## Chapter 8

# Long-term neurodevelopmental and cardiovascular outcome after intrauterine transfusions for fetal anaemia: a review

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## Abstract

Perinatal survival rates after intrauterine transfusions (IUT) for red cell alloimmunisation now exceed 90%, which demonstrates the safety and efficacy of one of the most successful procedures in fetal therapy. However, improved perinatal survival could lead to an increased number of children with long-term disabilities. The importance of long-term follow-up studies in fetal therapy lies in both the necessity of evaluation of antenatal management as well as in evidence-based preconceptional and prenatal counselling. This review describes the possible long-term cardiovascular and neurodevelopmental sequelae after IUT treatment for different indications including red cell alloimmunisation, parvovirus B19 infection, fetomaternal haemorrhage and twin anaemia-polycythaemia sequence.

## Introduction

Since the introduction of the intravascular intrauterine blood transfusion (IUT) in 1981 by Rodeck [1], this technique has become a safe and successful method for the treatment of fetal anaemia in centres all over the world [2, 3]. Nowadays, the standard direct access to the fetal vasculature for transfusion is the umbilical vein in the cord or the intrahepatic portion of the umbilical vein. IUT is considerably more successful at reversing hydrops than intraperitoneal transfusion [4]. which was the first concept of intrauterine fetal blood transfusion introduced by Liley in 1963 [5].

Universal use of Rh(D) immunoglobulin prophylaxis has dramatically reduced the need for IUT. However, the procedure continues to be an essential treatment of severe fetal anaemia for a variety of causes. The main indication for IUT is fetal anaemia due to red cell alloimmunisation. Other common causes of severe fetal anaemia are parvovirus B19 infection and chronic fetomaternal haemorrhage (FMH). Rarely, IUT is used in the management of inter-twin fetal transfusion due to twin anaemia-polycythaemia sequence (TAPS) or twin-to-twin transfusion syndrome (TTTS), inherited red cell disorders and fetal and placental tumours.

At our institution in the past 24 years, 1678 IUTs were performed in 634 pregnancies for the following indications: red cell alloimmunisation (86%, 548/634), parvo B19 infection (9% 55/634), FMH (1.3% 8/634) and TAPS/TTTS (3.6% 23/634). Survival rates were 91% (500/548), 76% (42/55), 100% (7/7, one pregnancy outcome was lost to follow-up) and 87% (20/23), respectively.

When left untreated, fetal anaemia may result in cardiac failure, hydrops, hypovolemic shock, fetal or neonatal death, and neurologic injury or cerebral palsy (CP) [6-8]. Nowadays, perinatal survival rates after IUT for red cell alloimmunisation exceed 90% [8-10], which demonstrates the safety and efficacy of one of the most successful procedure in fetal therapy. In parvovirus B19 infection, perinatal survival after treatment with IUT is lower and ranges from 67% to 85% [11-14]. As perinatal survival after IUT is improving, one of the concerns is that this may be associated with an increase of the number of children with long-term disabilities. The importance of long-term follow-up studies in fetal therapy lies in both the necessity of evaluation of antenatal management as well as in evidence-based preconceptional and prenatal counselling. Several long-term follow-up studies after IUT have been performed, but most of them focused on neurodevelopmental outcomes [11, 13, 14, 19-24, 26-28, 32]. There is a paucity of long-term outcome data on other organ systems, in

particular the heart. It is well recognised that events during early fetal life may have severe health repercussions in adult life and may lead to coronary heart disease, diabetes, hypertension and adult metabolic disease: the so-called developmental origins of adult disease (Barker) hypothesis [15].

This review focuses on long-term neurodevelopmental and cardiovascular follow-up of survivors after IUT and summarises follow-up data from the literature and from our study population. The review is structured according to different IUT indications. Cohort studies from the literature evaluating the long-term outcome after fetal anaemia treated with IUT were available for the indications maternal red cell alloimmunisation and parvovirus B19 infection.

