

Best practice guidelines for non-invasive prenatal diagnosis to determine fetal sex for known carriers of congenital adrenal hyperplasia (CAH).

Background

Fetal DNA is required for prenatal genetic testing. Traditionally invasive testing by amniocentesis or chorionic villus sampling has been required to obtain fetal DNA. These procedures carry a small but significant (around 1%) risk of miscarriage. In 1997 cell free fetal DNA (cffDNA) was identified in the maternal circulation. This is present from early pregnancy, is rapidly cleared from the circulation after delivery, but only constitutes a small proportion of cell free circulating DNA, the majority being from the mother (For review see RCOG 2009). cffDNA can be used as an alternative source of fetal DNA for prenatal testing for genes not present in the mother and has been used extensively in the UK and Europe for fetal sex determination (Finning and Chitty 2008, Hill et al 2010). Testing requires a simple blood test rather than an invasive procedure and thus avoids the risk of miscarriage.

This care pathway, describes an innovative method for fetal sex determination based on cffDNA which will massively improve equity of access and the quality of care offered to women whose pregnancy is at risk of congenital adrenal hyperplasia by removing the need for invasive testing, and thus potential iatrogenic pregnancy loss for around 50%. An economic analysis has shown that there are no cost implications for service providers as testing in these circumstances has been shown to be cost-neutral (Hill et al. Prenatal Diagnosis submitted August 2010). There has been a thorough audit of this service as currently offered by NHS genetics service laboratories in the UK demonstrating a high sensitivity and specificity (Hill et al 2010). A pilot NEQAS scheme has been established (Schlecht et al 2010) and educational materials for health professionals, information and competencies are being developed by the National Genetics Education and Development Centre.

Additional care pathway information

1. Pregnancy known to be at risk of CAH

- NIPD should be offered to couples when both are known carriers of CAH.
- In the majority of cases the disease causing mutation will have been previously been characterised.
- The majority of these women will already be under the care of the clinical genetics team and will have had a care plan for antenatal diagnosis discussed. Occasionally women whose pregnancy is known to be at risk of CAH will be under the care of the endocrinology team as practice varies with locality, but these women will also have a care plan for antenatal diagnosis in place.
- Prior counselling of known carriers will have included discussion of the possibility of prenatal treatment with dexamethasone, including dose and timing of treatment, potential side effects, and referral for maternal investigation from an appropriately experienced endocrinologist if necessary.
- Confirmation of fetal gender is important for guiding dexamethasone treatment. Standard practise is for the continuation of dexamethasone only when there is confirmation of an affected female fetus. Women known to be carrying a female fetus who decline invasive testing should be referred back to their genetics or endocrinology team for further discussion of management.

Red flag: Anyone presenting to obstetrics or GP without a previous genetics appointment should be given an urgent referral to genetics for counselling and initiation of urgent molecular testing if appropriate.

2. Steroid treatment

- When a known carrier of CAH becomes pregnant steroid treatment should be offered by the obstetrics or genetics team according to the previously determined care plan.

- Any woman without a suitable plan for dexamethasone administration should be referred urgently to the genetics team.

3. Offer of fetal sexing by NIPD

- When a known carrier of CAH becomes pregnant contact is made with the genetics team, either directly or through their GP or obstetrician.
- The genetics team speak to the woman about NIPD at an appointment or by phone.
 - o Discuss how the woman would like to receive results (genetics appointment, phone call or letter)
 - o Discuss how NIPD performed, accuracy of NIPD and possible occurrence of inconclusive results.
 - o Describe need for dating scan and for confirmation of gender by ultrasound.
 - o Discuss option of amniocentesis/chorionic villus sampling if female identified.
- Parents must be made aware that an invasive test will be required to confirm sex if NIPD is unable to confirm a male fetus as ultrasound is unreliable in this condition because of the risk of virilisation of female external genitalia.
- The woman will be referred to have a dating scan and the genetics team will organise for blood to be taken after 7 weeks gestation as confirmed by scan.

6. Dating scan

- Ultrasound scan performed at the woman's local maternity unit to establish gestation and confirm singleton pregnancy.

7. Discuss options with parents – when NIPD is declined

- Discuss options of invasive testing or standard antenatal care.

