Clinical Commissioning Urgent Policy Statement
Maternal intravenous immunoglobulin administration for prevention of alloimmune fetal and neonatal haemochromatosis

NHS England reference: 170124P

Commissioning Position

Maternal intravenous immunoglobulin administration for prevention of alloimmune fetal and neonatal haemochromatosis is recommended to be available as a treatment option through routine commissioning within the criteria set out in this document.

Information about maternal intravenous immunoglobulin administration for prevention of alloimmune foetal and neonatal haemochromatosis.

The intervention

The treatment population group are pregnant mothers with a history of previous fetus or neonate affected by alloimmune neonatal haemochromatosis (NH), in who there is a clear risk of recurrence. This rate of recurrence is over 90% of pregnancies after a previous affected pregnancy.

Immunoglobulin is extracted from donor blood and is a mixture of blood proteins (antibodies) that are made by the immune system. Antibodies are usually formed when the immune system comes into contact with foreign substances such as viruses, bacteria or toxins. These antibodies are normally protective. Immunoglobulin is usually given to patients as an intravenous infusion, called intravenous immunoglobulin (IVIg) (NHS England, 2013).

IVIg has been shown to successfully reduce the risk of liver damage/failure, the need for intensive care support in hospital, donor liver transplant and death during pregnancy and after birth. A woman who has had a previous baby affected by NH should be treated throughout all subsequent pregnancies to prevent recurrence of neonatal haemochromatosis.

Dose

The administration of IVIg at a dose of 1g/kg (dose capped at 60 grams per week) is first administered to at risk mothers at 14 weeks, then fortnightly (16 and 18 weeks) and then weekly from 18 weeks gestation until delivery between 37 and 38 weeks.

Such administration of IVIg works 3 ways to prevent fetal haemochromatosis by:

1) blunting maternal immune response to fetal antigens;
2) by flooding the placenta IgG transport mechanism with non-specific antibodies;
3) by non-specific antibody binding that limits the binding of reactive allo-antibodies to target antigens.

Committee discussion

The condition

Gestational alloimmune liver disease (GALD) is a materno-fetal alloimmune disorder. As with all such disorders, injury to fetal tissues is mediated by specific IgG antibodies passing to the foetus from a mother whose immune system has been sensitised to some foetal antigen not recognized as self by the mother.

The foetal/neonatal condition is caused by maternal alloimmune reaction - exposure to fetal antigens lead to overproduction of antibody by the mother, which crosses the placenta to the fetus leading to severe liver damage. This invariably leads to rapid onset hepatic failure, a need
for exchange transfusion, life sustaining intensive care, neonatal liver transplant and often neonatal death.

The incidence of GALD and GALD-related NH is unknown, but it is considered to be rare. One estimate from the United States is an incidence rate of 15 per million live births. It is important to note that neonatal haemochromatosis is an underdiagnosed condition, as not all mothers who lose a baby will obtain the diagnosis by undergoing a post-mortem examination.

Current treatments

There is no current standard treatment. Untreated, the inevitable outcome of these cases is either stillbirth or severe neonatal liver failure, leading to death in infancy unless treated by donor liver transplant. In milder cases where the baby is born alive, supportive treatment for liver failure followed by donor liver transplant is possible, however, overall survival for infants receiving a liver transplant for this indication is approximately 35%.

Comparators

The comparator outcome is untreated women. The evidence in one trial stated that it resulted in very high incidence of fetal death, miscarriage and fetus affected with severe allo-immune haemochromatosis. Out of 141 pregnant women, 30 pregnancies were lost before 18 weeks, 15 had foetal death after 18 weeks with most of these dead foetuses having evidence of NH. Of 97 born alive, 53 had haemochromatosis, 36 died without liver transplantation. The mortality rate of affected live-born infants was 81%, and 89% either died or required liver transplant.

Clinical trial evidence

Antenatal IVIg treatment dramatically improves outcome in at risk pregnancies with the research showing almost 100% children born after 26 weeks survived without evidence of overt liver failure at birth.


Forty-eight women were enrolled to be treated during 53 pregnancies. The gestational histories of these women demonstrated the high risk of occurrence of neonatal hemochromatosis. In the untreated group, 92% of pregnancies at risk resulted in intrauterine fetal demise, neonatal death, or liver failure necessitating transplant. In contrast, with gestational IVIg therapy, the 53 at-risk gestations resulted in three failures and 52 infants who survived intact with medical therapy alone. Two infants were lost after the mothers began therapy. Although neither can be said to have resulted from NH-related alloimmunity, the apparent rate of loss (2 of 48 women starting treatment) is somewhat greater than the stated rate of fetal loss in the second half of pregnancy, commonly estimated to be 1 in 150 pregnancies in developed countries. In addition, one woman withdrew from therapy because of a complication. When compared on a per-woman or per-infant basis, the outcome of gestation at risk for neonatal hemochromatosis was improved by gestational therapy.


In a second paper “women with a history of affected offspring were provided antenatal IVIg treatment and data were acquired prospectively from 1997 to 2015. The outcomes of treated pregnancies were compared to those of untreated pregnancies, and the effectiveness of starting at 14 weeks was compared to that of starting at 18 weeks. A total of 188 treated pregnancies in 151 women were analysed. Only 30% (n = 105) of untreated gestations resulted in healthy offspring as compared to 94% (n = 177) of treated pregnancies (p < 0.0001). Treated gestations of both the 14-week (n = 108) and the 18-week (n = 80) start cohort showed a decreased rate of
fetal loss relative to untreated gestations (p < 0.0001). Few adverse events or complications of antenatal therapy were recorded.

The authors report a case of neonatal haemochromatosis treated with immunoglobulin and review Paper 1 and 2.

Adverse events
According to the studies there were very small numbers of side effects which were those of an allergic nature such as urticaria, malaise and nausea. One patient in one study developed aseptic meningitis after having received one dose of IVIg. They withdrew from further treatment, and recovered from the aseptic meningitis without consequence.

Criteria
Pregnant mothers with a previous adverse pregnancy outcome and clear post-mortem evidence of fetal haemochromatosis or women who have had an offspring with neonatal liver failure confirmed to be allo-immune neonatal haemochromatosis.

Effective from
10 July 2019

Recommendations for data collection
All women receiving IVIg will be registered through the National MDSAS Immunoglobulin database and the following outcomes monitored using this register:

• Fetal loss (including gestation)
• Gestation at delivery
• Neonatal outcomes

Mechanism for funding
Immunoglobulin will be commissioned and funded by NHS England Specialised Commissioning under existing arrangements for the provision of specialised neonatal services.

Policy review date
This is an urgent policy statement, which means that the full process of policy production has been abridged: a full independent evidence review has not been conducted; and public consultation has not been undertaken. If a review is needed due to a new evidence base then a new Preliminary Policy Proposal needs to be submitted by contacting england.CET@nhs.net.

Links to other Policies
None.

Equality Statement
Promoting equality and addressing health inequalities are at the heart of NHS England’s values. Throughout the development of the policies and processes cited in this document, we have:
Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and

Given regard to the need to reduce inequalities between patients in access to and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.