live-born infants with NIHF survived to 12 months (54.5%). In the study by Steurer et al, 56.8% of live-born children with NIHF were alive at one year.

### TABLE 2

Same data on mortality as in Table 1 analysed in two different hierarchical orders. Each case was only included once

|                        | Stillbirth n = 45 | Death on day 0-27 after birth n = 93 | Death on day 28 or later n = 20 | Total number of deaths n = 158 |
|------------------------|------------------|-------------------------------------|---------------------------------|-----------------------------|
|                        | n    | %    | n    | %    | n    | %    | n    | %    |
| (a) Cause of death listed in hierarchical order 1 |           |           |           |           |           |           |           |           |
| 1. Cardiovascular       | 4    | 8.9  | 44   | 47.3 | 14   | 70.0 | 62   | 39.2 |
| 2. Haematological       | 1    | 2.2  | 8    | 8.6  | 0    | 0    | 9    | 5.7  |
| 3. Lymphatic            | 0    | 0.0  | 1    | 1.1  | 0    | 0    | 1    | 0.6  |
| 4. Genetic              | 1    | 2.2  | 3    | 3.2  | 1    | 5.0  | 5    | 3.2  |
| 5. Syndrome or birth defect | 1  | 2.2  | 3    | 3.2  | 0    | 0    | 4    | 2.5  |
| 6. IEM and endocrine disorder | 0 | 0.0  | 0    | 0    | 1    | 5.0  | 1    | 0.6  |
| 7. Gastrointestinal     | 0    | 0.0  | 1    | 1.1  | 0    | 0    | 1    | 0.6  |
| 8. Urogenital           | 0    | 0.0  | 0    | 0    | 0    | 0    | 0    | 0    |
| 9. Maternal or placental problem | 0 | 0.0  | 2    | 2.2  | 0    | 0    | 2    | 1.3  |
| 10. Congenital infection| 0    | 0.0  | 2    | 2.2  | 0    | 0    | 2    | 1.3  |
| 11. Thoracic abnormality| 0    | 0.0  | 17   | 18.2 | 0    | 0    | 17   | 10.8 |
| 12. Miscellaneous other | 38   | 84.5 | 12   | 12.9 | 4    | 20.0 | 54   | 34.2 |
| (b) Cause of death listed in hierarchical order 2 |           |           |           |           |           |           |           |           |
| 1. Genetic              | 1    | 2.2  | 10   | 10.8 | 3    | 15.0 | 14   | 8.9  |
| 2. Syndrome or birth defect | 1  | 2.2  | 10   | 10.8 | 1    | 5.0  | 12   | 7.6  |
| 3. IEM or endocrine disorder | 0 | 0    | 0    | 0    | 1    | 5.0  | 1    | 0.6  |
| 4. Cardiovascular       | 4    | 8.9  | 33   | 35.5 | 11   | 55.0 | 48   | 30.3 |
| 5. Lymphatic            | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0    |
| 6. Congenital infection | 0    | 0    | 2    | 2.1  | 0    | 0    | 2    | 1.3  |
| 7. Haematological       | 1    | 2.2  | 6    | 6.4  | 0    | 0    | 7    | 4.4  |
| 8. Thoracic abnormality | 0    | 0    | 17   | 18.3 | 0    | 0    | 17   | 10.8 |
| 9. Urogenital           | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0    |
| 10. Maternal or placental problem | 0 | 0    | 2    | 2.1  | 0    | 0    | 2    | 1.3  |
| 11. Gastrointestinal    | 0    | 0    | 1    | 1.1  | 0    | 0    | 1    | 0.6  |
| 12. Miscellaneous other | 38   | 84.5 | 12   | 12.9 | 4    | 20.0 | 54   | 34.2 |

Note: Hierarchical order 1 was constructed based on that applied by Bellini et al. Hierarchical order 2 was constructed by the authors as considered relevant for neonatologists and genetic counsellors.

Abbreviation: IEM, inborn error of metabolism.
hierarchically as applied by Bellini et al.

In agreement with this finding, Ota et al.\textsuperscript{29} cited developmental issues in many NIHF survivors. Our study did not provide any support for the suggestion that metabolic diseases, including lysosomal storage disorders, may be over-represented among survivors of NIHF.

The present study provides a comprehensive analysis of NIHF in a large number of pregnancies over a prolonged period. The information was obtained from the Swedish Medical Birth Register, which records information on 97%-99% of all births in the country, allowing an accurate assessment of the incidence of NIHF at birth in Sweden.

Long-term follow-up of morbidity and mortality was possible to be comprehensively assessed using two additional national registries, the Swedish National Patient Register and the Swedish Cause of Death Register. However, our results did not allow for an estimate of the total incidence of NIHF during pregnancy, and our study could only provide an incomplete assessment of cause of death for stillborn infants.

### 5 CONCLUSION

In this large population-based study, we found a lower incidence of NIHF at birth in Sweden than previously reported in other countries. The lower incidence of NIHF compared with earlier studies most likely reflected a combination of factors, primarily a widespread provision of free antenatal and obstetric care. It was confirmed that NIHF at birth is often an indicator of severe underlying diseases and is associated with a poor prognosis, with long-term survival just over 50%.

Our findings on pregnancy and obstetric complications associated with NIHF should be important considerations for healthcare professionals involved in antenatal care and genetic counselling.

### CONFLICT OF INTEREST

SH is co-founder and shareholder of Guard Therapeutics (former A1M Pharma), Lund, Sweden. RG has been medical affairs consultant to Ultragenyx. Other authors have no conflicts of interest to declare.

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| Diagnosis recorded on hospitalisation | Number | % |
|--------------------------------------|--------|---|
| Cardiovascular                       | 53     | 35.8 |
| Haematological                       | 53     | 35.8 |
| Thoracic abnormality                 | 32     | 21.2 |
| Syndrome or birth defect             | 31     | 20.5 |
| Lymphatic                            | 15     | 9.9  |
| IEM or endocrine disorder            | 12     | 7.9  |
| Congenital infection                 | 12     | 7.9  |
| Genetic                              | 5      | 3.3  |
| Miscellaneous other                  | 12     | 7.9  |

Abbreviation: IEM, inborn error of metabolism.
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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.