## Long-term neurodevelopmental outcome after IUT

**Red cell alloimmunisation**

Fetal and neonatal haemolytic disease results from maternal alloimmunisation to red cell antigens, for which mother and fetus are incompatible. Maternal IgG antibodies pass the placenta into the fetal circulation and cause destruction of fetal red cells. The most prevalent anti-red cell antibodies causing fetal anaemia are anti-D, anti-Kell and anti-c. In contrast to Rhesus D haemolytic disease, fetal anaemia in Kell immunisation results predominantly from suppression of erythropoiesis rather than from haemolysis of erythrocytes [15, 16]. Severe fetal anaemia may lead to impaired systemic oxygen supply and eventually to fetal cerebral injury. One study reported an increased incidence of cerebral abnormalities detected with cranial ultrasound in neonates treated with IUT [17]. This study was however hampered by important methodological limitations, including the lack of a control group. Because no follow-up was conducted, no conclusion could be drawn regarding possible associations between the sonographic cerebral lesions and impaired long-term neurological outcome. Severe anaemia in the neonatal period may also lead to increased risks of cerebral injury and adverse neurodevelopmental outcome [18].

The impact of severe fetal and neonatal anaemia on the development of the brain can only be estimated accurately with long-term follow-up studies. Until recently, only a few small studies reported on the long-term neurodevelopmental outcome after IUT for alloimmune anaemia. The incidence of severe adverse outcome ranged widely from 3% to 19% (table 1) [19-24, 26-28]. Doyle *et al*. first reported on the sensorineural outcome at 2 years of age in 38 survivors of IUTs [19]. The majority of these infants (87%) showed no minor or major

sensorineural disability. The transfusion group compared favourably with both high-risk survivors of very low birth weight and low-risk children of normal birth weight.

Stewart et al. compared the developmental outcome of eight infants who received IUT with eight infants requiring close monitoring for red cell alloimmunisation but no IUT [20]. In this small study group, the authors found no difference in developmental outcome, and neither group was different from the population as a whole. In a larger study performed by our group more than a decade ago, 69 infants ranging from 6 months to 6 years of age were followed up. The neurodevelopmental outcome of these children compared favourably with a group of high-risk, very low birth weight infants, but less favourably with a healthy control group [21]. Hudon et al. studied the neurodevelopmental outcome in 33 infants treated with IUT [22]. One child was diagnosed with right spastic hemiplegia and one child with bilateral deafness. Both the Gesell Scale (n = 22, 9–18 months) and the McCarthy Scale (n = 11, 36–62 months) developmental scores were within average, and no association was found with presence of fetal hydrops. Grab et al. described the neurological outcome in 35 infants treated with IUTs for severe erythroblastosis [23]. At 6 years of age, no minor or major neurological impairment was observed, even when severe cases with hydrops fetalis or extremely low haemoglobin levels were included. However, survivors were not individually investigated or tested for neurodevelopment, and conclusions were solely based on questionnaires completed by the child's primary care givers. Farrant et al. reviewed the neurodevelopmental status of IUT recipients [24]. Follow-up information on 36 infants revealed that one infant, born prematurely following the death of the co-twin due to TTTS, had CP and developmental delay. Fetal demise of a co-twin in monochorionic twins is an important risk factor for severe cerebral injury and neurodevelopmental impairment (NDI), irrespective of the presence of red cell alloimmunisation [25]. No other infant had neurodevelopmental abnormalities. Little information on the patients and methods was reported, for example, the age of the children at assessment. Harper et al. evaluated long-term outcome in 18 hydropic fetuses treated with IUT [26]. Death or major NDI occurred in 22% (4/18) of the infants, and 12% (2/16) of the survivors had major neurological sequelae. Six of the 16 survivors (38%) had minor physical or neurological impairment. With data obtained from computerised questionnaires, Weisz et al. reported developmental outcome in 40 infants [27]. Pregnancies treated with IUTs for fetal anaemia were divided into two groups: mild to moderate anaemia and severe anaemia. Major NDI was not reported. There were no significant differences in motor development score, incidence of abnormal cognitive development and percentage of children needing supportive therapy between the mild and severe cases. Accurate interpretation of the results of these studies is limited by several methodological factors including small sample size and often less optimal methods used to assess the neurodevelopmental outcome. To enable

valid comparisons between these follow-up studies, uniform and well-described criteria for an adverse outcome are needed.

