NHS England Clinical Commissioning Policy: Management of fetal anaemia secondary to red cell alloimmunisation (Fetal transfusion)

Reference: NHS England E12/P/

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NHS England Clinical Commissioning Policy: Management of fetal anaemia secondary to red cell alloimmunisation (Fetal transfusion)

First published: January 2015

Prepared by NHS England Clinical Reference Group for Fetal Medicine

Published by NHS England, in electronic format only.

Contents

Policy Statement
NHS England will commission the provision of intrauterine transfusion for fetal anaemia secondary to maternal red cell alloimmunisation, in accordance with the criteria outlined in this document.

In creating this policy NHS England has reviewed this clinical condition and the options for its treatment. It has considered the place of this treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources.

This policy document outlines the arrangements for funding of this treatment for the population in England.

Equality Statement
Throughout the production of this document, due regard has been given 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 in under the Equality Act 2010) and those who do not share it.

Plain Language Summary
"Rhesus disease" is caused by the mother developing 'immune proteins' called antibodies against the baby's red blood cells. This can cause the baby to become anaemic in-utero and may be potentially life threatening. Babies that are born with this condition often develop jaundice and require close follow up by the newborn baby doctors.

Once the mother has been noted to have antibodies against certain red cells, identified at routine screening in pregnancy, it is important to perform further tests to ascertain the level and potency of these antibodies and also the risks to the unborn baby (by checking the inherited status form the father). This involves a blood test from the father of the baby.

It is likely that the pregnancy will need to be followed more closely. This will involve you seeing a local fetal medicine specialists and midwife at your hospital. They will regularly (probably every two weeks) need to repeat your blood tests and perform a specialist ultrasound scan. This will screen the baby to detect if it is developing anaemia.

If the baby is at low risk of anaemia then the baby will need to followed throughout the pregnancy and the specialist will discuss with you and your partner the need for delivery at approximately 38 weeks and the need for specialist newborn baby follow up.

If the regular ultrasound scans demonstrate that the baby is becoming anaemic, then you will be transferred to see a specialist at your regional hospital. They will assess the need for in-utero treatment for your baby. This is regular treatment of the baby whilst it is in the womb and occurs during the pregnancy until delivery. Delivery is often 34-38 weeks (but care is individualized). Your baby will need to be seen by

the newborn team of doctors at the hospital and will probably need surveillance and care of the special care baby unit.

Postnatally, you will need to discuss the risks and management of future pregnancies.

1. Introduction

Maternal red cell alloimmunisation is relatively rare today but when it occurs may cause significant perinatal mortality and morbidity. The identification of severe fetal anaemia and the provision of fetal transfusion will significantly reduce perinatal mortality.

At present there is a Royal College of Obstetricians and Gynaecologists Green- top Guideline has been published in July 2014 on the topic of 'the management of pregnancies complicated by red cell alloimmunisation'.

The purpose of this policy is to guide the provision and practice of intrauterine transfusion in the management of fetal anaemia in red cell alloimmunisation. Its aim is to outline the best practice and commissioning responsibility in the management of pregnant women in whom red cell antibodies are identified and define where sub specialty fetal medicine services are required.

2. Definitions

Feto-maternal red cell alloimmunisation

This is defined by the presence in a pregnant woman of allo-antibodies directed against blood group antigens present on the red blood cells of the fetus and inherited from the father.

Once red cell alloimmunisation has been identified on screening (routinely offered to pregnant women in England), the antibody type requires triage by a knowledgeable clinician to ascertain risk of anaemia (i.e. type of antibody [i.e. anti-D, anti-K or anti-c] and quantification of antibody (by concentration or titre)(1). The partner also requires blood group genotyping.

Where the partner is heterozygous for the relevant blood group antigen, fetal genotype can be determined by analysing fetal cell free DNA in the maternal circulation. This can be performed in secondary care by a specialist in fetal medicine. Fetal antigen positivity is indicative of increased risk of the fetus developing fetal anaemia. Continue antibody testing at 2 weekly intervals (1).

3. Aim and objectives

The aim of this policy is to outline the best practice and commissioning responsibility in the management of pregnant women in whom red cell antibodies are identified and define where sub specialty fetal medicine services are required.