8. NIPD blood test

- Blood can be taken any time after 7 weeks (confirmed by dating scan). There is no upper limit on gestation for NIPD.
- A second blood sample may be required for testing for pregnancies below 9 weeks gestation. Please refer to the testing pathways of the specific laboratories providing this test.
- Blood can be taken wherever convenient for the woman - genetics appointment, GP or obstetrician/midwife appointment.
- Blood should arrive in the laboratory within 48 hours of sampling.
- The laboratory performing NIPD is notified to ensure rapid sample processing on arrival.
- Sexing test is performed with a target turnaround time of 3 days and report faxed to a named genetic counsellor or consultant.

9. Standard antenatal care

- If invasive testing has been declined and the woman is on dexamethasone the treatment options regarding continuing or stopping treatment should be discussed.
- Standard antenatal care should include the offer of Down syndrome screening according to local practise.

17. Confirm gender by ultrasound

- When NIPD predicts a male fetus an ultrasound scan performed at the woman's local maternity unit is used to confirm gender. Caution should be used in interpretation as a severely virilised female may be difficult to distinguish from a male fetus both on antenatal ultrasound and in the newborn period. Repeat scans may be needed.

19. Discuss options with parents - when the NIPD result is inconclusive

- When NIPD gives an inconclusive result parents should be offered the options of repeating the NIPD or having an invasive test.

21. Amniocentesis / chorionic villus sampling

- Discuss with the woman how she would like to receive results (genetics appointment, phone call or letter)

- Advise woman:
 - o to rest for a day or two after the procedure, avoiding lifting, bending or stretching where possible
 - o that she may experience discomfort in the lower abdomen after the procedure, which can be relieved with simple analgesics, eg. Paracetamol
 - o to contact her GP if she has a pyrexia (there is a slight risk of infection with invasive procedures), losing either fresh blood or water type loss (not urine) from the vagina, losing any discharge with an offensive odour from the vagina, severe lower abdominal pain, feeling generally unwell or decreased fetal movement (after amniocentesis only where some women have already experienced fetal movements)
 - o that she will not require Down syndrome screening if the pregnancy continues as the fetal cells obtained following the invasive test will also be sent for cytogenetic analysis.

Amniocentesis:

- procedure is suitable from 15+0 weeks of pregnancy
- is performed under continuous ultrasound guidance
- the procedure involves inserting a fine needle through the abdomen into the womb and then into the amniotic sac and aspirating a sample of amniotic fluid (fluid surrounding baby)
- at the laboratory, DNA testing is performed to identify the presence/absence of the mutation and in addition maternal cell contamination of the fetal sample is excluded. Fetal cells extracted from the amniotic fluid are examined; the number, arrangement and shape of the fetal chromosomes are checked
- about 1 in 100 samples proves to be inadequate
- the risk of miscarriage associated with amniocentesis is 1 fetal loss in 100 procedures

Chorionic villus sampling (CVS):

- procedure is usually performed from 11+0-12+6 weeks of pregnancy
- usually performed in a fetal medicine unit by a specialist trained in fetal medicine
- two types of CVS - Transcervical (TC) and Transabdominal (TA) **a) Transcervical (TC)** The procedure involves inserting a fine plastic catheter in the vagina, through the cervix and into the placenta (whilst simultaneously undertaking an abdominal scan). A small amount of placental tissue is then aspirated and sent for cytogenetic investigation. This is rarely performed **b) Transabdominal (TA)** Similar to an amniocentesis, this procedure is usually undertaken in up to 13+6 weeks but can be performed later in pregnancy. The procedure involves inserting a fine needle through the abdomen, into the womb and into the placenta and then aspirating a small amount of placental tissue for analysis
- at the laboratory, DNA testing is performed to identify the presence/absence of the mutation and in addition maternal cell contamination of the fetal sample is excluded. Fetal cells extracted from the CVS are examined; the number, arrangement and shape of the fetal chromosomes are checked
- about 2 in 100 samples prove to be inadequate
- the fetal loss rate associated with a TA CVS is 2 in 100 procedures. The risk associated with TC is slightly higher

25. Standard antenatal care

- Standard antenatal care should include the offer of Down syndrome screening according to local practise.

22. Decline invasive test

- Refer back to genetics team for further discussion regarding management including cessation of dexamethasone.

28. Standard antenatal care

- Standard antenatal care should include the offer of Down syndrome screening according to local practise.

31. Discuss options with parents – when CAH is confirmed

- Provide information and support to the woman whose pregnancy is affected by CAH.

