Mid Essex Hospital Services NHS
NHS Trust

DOWN'S SYNDROME SCREENING USER HANDBOOK	CLINICAL GUIDELINES Register No: 09066 Status: Public

Developed in response to:	Best Practice: Guidelines for antenatal clinics and laboratories using the Essex Down's Syndrome Screening Service
Contributes to CQC Outcome	4, 11, 13

Consulted With	Post/Committee/Group	Date
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It is the personal responsibility of the individual referring to this document to ensure that they are viewing the latest version which will always be the document on the intranet

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1. Purpose

1.1. This document is intended to provide antenatal clinics and other users of the laboratory service with an up to date reference guide for the service, incorporating all current national recommendations.

2. Background

2.1. The Clinical Biochemistry laboratory at MEHT offers a maternal serum Down's Syndrome Screening service (first trimester) for the following Essex Trusts:

- Mid Essex Hospitals NHS Trust (MEHT)
- Essex Rivers Hospital NHS Trust (ERS)
- Princess Alexandra Hospital NHS Trust (PAH)
- Basildon and Thurrock University Hospitals NHS Foundation Trust
- Southend NHS Trust (SOU)

2.2. It may also be downloaded from the MEHT website at http://www.meht.nhs.uk

3. Responsibility

3.1. Responsibility for producing, updating and circulating this document lies with the Principal Clinical Scientist

4. Specimen Criteria

Specimens must comply with individual Trusts minimum labelling policy

4.1. **Specimen collection tube**

Only plain serum specimens are accepted. Tubes containing gel are not acceptable due to potential assay interference. EDTA or citrate tubes are not accepted since they chelate the europium label used in the AutoDelphia assay and give a falsely low result.

4.2. **Unlabelled specimens**

Specimens are not accepted if they are received unlabelled and the clinic is informed by phone or fax that a fresh specimen is required.

5. Request Form Information

5.1. Specimens must be accompanied by a fully completed Down's Syndrome Screening request form. The following information must be provided:

- Surname and forename*
- Patients full address and post code*
- Date of birth*
- NHS Number
- Hospital number (where available)
- Hospital
- Consultant (where available)
- GP
- Date of LMP (including whether certain/doubtful) *
- Weight in Kg*
- Ethnic group*
- Smoking status at time of screening*

- If patient has Previous Downs; Previous NTD; Multiple Pregnancy*; IDDM*; IVF*
- Date of most recent scan*
- BPD, CRL or HC measurement*
- Nuchal measurement in mm*
- Number of foetus' present
- Gestation assessment
- Sample date*
- Signature of midwife

5.2. If any of the information marked * is missing, a copy of the request form is faxed to the clinic asking for the missing information to be supplied.

6. Trust Laboratory Role

6.1. All Down's screening requests will be forwarded to the individual Trust's laboratory in the first instance. There they will be centrifuged (to obtain a serum sample), ID matched and labelled and separated into analyser tubes. It is the responsibility of each Trust's biochemistry laboratory to ensure that specimens are correctly labelled, processed, appropriately recorded and packaged for transport.

6.2. If specimens are taken on a Friday and will not be transported until the following week they should be centrifuged and the serum aliquot :
- stored frozen 1st trimester
- stored at 4°C 2nd trimester

7. MEHT Laboratory Analysis and Risk Calculation

7.1. Analysis of serum markers is carried out using the Perkin Elmer AutoDelphia analyser and the risk calculation software is also provided by Perkin Elmer (Lifecycle/Elipse).

7.2. Cut-off's used are as follows:

First trimester cut-off:	1	in 150
Second trimester cut-off:	1	in 200

7.3. The software uses Robson & Fleming (1975) in order to calculate gestation from CRL/HC. The software uses this gestation to determine whether a first or second trimester screen is required, and automatically requests the correct set of tests.

