

NHS Fetal Anomaly Screening Programme

First trimester screening for T18 and T13 syndromes

National draft policy proposal

Online consultation event

7 November - 12 December



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Background

- Edward's syndrome, trisomy 18 (T18) and Patau's syndrome, trisomy 13 (T13) are, after Down's syndrome, trisomy 21 (T21) the most common autosomal trisomies observed in fetuses and newborns. They are associated with a range of complex congenital abnormalities that result in permanent physical and mental impairment, miscarriage or intrauterine death. It is well documented that the live birth prevalence for these trisomies increases exponentially with maternal age. Where maternal age was known, 69% of trisomy 18 and 59% of T13 cases were in women aged 35 years or more at expected or observed delivery date.(1)
- Data (see Table 1 and Table 2) sourced from the 'National Down's Syndrome Cytogenetic Register' (NDSCR), demonstrates that 91% of fetuses affected with T18 and 87% of fetuses affected with T13 were diagnosed prenatally in 2009.(2) The Fetal Anomaly Screening Programme recommends that ultrasound screening during 18⁺⁰ to 20⁺⁶ weeks gestation should detect 95% of cases of T18 and 13.(3) In reality, the majority are diagnosed in the first trimester following first trimester screening for Down's Syndrome. Fifty six per cent of cases with T18 and 54% of cases with T13 were detected by first trimester screening, 19% and 13% respectively by second trimester screening, and 20% and 27% during ultrasound scans. This therefore means that whilst women are routinely asked to consent to Down's Syndrome screening, they are in fact being screened for other common autosomal trisomies without consent.
- One could argue that screening for T18 and T13 are not necessary because the majority of fetuses will die in utero. Recently, *Morris et al* established gestational-age-specific loss rates for T18 and T13 and the intrauterine lethality is not as high as previously thought. Approximately, 72% of fetuses with T18 and 49% with T13 will suffer demise from week 12 to term.(2) By implementing a national policy with appropriate standards, it has been estimated that up to 95% of fetuses with T18 and T13 can detected in the first trimester using specific risk algorithms for these aneuploidies(4).

Table 1: T13 cases according to outcome (NDSCR, 2009)

	Number	%
Termination of pregnancy	107	66
Live birth	19	12
Still birth / miscarriage / fetal death	12	7
Unknown outcome	25	15
Total	163	100



Table 2: T18 cases according to time and outcome (NDSCR, 2009)

		Number	%
Prenatal	Termination of pregnancy	340	67
	Live birth	9	2
	Still birth / miscarriage	29	6
	Unknown outcome	82	16
Postnatal	Live birth	30	6
	Still birth / Fetal death	16	3
Total		506	100

Problem description

Current screening strategy

- Screening for T21 is currently offered to all pregnant women in England in accordance with policy recommendations from the Department of Health and it is the only approved national policy which relates to fetal anomaly screening before 14 weeks of pregnancy.^(6;7) Specific targets set out are set out by the NHS Fetal Anomaly Screening Programme (NHS FASP), one of several screening programmes working under the auspices of the UK National Screening Committee (UK NSC). The aim of T21 screening is to identify those women who have a risk of more than the 'cut off' value of 1 in 150 of having an affected baby at term. All services providing a T21 screening programme are expected to reach a $\geq 90\%$ or greater detection rate (DR) for a $\leq 2\%$ or less screen positive rate (SPR) using the 'Combined Screening' programme at 1 in 150 'at term'.ⁱ

Clinical application

- In practice, Combined Screening comprises of an ultrasound scan at 11 weeks, 2 days to 14 weeks, 1 day of gestation and a blood test to measure maternal serum levels of free-beta human chorionic gonadotrophin (free- β hCG) and Pregnancy Associated Plasma Protein –A (PAPP-A). Ultrasound examinations are performed by sonographers with accreditation in the measurement of fetal nuchal translucency (NT) (fluid collection at the back of the baby's neck). Maternal serum biochemical markers, are quantified and 'combined' with maternal age, the linear fetal crown rump length (CRL: range 45.0mm to 84.0mm) and NT measurement.ⁱⁱ Since recommending this policy, 97% (198/205) of hospital Trusts across the country have implemented Combined Screening as the standard to screen for T21.⁽⁸⁾ Uptake across the Trusts is variable as women's choices differ depending on their perceptions of the condition, life experiences and cultural beliefs. Therefore, an uptake target does not exist as the ethos of the programme is about choice.