32. Standard antenatal care

- Standard antenatal care does not include offer of Down syndrome screening at this point as karyotyping is done on chorionic villi or amniocytes.

References

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Chorionic villus sampling (CVS) - information for parents. 2009. NHS Fetal Anomaly Screening Programme

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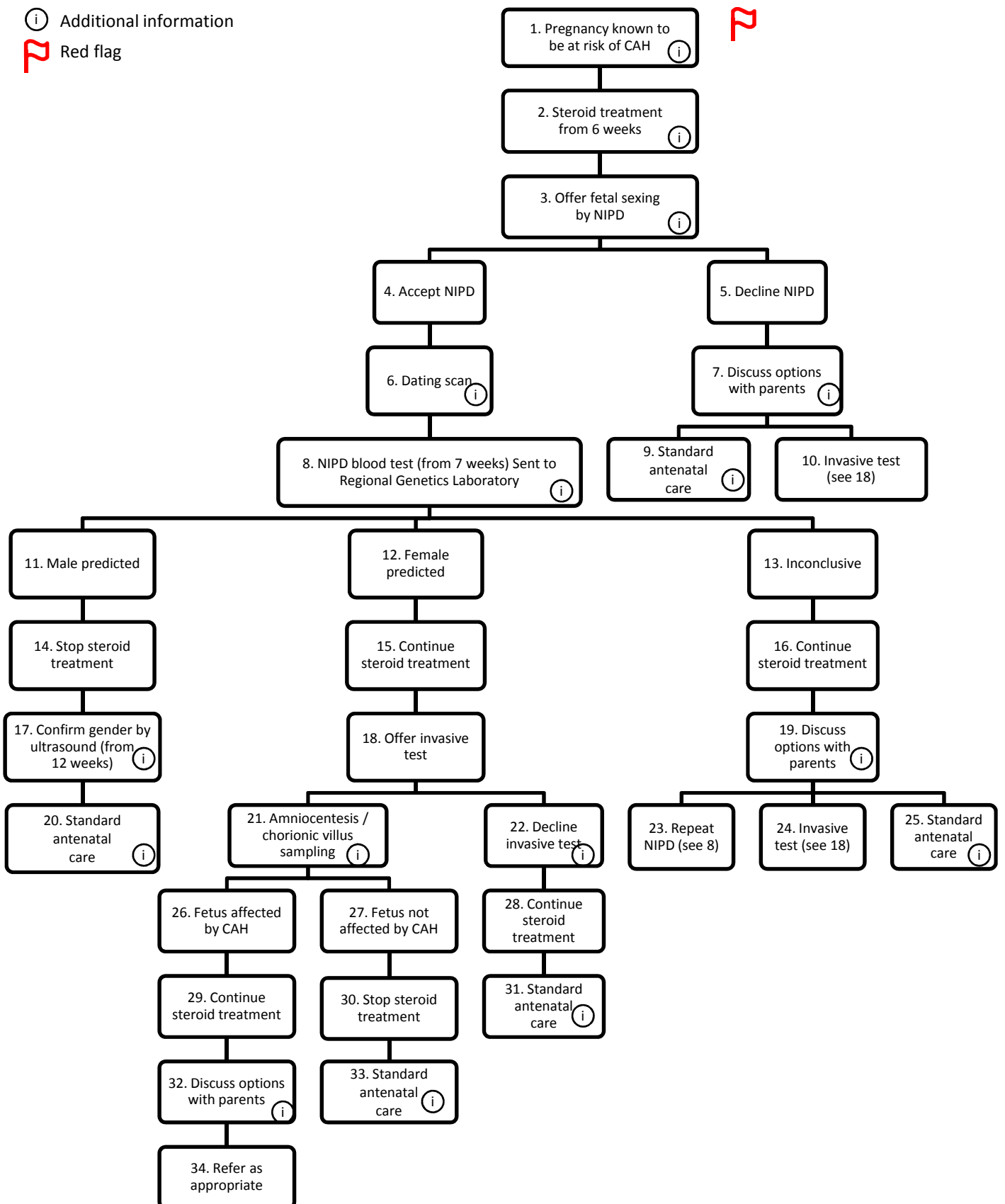
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MANCHESTER CARE PATHWAY

Fetal sexing by non invasive prenatal diagnosis for Congenital adrenal hyperplasia (CAH)


 Additional information

 Red flag



BIRMINGHAM AND GREAT ORMOND STREET CARE PATHWAY

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 Additional information

 Red flag