7.4. Specimens are analysed in batches Monday – Friday and reported on the next working day.

8. First Trimester Screen

8.1. The first trimester screen offered comprises:
- Nuchal translucency (NT)
- PAPP-A
- Free b-HCG

8.2. This combination of markers is that recommended by the National Screening Committee as being capable of achieving a 75% detection rate with 3% false positive rate. First trimester analysis has been operational since Sep'07 and data from DQASS, and NEQAS scheme indicate that the laboratory performance is well within these targets.

8.3. In a Down's Syndrome pregnancy there tends to be: Increased nuchal translucency (NT >3 considered high risk); higher free b-HCG and lower PAPP-A.

8.4. Account is also taken of the so-called age-related risk of having a Down's Syndrome baby. This is because the risk of having an affected infant rises with increasing maternal age. Overall the incidence of Down's Syndrome pregnancies is approximately 1 in 800 but this will vary with the age distribution of the pregnant population.

8.5. A risk of 1 in 150 or less (i.e. a high risk result) would normally be followed by the offer of a diagnostic procedure to sample foetal cells and determine if they carry the chromosomal defect associated with Down's Syndrome. In the first trimester – this is generally done by Chorionic Villus sampling (CVS).

8.6. If invasive testing is declined a second trimester high resolution ultrasound would be offered to check if the foetus is affected by any of the congenital abnormalities associated with Down's Syndrome which are present in 40-50% of Down's Syndrome cases.

9. Gestation limits

9.1 Blood specimens are accepted for testing when taken between 11 weeks 2 days and 14 weeks 1 day of pregnancy. If blood is taken outside of these limits, a Down's risk cannot be generated and the clinic is informed by phone or fax. These gestations correspond to a CRL of 42-84 by the Robson Fleming chart.

10. Twin Pregnancies

10.1 Specimens are accepted for Down's screening in cases of twin pregnancies for first trimester screening only. Screening is not available for triplets or higher order pregnancies

10.2 Vanishing twin pregnancies: In cases where only 1 viable twin is present the Down's risk will be calculated using maternal age and NT measurement only – ie no biochemical markers are required. Until version 3 of Lifecycle software is installed, this calculation will be performed at the Wolfson Institute, London.

11. Factors which affect Biochemical Marker Levels

11.1 Maternal weight

11.1.1 The feto-placental unit is the source of the markers measured in the blood tests. The weight or size of this unit is largely unaffected by maternal weight in the first and second trimesters. However the marker levels in maternal blood are affected by maternal weight as blood volume is increased in heavier women.

11.1.2 Marker levels will be more diluted in the blood of heavier women and those with lower BMIs will have relatively higher amounts. To allow for this variation, all marker levels are weight corrected and where the weight is not known, to a weight of 68 Kg. In order to obtain an accurate risk calculation it is essential that the patient's weight is recorded.

11.1.3 Correction for weight improves detection rates by a further 1%.

11.2 **Insulin dependent diabetes (IDDM)**

11.2.1 Babies born to mothers with IDDM tend to be developmentally less mature and levels of free b-HCG tend to be lower for a given gestation. Each MoM is corrected to allow for this reduction.

11.2.2 Correction factors for IDDM: 0.96 (b-HCG); 1.02 (PAPP-A)

11.3 **Ethnicity**

11.3.1 Afro Caribbean women tend to have PAPP-A levels approximately 1.6 times higher than that seen in Caucasians, therefore where ethnicity is recorded as Black African or Afro-Carribean, a correction factor is manually applied.

11.3.2 Variations in marker levels are also seen in other ethnic groups but currently these are not corrected for although the ethnicity data is still recorded for future development work.

11.4 **Twins**

11.4.1 Twin pregnancies can undergo first trimester screening as each foetus's NT measurement can be recorded separately and combined with the maternal serum biochemistry to generate separate risks. Serum marker levels (particularly PAPP-A) are approximately double those seen in a singleton pregnancy. An automatic correction factor will be applied to the results.