4. Epidemiology and needs assessment

The incidence of 'Rhesus disease' or haemolytic disease of the fetus and newborn (HDN) depends on the proportion of the population who are RhD negative. This varies within ethnic minorities but, in the UK, it is highest in the Caucasian population (approximately 15%).

Before immunoprophylaxis was available, HDN affected 1% of all newborns and

was responsible for the death of one baby in every 2,200 births.(11)

Anti-D prophylaxis (mostly administered postnatally but increasingly given prophylactically prenatally) and advances in neonatal care have reduced the frequency of HDN by almost a factor of 10 to 1 in 21,000 births (12). Deaths attributed to RhD alloimmunisation fell from 46/100,000 births before 1969, to 1.6/100,000 in 1990. This may not be entirely attributable to immunoglobulin; changes in abortion rates and racial composition may also play a part. In addition, the use of prophylactic anti-D administered antenatally in many areas within NHS-E will further lead to a reduction in alloimmunisation.

One American study quoted a prevalence of RhD alloimmunisation of 6 in 1,000 births and suggests that this should now be considered a rare condition. No UK prevalence data is available (13). However, a recent study from the Netherlands found red cell antibodies detectable in 1.2% of pregnancies whilst the prevalence of 'clinically significant' antibodies was 0.4% (14). Anti-D is still the most commonly encountered red cell antibody during pregnancy. But as immunoprophylaxis begins to have 'population-based' effects, it is likely that a higher proportion of pregnancies with serious alloimmunisation complications will be secondary to anti-Kell and anti-c, in the future.

5. Evidence base

5.1. Non-invasive, prenatal screening test of detecting fetal anaemia

Recent data for a retrospective cohort from the British Isles, has indicated that an anti-D threshold of 6iu maximizes the detection rate of babies with significant anaemia, whilst minimizing false positive cases (2).

Once a fetus is at moderate to severe risk of developing fetal anaemia then regular ultrasound examination and serial measurement of Middle Cerebral Artery Peak Systolic Velocity (MCA PSV) are required (1).

In a systematic review and meta-analysis, pooled results of 14 studies (n= 675) reported a diagnostic accuracy with a positive likelihood ratio (LR) of 4.30 (95% CI: 2.50 to 7.41) and a negative LR of 0.30 (95% CI: 0.13 to 0.69) at detecting moderate to severe fetal anaemia when a test threshold for MCA-PSV of 1.5 multiples of median (MoM) and a cut off for severe fetal anaemia of haemoglobin ‡0.55 MoM was used (3). This study and another systematic review, both reported that although Doppler insonnation of MCA PSV has limited diagnostic accuracy, it currently remains the "gold standard" for non-invasive screening of fetal anaemia and to determine the need for the first intrauterine transfusion (3,4). Assessment of the MCA PSV can be used to time the second transfusion, but its use to decide when to perform subsequent procedures awaits further study (4).

5. 2. Fetal blood sampling and Fetal transfusion

The technique of fetal blood sampling, the diagnosis of fetal anaemia (when the fetal haematocrit is ≤ 0.30 (or haemoglobin <5th centile for gestation)) and intravascular fetal transfusion has been shown to be of significant value in reducing perinatal mortality in observational studies (non-RCT) and the contemporaneous literature

indicates >90% survival for the fetus (5,6,7). A systematic review reported normal neurologic outcome in 94% of cases after intrauterine transfusion (although severe hydrops fetalis may be associated with a higher risk of impairment) (4).

The timing of fetal transfusion is variable; being dependent upon several complex factors. These include: a) the absolute fetal haematocrit / haemoglobin concentration (usually if fetal haemoglobin is <5th centile for gestational age); b) the past history of severity of the disease process and c) rate of fall of haematocrit / haemoglobin between transfusions. Usually, the transfusions are more frequent at initiation (every 1-2 weeks) and the inter-transfusion interval may be extended subsequently (2-4 weeks). The interval between transfusions is presently determined from the estimated rate of fall of fetal haematocrit / haemoglobin. However, at present there is an RCT ongoing (the ARCH study) to compare the rate of fall of fetal haemoglobin with MCA PSV in determining the timing of subsequent fetal blood sampling (8).

In babies where anti-D is <6iu (or equivalent antibody levels)(at low risk of fetal anaemia), there needs to be discussion with neonatal colleagues, as to whether the baby should be delivered at a level 3 neonatal unit. A significant number of these babies will require assessment for haemolytic disease of the newborn with management of jaundice and the potential need for exchange transfusion.