**Long-term outcome after IUT at our centre**

We recently performed a large study (LOTUS 1 study) in 291 children with an age at follow-up ranging from 2 to 16 years (median age: 8.2 years) (table 1) by using standardised developmental tests according to the children's age [28]. The lost-to-follow-up rate was 15% (51/342). Major NDI was defined as the presence of at least one of the following: CP, severe developmental delay, bilateral blindness and/or deafness. Minor NDI was defined as a moderate abnormality of tone, posture and movement leading to only minor functional impairment or mild developmental delay. A developmental test score of 70 to 84 indicates mild delay (i.e., less than −1 SD), and a score <70 indicates severe delay (i.e., less than −2 SD).

The vast majority (over 95%) of children had a normal neurodevelopmental outcome. The incidence of severe developmental delay found in our study (3.1%) was in line with the Dutch normative population (2.3%). However, the rate of CP (2.1%) was slightly higher compared with the general population (0.7% at 32–36 weeks' gestation [29] and 0.2% at 37 weeks' gestation [30]). The overall rate of NDI was 4.8% (14/291). In a multivariate regression analysis, including prenatal and postnatal factors, the following risk factors were independently associated with NDI: number of performed IUTs (odds ratio (OR) 2.3 per IUT; 95% confidence interval (CI) 1.1–4.6; $p = 0.02$), severe neonatal morbidity (OR 85.6; 95% CI 9.7–755.3; $p < 0.001$) and parental education (OR 8.4; 95% CI 2.2–31.5; $p = 0.002$). In another multivariate regression analysis including only preoperative risk factors, only severe hydrops was independently associated with NDI (OR 11.2; 95% CI 1.7–92.7).

Importantly, even in children without obvious disabilities, subtle abnormalities may occur, which include increased behavioural problems or quality of life issues. These issues were not included in the LOTUS 1 study but are currently being evaluated in the LOTUS 2 study. Results of this study will be available in 2013.

In conclusion, long-term neurodevelopmental outcome after IUT for maternal red cell alloimmunisation is favourable. Risk factors for severe NDI are severe hydrops, number of IUTs performed, severe neonatal morbidity and lower levels of parental education.

**Parvovirus B19 infection**

Human parvovirus B19 is a potent inhibitor of haematopoiesis. It causes bone marrow failure, by affecting the erythroid-lineage cells, which are well-known target cells for B19. These target cells are found on erythrocyte progenitor cells (erythroblasts and megakaryocytes) and also on erythrocytes, synovium, placental tissue, endothelial cells and fetal myocardium. A fetus affected by parvovirus B19 may show signs of severe hydrops, anaemia and cardiomegaly on ultrasound investigation.

A neuroimaging study in neonates with intrauterine parvovirus B19 infection suggested that this virus may have neurotropic characteristics (infecting nerve cells) and therefore causes cerebral injury [31]. Four studies evaluated the long-term outcome after IUT for parvovirus B19 infection during pregnancy, all limited by a small sample size [11, 13, 14, 32]. These studies are summarised in Table 2.

Miller et al. described seven hydropic fetuses of which three survived, two after IUT [32]. A questionnaire sent to the parents and general practitioner did not reveal developmental or general health problems. The small size of this study and the suboptimal follow-up programme using questionnaires prevented meaningful conclusions. In 2002, Dembinski et al. described long-term follow-up in 20 survivors of parvovirus B19-induced fetal hydrops treated with IUT until 13 months to 9 years of age [13]. On clinical follow-up, no major neurodevelopmental sequelae were evident. Neurodevelopmental scores of all children ranged within 2 SD of a normal population (median 101, range 86–116) and exceeded 1 SD in three children. However, this study was limited by a high lost-to-follow-up rate (35%).

**Long-term outcome after IUT at our centre**

Our research group published two follow-up studies evaluating the long-term outcome after parvovirus B19 infection in pregnancy requiring IUT (table 2) [10, 11]. In 2007, Nagel et al. evaluated the long-term outcome in 16 hydropic fetuses. Neurodevelopment was normal in 11 children (68%) [11]. Two children had severe developmental delay and neurological abnormalities (ataxia and hypertonia), and three children were diagnosed with mild developmental delay. Two children had minor congenital defects. However, five children were younger than 1.5 years of age at the time of testing and thus too young for reliable assessment. More recently in 2012, we studied a larger group (28 children) and evaluated the long-term outcome at an older age (median age of 5 years; range 1.5–13) [10]. Criteria for adverse outcome were previously described. [28] Hydrops was present in all fetuses. NDI was diagnosed in 3 of 28 (11%) children, including one child with combined CP and severe developmental delay and two children with isolated severe developmental delay.