11.4.2 Correction factors for twins: 2.08 (b-HCG); 1.83 (PAPP-A). It is important to know if twins are monochorionic (ie they are identical twins developed from a single egg) or dichorionic. If they are identical, it is not genetically possible for only 1 twin to have T21, therefore any differences in risk are likely to relate to differences in each twins NT measurement.

11.5 **In vitro fertilisation (IVF)**

11.5.1 There is some evidence that mothers who have undergone IVF carry a slightly higher risk of having an affected infant. Compounding factors include the age of the donor (when donor eggs are used). For the purposes of Down's risk calculation it is important that we know the age of the donor (in years) at the time when the egg was harvested. If the egg used was the patients own and fresh (or frozen for less than 1 year) the patients own date of birth should be used.

11.6 **Previous Down's or family history of Down's**

The relative risk of having a Down's baby is increased when the mother has had a previously affected pregnancy. Although it is still less than 2% when there is a strong family history it is necessary to find out what type of Down's syndrome occurred. Standard Down's have little increase in risk but translocated Down's have an occurrence rate which follows the normal Mendelian mode of inheritance. If the type of defect is not known then a blood chromosome test should be performed on the affected family member (if possible.) If the Down's type is non-Mendelian, then the blood screening should be performed in the normal manner. Again, the patient's consultant should be advising them of their options.

11.7 Smoking

There is evidence that mothers who smoke have foetuses with slower in-utero growth compared to those who do not smoke. In addition, levels of PAPP-A are markedly

affected by maternal smoking. Smoking status is now recorded and if the box is checked at data entry, correction factors are automatically applied to the results. Correction factors for smokers: 0.92 (b-HCG); 0.82 (PAPP-A)

12. Second trimester

12.1 Specimens for second trimester Down's screening are referred on to the Wolfson Institute for Preventative Health (Bart's and the Royal London NHS Trust). This is the 'Quad' test comprising:

- Alpha feto protein (AFP)
- Human Chorionic Gonadotrophin (HCG)
- Unconjugated oestriol (UE3)
- Inhibin A

12.2 This combination of markers gives the 60-75% detection rate with 3-5% false positive rate. It is recognised that this performance does not meet the standard set out by the Foetal Anomaly Screening Programme (FASP) but at present this is the only screening option available to women who present too late for first trimester screening.

12.3 It is recommended that Down's screening is carried out between 14 weeks 5 days and 19 weeks 0 days of pregnancy. However, if later testing is required, the Wolfson Institute will accept specimens from 14+0 to 22+6 weeks. If blood is taken outside of these limits, a Down's risk cannot be generated and the clinic is informed by phone or fax.

12.4 Second trimester Down's screening is available for Twin pregnancies – but a single risk for the pregnancy is issued – not one risk for each twin.

13. Risk reporting – High risk results

13.1 High risk results are faxed through to the relevant ANC on the day of analysis, wherever possible. A photocopy of the report is attached to the fax log sheet so that the laboratory has a record of which reports have been faxed and when.

13.2 The printed clinic report and GP copy is then sent back to the clinic by dedicated van delivery on the next working day.

13.3 The ANC report is returned with an audit information sheet. The outcome information should be completed by the ante-natal screening co-ordinator and returned to the laboratory in order to allow accurate outcome information to be recorded.

13.4 High risk results are not sent directly to the patient. It is the responsibility of the ANC to contact the patient, explain the findings of the test and to arrange for follow-up.

14. Risk reporting - Low risk results

14.1 ANC reports: Sent out by dedicated van delivery on the day after analysis. Reports for Mid Essex are sent out on the same day if possible.

14.2 GP and Patient reports: Sent out by 1st class post two working days after the ANC reports. This delay in dispatch is deliberate and is to allow time for the ANC to receive the reports and be ready to respond to any queries.

15. Electronic transmission of results

15.1 Basildon and Southend receive their results electronically by means of a text file sent via secure nhs.net email.

16. Retention of specimens and forms

16.1 Patient specimens are retained for two months (current month plus previous month) before being discarded. This is in line with recommendations by the National Screening Committee. Results on specimens analysed after more prolonged storage are difficult to interpret due to changes in reagent batch lot number and assigned medians, which may in combination be sufficient to alter the calculated risks.