In those pregnancies at moderate risk (anti-D>6iu but MCA PSV <1.5MoM) then delivery should be by 37-38 weeks. Those at low risk should be delivered by 38 weeks. Again discussion with informed neonatal colleagues as to the timing of delivery to minimize newborn morbidity and place of delivery are strongly advised.

Several case series suggest a beneficial role in delaying the onset of severe fetal anaemia requiring invasive intrauterine transfusion. However, a systematic review reported that there is no information is available from randomised controlled trials to indicate whether antenatal use of intravenous immunoglobulin is effective in the management of fetal red blood cell alloimmunisation (9). Therefore, it should be used in exceptional and specialised circumstances (if a past pregnancy has been complicated by fetal hydrops <20 weeks).

6. Rationale behind the policy statement

Once a fetus is at moderate to severe risk of developing fetal anaemia then regular ultrasound examination and serial measurement of MCA PSV are required. This is commonly performed in secondary fetal medicine units with specialists who have ATSM training (or equivalent) in Fetal Medicine.

Referral to a specialist in fetal medicine will ensure, provision of multidisplinary care and liaison that leads to timely delivery of the fetus at significant risk of fetal anaemia and optimal management of haemolytic disease of the newborn in the early neonatal period.

Intrauterine transfusions are performed in tertiary fetal medicine centre with subspecialty accredited and trained individuals with experience of this form of fetal therapy.

Ongoing monitoring of numbers and audit outcomes must be undertaken.

7. Criteria for commissioning

Provision of multidisplinary care and liaison that leads to timely delivery of the fetus at significant risk of fetal anaemia and optimal management of haemolytic disease of the newborn in the early neonatal period which should consists of:

1. Recognizing the significance of maternal red cell antibodies that may cause fetal anaemia (principally anti-D, c and Kell).

2. Investigating the mother and fetus to ascertain risk of anaemia and timely referral of women at moderate to high risk of fetal anaemia. These pregnancies should be promptly referred to a fetal medicine centre for ultrasound assessment.

Women at moderate to high risk of fetal anaemia are defined as those who:

a) Have an absolute level of antibody, usually >6iu (or equivalent)(2).

b) Have a "doubling in antibody level" over a two weekly period (if baseline anti-D level is >6iu)

c) An ultrasound anomaly suggestive of anaemia (i.e. fetal effusion) or MCA PSV>1.5 MoM.

d) in-utero transfusion in a previous pregnancy.

(The above 2 stages are the responsibility of secondary care with responsibility for the provision of care transferring at point 3 to fetal medicine sub specialty services and under the commissioning remit of NHS England.)

3. Women at moderate to high risk of fetal anaemia referred to a fetal medicine centre should be offered assessment by prenatal ultrasound including middle cerebral artery Doppler peak systolic velocity ((MCA- PSV) and where indicate, treatment with fetal blood sampling ± fetal transfusion.

3.1 Assessment and diagnostics

Fetal ultrasound examination including serial MCA-PSV may be performed serially from 18 weeks gestation. Monitoring is often shared with specialist in fetal medicine in a secondary centre and the frequency of ultrasound assessment is individually tailored to the patient and dependent upon level of risk of fetal anaemia;

3.1.1. If MCA PSV remains <1.5 MOM then monitoring should be continued at intervals up to 2 weeks, with elective delivery at 38 weeks. In this 'lower' risk situation, there should be multidisplinary discussion between the obstetrician and neonatal paediatrican. This is because of the possibility (albeit relatively low) of the need for treatment of severe jaundice including exchange transfusion. Blood will be cross matched electively for the baby.

3.1.2. In moderate to high risk cases (defined above) weekly measurement of MCA PSV is necessary.

3.1.3. If there is hydrops fetalis (or even a single fetal effusion) on diagnostic prenatal ultrasound and/or the MCA PSV is >1.5 MOM are found at a secondary care unit, urgent, referral to a tertiary fetal medicine centre is required.

3.1.4. If the MCA PSV is confirmed to be >1.5 MOM at a fetal medicine centre, fetal blood sampling is required. Prior to fetal blood sampling, liaison will be required with the national blood transfusion centre(s) to obtain cross matched, irradiated packed red cells for fetal transfusion.