Overall, severe neurodevelopmental problems after IUT for parvovirus B19 infection in pregnancy is not a rare finding and may occur in up to 12.5% of children. The causes for a possible increased rate of cerebral injury and adverse neurodevelopmental outcome in parvovirus B19 infection are still not fully understood. Adverse outcome may be directly related to either viral infection itself or, alternatively, the compromised condition of the fetus with severe anaemia and hydrops.

**Table 1**. *Long-term neurodevelopmental outcome after IUT for red cell alloimmunisation; summary of the literature.*

| First author (year) | Patient number | Follow-up years | Fetal hydrops % | Outcome measures | Normal neurodevelopmental outcome % | Minor neurodevelopmental impairment % | Major neurodevelopmental impairment % |
|---|---|---|---|---|---|---|---|
| **Doyle (1993)** | 38 | 2 | 29 | Bayley Scales | 87 | 5.3 | 7.9 |
| **Stewart (1994)** | 8 | 3 - 4 | NA | Cattell infant intelligence test | 100 | NA | 0 |
| **Janssens (1997)** | 69 | 0.5 - 6 | NA | Van Wiechen, POPS, Gesell Schedules, Denver Screening Test | 84 | 9 | 7 |
| **Hudon (1998)** | 33 (22+11) | 1.3 - 5.2 | 45 | Gesell developmental studies (n=22), McCarthy Scales of Children's Abilities (n=11) | 97 | NA | Spastic hemiplegia 3.0 (1/33) Bilateral deafness 4.8 (1/22) |
| **Grab (1999)** | 35 | 6 | 20 | Neurological examination based on questionnaires | 100 | 0 | 0 |
| **Farrant (2001)** | 36 | NA | NA | Local paediatrician requested information | 97 | NA | 2.8 |
| **Harper (2006)** | 16 | 4.5 – 12.9 | 100 | Differential Ability Scales, Wide Range Assessment, Gordon Diagnostic System | 49 | 38 | 13 |
| **Weisz (2009)** | 40 | 1-9 | 13 | Computerised questionnaires | 97 | 3 | 0 |
| **Lindenburg (2011)** | 291 | 2 - 17 | 26 | Bayley Scales, Wechsler Scales, Touwen | 81 | 14 | 4.8 |

NA = not available

**Table 2.** *Long-term neurodevelopmental outcome after IUT for parvovirus B19 infection; summary of the literature.*

| First author (year) | Patient number | Follow-up *years* | Fetal hydrops % | Outcome measures | Normal neurodevelopmental outcome % | Minor neurodevelopmental impairment % | Major neurodevelopmental impairment % |
|---|---|---|---|---|---|---|---|
| **Miller (1998)** | 2 | 7-10 | 100 | Questionnaires | 100 | 0 | 0 |
| **Dembinski (2002)** | 20 | 1.1-9 | 100 | Snijders Oomen Non-Verbal Intelligence Test, Kaufmann Assessment Battery for Children, Griffiths Test | 100 | 3 | 0 |
| **Nagel (2007)** | 16 | 0.5-8 | 100 | Bayley Scales, Snijders Oomen Non-Verbal Intelligence Test | 68 | 18.8 | 12.5 |
| **de Jong (2012)** | 28 | 1.5-13 | 100 | Bayley Scales, Wechsler Scales | 79 | 11 | 11 |

**Fetomaternal haemorrhage**

Chronic or acute FMH can also lead to fetal anaemia. When severe, these pregnancies present clinically because of decreased or absent fetal movements. The fetal heart rate may be sinusoidal, and ultrasound examination often reveals hydrops and high middle cerebral artery peak systolic velocities. A Kleihauer–Betke test, or other technique for detection of fetal blood in the maternal circulation, is needed to confirm the diagnosis.