16.2 Request forms are retained indefinitely in line with recommendations by the Foetal Anomaly Screening Programme (FASP)

17. Infection Control

17.1 All staff should follow Trust guidelines on infection control by ensuring that they effectively 'decontaminate their hands' before and after each procedure.

17.2 All staff should ensure that they follow Trust guidelines on infection control using Aseptic Non Touch Technique (ANTT) when carrying our procedures i.e. obtaining blood specimens.

18. Audit Procedures

Audit	Details	Frequency
Review of MoMs	Review of MoMs and medians for each marker	Monthly
Review of medians	Medians are reviewed against gestation and weight	Monthly
CUSUM plots	CUSUM plots are updated monthly to assess trends/changes	Monthly
Detection rates	Review of detection rates	Monthly
Request form completeness	Random check of 50 request forms	Monthly
Outcomes	Review of previous months high risk results and outcomes	Monthly
Turnaround time	Review of turnaround time from specimen collection to issue of report	Monthly
ASCAL	Provision of screening results and demographic information to ASCAL	Annual
DQASS	Provision of marker medians, MoMs, coefficients and screening results to DQASS	Annual

19 Quality

19.1 Internal Quality Control (IQC): This material is run with each batch of patient results – 3 levels for each marker. A written record of the IQC results is retained on each batch sheet.

19.2 External quality assessment (EQA): The laboratory participates in the NEQAS national scheme for maternal serum Downs Syndrome screening.

20. Implementation and Communication

20.1 This guideline will be issued to the following staff groups to disseminate and ensure their staff are made aware of the guideline:

- Antenatal clinics – at the Trusts served by the screening service
- Down's screening co-ordinator
- Clinical Scientist staff within Clinical Biochemistry at the Trusts served by the screening service

20.2 The guideline will also be made available on the Intranet, website and notified in Focus.

21. Abbreviations used

MEHT	Mid Essex Hospital Services NHS Trust
ERS	Essex Rivers
WE	West Essex
BAS	Basildon
SOU	Southend
NTD	Neural Tube Defect
IDDM	Insulin dependent diabetes
ANC	Ante-natal clinic
LMP	Last menstrual period
BPD	Bi-parietal diameter
CRL	Crown-rump length
HC	Head circumference
NT	Nuchal translucency
BMI	Body Mass Index
FASP	Foetal Anomaly Screening Programme
NEQAS	National External Quality Assessment Service
DQASS	Down's Syndrome Screening Statistical Support Service

22 References

Screening for Down's Syndrome. Department of health 2003

Antenatal screening for Down's Syndrome – Policy and quality issues. National screening committee. June 2003.

National Down's Syndrome Screening Programme for England: Annual programme report 2002/3. National screening committee. December 2003.

Antenatal screening – working standards for Down's Syndrome Screening 2007

Appendix 1 Glossary

Medians

The level of each biochemical marker varies with gestation. The level of each marker may also vary because of different analytical methods used for measurement. In order to compare values at a particular gestation and with the results obtained by other methods, medians are used by all laboratories undertaking this service.
Medians are a means of producing an average value for a particular gestation and multiples of the median (MoMs) are then used to determine the relative risk of having an affected baby. Strictly speaking, the median is not the average value but the 'middle' value of a range of values.

Detection rate (DR)

This is the % of Down's syndrome pregnancies detected as a result of screening. The detection rate may be expressed as % detected in the screened (by blood test) population, % detected by blood test, ultrasound and amniocentesis (i.e. detected by the whole screening service).
It is also important to state whether the detection rate was determined in the screened population only or in the total population. Take-up rate can significantly affect detection rate.

False positive rate (FPR)

The percentage of patients with a risk worse than 1:150 (first trimester). The target is 3% but this can be affected by several variables (e.g. correct scan information, assay variability etc).