3.1.5. If, at fetal blood sampling, the fetal haematocrit is found to be ≤ 0.30 (30%) or fetal haemoglobin is <5th centile for gestation; fetal transfusion is indicated (if gestation <34 weeks).

3.2 Intrauterine Transfusion:

3.2.1 A centre performing intrauterine transfusion should have at **least two subspecialty trained practitioners in fetal medicine** (forming part of a multi-disciplinary team) who have competence in performing intravascular fetal transfusion.

3.2.2 Each centre should treat **a minimum of 15 intrauterine transfusions per year** (as adopted by the Fetal Medicine CRG dashboard).

3.2.2 Centres offering fetal transfusion should document and **regularly audit complications and outcomes.**

3.2.3 the technique should utilize the ultrasound guided, percutaneous placement of a 20-22 gauge needle into the fetal circulation (via the umbilical cord or intrahepatic portion of the umbilical vein) and the infusion of irradiated, pack red cells (prepared by a regional Blood Transfusion Service). The individual performing this technique should be a subspecialist with training and expertise in fetal transfusion.

3.2.4 Timing of transfusion interval should be based upon a combination of practitioner experience and the use of serial fetal middle cerebral artery Doppler peak systolic velocity measurements. It is recognized that the results of a randomized controlled trial comparing these two factors in guidance of transfusion interval will be published in late 2014.

3.2.5 If the fetal gestation is >24 weeks then prophylactic betamethasone should be considered.

3.2.6 In transfusion-dependent cases, delivery is usually planned at 36-37 weeks after consultation with neonatal paediatric colleagues at the fetal medicine centre. This is a moderate to high risk of exchange (or more likely 'top up') transfusions in the neonatal period and hence the infant should be delivered in a unit with appropriate neonatal centre experience. Care and timing of delivery is often tailored to the individual patient.

3.2.7 The centre performing intrauterine transfusions must produce a rolling audit of experience, including indications for and outcomes of fetal transfusion. This information will be collated into 3 year summary figures in an attempt to minimize year to year variations.

3.3. In exceptional, and specialised circumstances (if a past pregnancy has been complicated by fetal hydrops <20 weeks), the use of IVIG and/or intraperitoneal transfusion (from 16 weeks) should be considered.

3.4. Patients should give written, informed consent to all treatments.

3.5. A postnatal plan of care that ensures appropriate access to contraception and advice about future pregnancies. Postnatally, couples should receive information as to the risks and potential complications of a future pregnancy and contraception should be discussed.

8. Patient pathway

The service specification for fetal medicine services describes the detail of the care pathways and the key aspects of services being commissioned and should be referred to in conjunction with this policy.

The tertiary, fetal medicine subspecialty service will accept referrals from consultant medical staff and the appropriate specialist from secondary care.

Women at moderate to high risk of fetal anaemia should be referred to a fetal medicine sub-specialty centre and will be offered assessment by prenatal ultrasound including middle cerebral artery Doppler peak systolic velocity ((MCA-PSV) and where indicate, treatment with fetal blood sampling ± fetal transfusion.

Fetal ultrasound examination including serial MCA -PSV may be performed serially from 18 weeks gestation. Monitoring is often shared with specialist in fetal medicine in a secondary centre. Frequency of ultrasound is dependent upon level of risk of fetal anaemia

9. Governance arrangements

The service specification for fetal medicine describes the care pathways and key aspects of fetal medicine services being commissioned and should be referred to in conjunction with this policy.

10. Mechanism for funding

All fetal medicine is currently funded through the Maternity Pathways Payment and Sub specialty services should invoice the booking hospital for these treatments within the fetal episode of care.

The neonatal on going management will be picked up within the current Neonatal critical care funding.

11. Audit requirements

Data and information should be submitted as detailed in contracts to the fetal medicine dashboard.

12. Documents which have informed this policy

See reference list below.

13. Links to other policies

This policy follows the principles set out in the ethical framework that govern the commissioning of NHS healthcare and those policies dealing with the approach to experimental treatments and processes for the management of individual funding requests (IFR).

14. Date of review

This policy will be reviewed in April 2016 unless information is received which indicates that the proposed review date should be brought forward or delayed.

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Version Control Sheet

Version	Section/Para/Appendix	Version/Description of Amendments	Date	Author/Amended by
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