First trimester screening for T18 and T13 syndromes

6. Combined screening for T21 in the first trimester, has resulted in a paradigm shift in the screening service offered to women. This is evidenced by information published as a result of the NDSCR which demonstrates that first trimester screening is detecting more cases of T18 and T13 than conventional second trimester sonography.
7. At least a quarter of all biochemistry screening laboratories in England also routinely report risk figures for T18 and T13 because the markers used for T21 screening can also be used for T18 and T13 albeit that, a formal policy has not been approved by the UK NSC. Nuchal Translucency is the single most effective marker for all major chromosomal disorders and tends to be significantly increased in both T18 and T13.(9;10) In addition, lower concentrations of maternal serum PAPP-A and free- β hCG are associated with T18 and T13. Using a risk of 1 in 150 at term as a cut off, it is possible to achieve a 95% DR, for a 0.3% FPR for these aneuploidies.(11) In a large prospective population based study in Denmark, the DR for T18 and T13 was 78.8% using a risk cut off of 1 in150.(12)
8. In addition to nuchal translucency there are major structural malformations detected during first trimester ultrasound scanning that increase the detection rate of T18 and T13. These anomalies include: holoprosencephaly (the physiological failure of the brain to divide into lobes or hemispheres); exomphalos (herniation of the fetal abdominal contents due to the physiological failure of the abdomen to close around the base of the umbilical cord) and megacystis (enlarged fetal bladder because of ureteric obstruction), all of which are easily detectable by ultrasound scan at 11-14 weeks of pregnancy and strengthen the effectiveness of first trimester screening.(5)

Second trimester screening for T18 and T13 syndromes

9. Detection rates for T18 and T13, in the second trimester, determined using ultrasound scans, have been reported to be 80 – 86% for T18 and 90 – 100% for T13. (13). However, other studies have suggested that increased detection of both T18 and T13 through ultrasound screening in the second trimester may be at the expense of increased false positive rates (FPR) because many of these anomalies are not uniquely associated with T18 or T13. Therefore, unlike first trimester screening, the FPR can be higher than 10%; (14) which is less than ideal, as a key aim of the screening programme is to prevent unnecessary invasive testing.
10. The use of Quadruple Screening is effective for T18 screening as low concentrations of markers are associated with this trisomy, and the detection rate is comparable to T21 which yields a DR of approximately 75%. Quadruple screening, however does not appear to be effective in screening for T13.(15;16)



Benefits of including T18 and T13 screening for women

11. The rationale for T18 and T13 reporting is that withholding information which potentially could be of benefit the woman is unethical; particularly as both syndromes are associated with significant morbidity and mortality. It cannot be disputed that first trimester screening for T18 and T13 performs well and that given the choice, like T21 screening, most women prefer to know about health risks to their unborn fetus at an earlier opportunity for a number of good reasons:(17) earlier detection might result in an early termination of pregnancy on grounds of fetal anomaly; not feeling fetal movements may be less traumatic; early termination of pregnancy is more acceptable for some women because it can be undertaken under a general anaesthetic as opposed to 'giving birth'. Islam states that on the 120th day after conception the soul enters the body, therefore, some women will find early termination of pregnancy more culturally acceptable.(18)
12. For those families, who decide to continue with their pregnancy, this enables health professionals to individualise care in the antenatal, intrapartum and postnatal period and involve the wider members of the multi-disciplinary team; including neonatologists, counsellors and geneticists.

Conclusion

13. The proposed policy advances the argument that all pregnant women are offered the Combined Screening Test for T21, T18 and T13 conditions.
14. In the second trimester, there should be a policy for a T18 (but not a T13) single risk from Quadruple Screening. This should become an additional part of existing T21 screening programme (BUT only where the Combined Screening Test cannot be performed or for women who book in the second trimester of pregnancy). It is possible to calculate a risk for Trisomy 18 using the same blood sample. However to calculate a risk for T18, the algorithm uses AFP, intact (total) hCG and UE3 but not Inhibin A, using a risk cut off of 1 in 150 at term.
15. A single 'composite' risk will be generated in the first trimester for T18 and T13 screening (separate from the T21 risk), and a single risk for T18 and a single T21 risk for second trimester screening.

Policy methodology

16. Using the UK NSC Policy Review Process underpinned by principles of project management the proposed policy was developed for consultation.(19;20) Initial steps included commissioning the 'Socio-Economic Research and Intelligence Observatory' (SERIO) to search for relevant and recent research related to T18 and T13 syndromes(21) and setting up a group of 25 individuals (healthcare and parent representatives) to develop through



internal and external consensus a 'T18 and T13 first trimester screening policy for England'. At the first of 4 meetings planned until 2012, both parent and provider experiences were presented with the aim of reaching a consensus about devising a policy proposal that could align with current antenatal screening strategies. The same group will analyse all feedback and use the information to inform and refine the draft policy. Policy approval will be sought from the UK NSC.

Topics outside the scope of this policy

17. Additional markers such as fetal heart rate,(22) nasal bone assessment,(23) ductus venosus flow, single umbilical artery and tricuspid regurgitation(24) may offer improved screening performance over the screening programme outlined above. However, given the time and cost currently invested for training and monitoring the quality of NT scanning across the country, there are no plans to adopt these additional markers at present.