The available evidence for the long-term neurodevelopmental outcome after FMH in pregnancy consists of isolated (dated) case reports and small series of cases treated without intrauterine intervention [33-37]. Fay et al. in 1983 described an infant with CP after severe FMH [33]. Boyce et al. reported an infant born after an estimated FMH of 240 mL [34]. At age 1 month, an MRI revealed an area of focal brain atrophy. The neurologic evaluation at that time was considered normal. However, additional follow-up was not documented. Almeida et al. reported the neurological outcome in 15 patients with FMH of at least 80 mL [35]. One infant was diagnosed with CP at 6 years of age. A head computer tomography showed periventricular cysts. Kesckes et al. evaluated the short-term neurological outcome of 16 neonates with demonstrated FMH > 20 mL [36]. Five (31%) had an adverse outcome: death in three patients and periventricular leukomalacia in two patients. Adverse outcome was better predicted by haemoglobin at birth than by estimated volume of haemorrhage as calculated with the Kleihauer test. Rubod et al. studied 31 children at a mean age of 4.7 years (range 1.5–8.9) [37]. Lost-to-follow-up rate was high, 26% (11/42). Long-term outcome was assessed with a questionnaire. One infant had developmental delay at 1 year of age and was diagnosed with mitochondrial cytopathy. Except for this child, none of the children in this follow-up group died or had neurological sequelae.

In conclusion, the risk of adverse neurodevelopmental outcome in long-term survivors after severe FMH-induced anaemia (without IUT treatment) appears to be increased. Whether the outcome could be improved in cases with FMH treated with IUT is not known because of lack of follow-up studies. Large multicenter follow-up studies are therefore urgently required in order to determine the long-term outcome in this subgroup of children with severe FMH.



**Twin anaemia-polycythaemia sequence**

Twin anaemia-polycythaemia sequence is a newly described disease in monochorionic pregnancies that is characterised by large intertwin haemoglobin differences without signs of oligo-polyhydramnios sequence [38]. The pathogenesis of TAPS is based on a unique

placental angioarchitecture characterised by the presence of only few, minuscule arteriovenous vascular anastomoses. These minuscule anastomoses allow a slow transfusion of blood from the donor to the recipient leading gradually to highly discordant haemoglobin levels. TAPS occurs spontaneously in 3% to 5% of monochorionic twins (spontaneous TAPS) and in up to 13% of TTTS cases treated with laser surgery (post-laser TAPS). There are several treatment options in TAPS, including expectant management, induction of labour, selective feticide, (repeat) fetoscopic laser surgery or IUT. IUT treatment is considered as a temporary symptomatic treatment (for the donor) and not as a causal treatment. Transfusing the donor may potentially result in worsening the polycythaemia in the other twin. Perinatal outcome in TAPS varies from mild haematological complications to severe cerebral injury and perinatal death [39].

We recently described the short-term outcome in 38 neonates after TAPS in a case–control study [40]. Each twin pair with TAPS was compared with two monochorionic twin pairs unaffected by TAPS or TTTS. We found no difference in risk of severe cerebral injury in the TAPS group compared with the control group. The long-term outcome was not reported. In a recent case report describing three donor twins treated with IUT, cerebral injury was detected in one neonate [41]. Magnetic resonance imaging showed numerous large cysts in the basal ganglia, bilateral white matter injury, multiple micro-haemorrhages and a parenchymal haemorrhage in the right occipital lobe. Because of the severe cerebral injury, intensive care treatment was withdrawn, and the infant died 6 days after birth. In the two other donors, no abnormalities were found on neonatal cerebral ultrasound examinations. In contrast, in another spontaneous TAPS case, severe cerebral injuries were detected in the recipient twin due to severe polycythaemia-hyperviscosity [42]. Both fetal anaemia and fetal polycythaemia may thus lead to cerebral injury in neonates with TAPS.

Follow-up data on the long-term neurodevelopment outcome in TAPS are very limited. In a large multicenter long-term follow-up study of 212 TTTS pregnancies treated with laser surgery, 16 pregnancies (4%) were affected by TAPS [43]. Four donor twins were treated with IUTs. Perinatal survival in these 16 post-laser surgery TAPS cases was 75% (12/16). All 12 surviving TAPS infants were evaluated at 2 years of age with a complete follow-up examination that included a Bayley developmental test. None of these infants had long-term NDI.

In conclusion, cerebral injury in TAPS cases treated with or without IUT may be less uncommon than initially thought. Large multicenter follow-up studies are therefore urgently needed to determine the long-term neurodevelopmental outcome in TAPS.

## Long-term cardiovascular outcome after IUT

**Red cell alloimmunisation**

The chronic, progressive anaemia caused by immune-mediated haemolysis in the fetus results in the need for increased cardiac output. Chronic cardiac compromise may lead to myocardial hypertrophy. Oberhoffer et al. evaluated fetal cardiac changes associated with alloimmune anaemia by means of echocardiography [44]. Thirty anaemic fetuses received a total of 76 IUTs. Before the procedure, end-diastolic myocardial wall thickness and ventricular dimensions together with Doppler flow patterns at the atrioventricular and semilunar valves were measured. Symmetrical myocardial hypertrophy was observed in these anaemic fetuses. Fetal myocardial hypertrophy in anaemia may be the result of an increased cardiac workload, indicated by the increased left ventricular mean velocities.

Animal studies have shown that even a brief period of fetal anaemia may result in permanent changes of the coronary vasculature [45]. The impact of these vascular changes on cardiovascular disease in sheep adult life is not clear. Bigras et al. evaluated the cardiovascular impact of fetal anaemia by reviewing echo-Doppler examinations in 24 human fetuses [46]. This study demonstrated that severe fetal anaemia alters the fetal circulation significantly, shown by an enlargement of cardiac cavities and by increased Doppler flow velocities through the mitral valve and the aortic outflow tract. The increased velocities and decreased pulsatility index are most likely resulting from increased cardiac output, vasodilatation and decreased blood viscosity, similar to the well-known increased flow velocities in peripheral vessels. The authors conclude that fetuses with severe anaemia develop mild cardiomegaly but do not manifest tachycardia or increased cardiac contractility.

Only a few small studies have evaluated the cardiovascular impact of severe fetal anaemia after birth. Myocardial hypertrophy in neonates with haemolytic disease was first described in 1990 [47]. Echocardiograms were performed in the first 48 h of life in ten newborns. In five patients, disproportionate septal hypertrophy was demonstrated. Neonates who had not received IUTs had a higher mean septal : left ventricular free-wall ratio than neonates after IUT treatment, which may indicate a sparing effect of IUTs. Only one study evaluated cardiac function in children who received IUTs for alloimmune anaemia, using echocardiography to estimate cardiac structure and function in order to investigate the potential effects of anaemia and hypoxia on the developing fetal heart [48]. Twenty-five children at a mean age of 10 years (range 3.6–15.8) were recruited for the case group and matched with 25 healthy children for the control group. Hydrops was present in 32% (8/25) of children in the case group. An echocardiography examination with 12 different measurements was performed to

evaluate cardiac structure and function. The authors concluded that these children had significantly smaller left ventricular mass. However, this is currently speculative and limited by small sample size and requires validation from further studies.

To conclude, limited data indicate that haemolytic disease of the fetus and neonate treated with IUT may lead to less myocardial mass in childhood. The long-term cardiovascular impact into adult age requires further investigation.

**Parvovirus B19 infection**

In children, parvovirus B19 infection has been implicated as a causative agent of myocarditis. Although myocarditis is relatively uncommon, it can cause significant morbidity and mortality [49]. With the end-point death or heart transplantation, Mc Carthy et al. evaluated 15 patients with fulminant myocarditis due to parvovirus B19 infection [50]. Aggressive haemodynamic support was warranted for patients with this condition. However, long-term cardiovascular impact of parvovirus B19 infection in childhood was not reported. In a retrospective study of 11 children with fulminant myocarditis, Amabile et al. reported only one death [51]. The remaining ten survivors had normalisation of systolic function within the first year. In this cohort, two patients had parvovirus B19 myocarditis and had a complete recovery after intensive care hospitalisation.

Overall, parvovirus B19-induced fetal anaemia may lead to cardiovascular sequelae on the long-term, which may result from severe intrauterine anaemia or viral-induced myocarditis, or a combination of both.

## Discussion and conclusion

Long-term neurodevelopmental outcome after IUT for maternal red cell alloimmunisation is considered favourable as the vast majority (>95%) of children have a normal neurodevelopmental outcome. The risk of delayed neurodevelopment in long-term survivors after IUT for parvovirus B19 infection appears to be increased. However, the evidence thus far is limited by small numbers and absence, in most centres, of a structured long-term follow-up strategy. The causes for a possible increased rate of NDI are still not fully understood and could be related to cerebral injury caused by parvovirus B19 itself. Cerebral injury caused by ischaemia after severe fetal anaemia and fetal hydrops might provide another explanation for the increased rate of developmental delay. Fetuses requiring IUT for alloimmune anaemia may be at increased risk for NDI, particularly in the presence of fetal hydrops [28]. In the LOTUS study, the incidence of CP and severe developmental delay in the subgroup with fetal hydrops was 12% (9/75), which is in line with the reported rate after IUT for anaemia due to parvovirus B19 infection [14]. The underlying mechanism causing cerebral damage and long-term NDI in hydropic fetus is not yet known. Prevention of fetal hydrops by timely detection, referral and treatment may improve long-term outcome. Routine perinatal neuroimaging after IUT treatment cannot yet be recommended because of the limited data on benefit and long-term outcome prediction. Data on long-term neurodevelopmental outcome after IUT for other indications are extremely limited. In neonates with severe FMH-induced anaemia, the risk of cerebral injury appears to be increased. However, no conclusions can be made regarding the long-term neurodevelopmental outcome in survivors after FMH treated with IUT because of lack of follow-up studies. Moreover, a uniform definition of (severe) FMH is lacking. In neonates with TAPS, recent studies suggest that cerebral injury may occur in the anaemic donor as well as in the polycythaemic recipient. In analogy with FMH, lack of follow-up studies in TAPS prevents reaching reliable conclusions on the long-term neurodevelopmental outcome in this subgroup.



The short-term and long-term cardiovascular outcome after IUT is also not well known. Haemolytic disease of the fetus and neonate may lead to less myocardial mass in childhood. Parvovirus B19-induced fetal anaemia may lead to cardiovascular sequelae on the long-term, which may result from severe intrauterine anaemia or viral-induced myocarditis (or a combination of both). However, this is currently speculative and requires validation from further studies. Although there are data to assess the cardiovascular impact of fetal anaemia, no studies on long-term cardiovascular effects of fetal anaemia into adulthood have been reported to date. The oldest survivors after IUT treatment are now older than 30 years.

According to the so-called developmental origins of adult disease (Barker) hypothesis, accurate monitoring of the cardiovascular impact and general health in these adults would be of great interest. This is currently being investigated in the ANAEMIA study at the University of Auckland in New Zealand, the same place where Sir William Liley actually performed the first in utero transfusion in 1963 (http://www.liggins.auckland.ac.nz/uoa/anaemia-study). In addition, whether the outcome differs from alloimmune anaemia still remains unanswered and provides a basis for further study.

Because of the rarity of the clinically recognised cases, the required adequately sized and appropriately performed long-term follow-up studies are difficult to perform. Therefore, international collaboration between studygroups involved in the care of these children is of great importance in order to increase our knowledge and understanding of the possible deleterious effects of fetuses with fetal anaemia due to different pathogenesis. A better understanding of the effect of IUT and fetal anaemia on child development will allow more evidence-based parental counselling and targeted interventions to optimise child development when needed. Uniform criteria for NDI including formal psychological testing with standardised measures are essential.

**WHAT'S ALREADY KNOWN ABOUT THIS TOPIC?**

- IUT is the international standard treatment for severe fetal anaemia.
- Short-term perinatal outcome after IUT for red cell alloimmunisation is good, with perinatal survival rates exceeding 90% in experienced centres.

**WHAT DOES THIS STUDY ADD?**

- Long-term neurodevelopmental outcome after IUT for maternal red cell alloimmunisation is favourable as the vast majority (>95%) of children have a normal neurodevelopmental outcome.
- Severe fetal hydrops is a risk factor for adverse long-term outcome.
- The risk of neurodevelopmental impairment in long-term survivors after IUT for parvovirus B19 infection appears to be increased.
- The impact of severe fetal anaemia on cardiovascular disease into adult life has not been investigated and requires further study.

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