Quality assurance

18. Audit and monitoring are a central function of the UK NSC Screening Programmes which drive continuous improvements in the quality of screening and ensure women receive the best available risk evaluation. It is therefore recommended, that all screening strategies including those using NT are subject to external quality assurance checks. As a minimum this includes participation in the Downs' Syndrome Screening Quality Assurance Support programme (DQASS). Centres submit anonymised biochemistry and ultrasound NT data to DQASS, who assess the performance of the screening programme, offer support to centres and maintain the national database in order to improve the screening programme nationally.

Choice of solution: Preferred policy option for screening T18 and T13

19. In terms of effectiveness, a substantial portion of biochemistry screening laboratories are already undertaking routine T18 and T13 risk analysis. Since these conditions are already being screened for as a by-product of Combined Screening, it would seem preferable on the grounds of consistency and transparency for them to be adopted within a formal policy. In terms of efficiency and the feasibility of implementing policy in this area, the markers and techniques employed for T21 screening are the same for T18 and T13 screening; therefore no additional funding is required for implementation.



Policy recommendations

Reform in this area should include the following:

- a. All pregnant women should be offered the Combined Test which can screen for T21, T18 and T13 set at a cut off value of 1 in 150 'at term'.
- b. A second trimester policy for a T18 (but not T13) single risk from Quadruple Screening at a cut off value of 1 in 150 'at term' should become an additional part of existing T21 screening programme (BUT only where the Combined Screening Test cannot be performed or for women who book in the second trimester of pregnancy).
- c. Women should be offered CVS in the first instance if they have a high risk (screen positive) composite single risk for T18/T13. Amniocentesis should be undertaken if a woman has been unable to participate in Combined Screening. Both procedures carry approximately a 1% risk of procedure related loss.ⁱⁱⁱ
- d. The type of laboratory analysis provided will depend on the indication for referral.
- e. Placental tissue /amniotic fluid should be analysed in accordance with recommendations of the Association of Clinical Genetics (ACC) standards and guidelines.(25)

Benefits to women

- f. First trimester Combined Screening is an effective way to screen for T18 and T13. In addition, it is possible to detect major malformations associated with these conditions such as: exomphalos, holoprosencephaly and megacystis when performing ultrasound assessment (fetal CRL and NT measurements) for the Combined Test in the first trimester.
- g. Given the choice, women may wish to know whether their pregnancy may be affected by one of these conditions in order to prepare themselves emotionally and make an informed decision at an earlier time in pregnancy.



Policy summary

Timeline to be agreed

As part of the first trimester Combined Screening programme incorporating an ultrasound examination and a maternal serum blood sample for measurement of:

- Free-beta human chorionic gonadotrophin (free- β hCG)
- PAPP-A
- Sonographic measurement of the fetal CRL (range 45.0mm to 84.0mm)
- Sonographic measurement of the fetal Nuchal translucency

Or for those where Combined Screening cannot be undertaken or present later in pregnancy, Quadruple Screening should be offered (without Inhibin A). A maternal serum blood sample should be taken for biochemical analysis of:

- Intact (total) or free- β hCG
- uE3
- α -fetoprotein

The mid-trimester fetal anomaly scan should also be offered and undertaken from:

- 18 weeks, 0 days to 20 weeks, 6 days

Core screening standard: Timeframe to be agreed

- For T21, T18 and T13 screening programme a 90% DR with an overall SPR of 2.2%
- For T18 and T13 greater than >90% DR, for equal to, or less than $\leq 0.2\%$ ^{iv}

Screening threshold

- 1 in 150 cut off value at term for T21, T18 and T13 across both trimesters

Confirmatory testing for higher risk results

- Chorionic villus sampling (CVS) under direct continuous ultrasound guidance for a 'higher risk' (screen positive) first trimester serum screening result
- Amniocentesis under direct continuous ultrasound guidance for those who present later in pregnancy with a 'higher risk' (screen positive) result from Quadruple Screening or are found to have abnormal ultrasound findings.

Confirmatory analysis

- QF-PCR



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Endnotes

ⁱ A 'cut off' value is set arbitrarily with a 'low risk' false negative (screen negative) result expressed below the cut off value and a 'high risk' - false positive (screen positive) result above the cut off value. As quality assurance data has demonstrated improvements in detection without an increase in the false positive rate, this new policy will adopt a 1 in 150 rate the same as for the Combined Screening programme. To ensure that the measurement of performance, quality assurance and decision-making are nationally consistent, individual results should be categorised as higher or lower risk.

ⁱⁱ Key requisites for T18 and T13 are the same for Combined Screening. The linear measurement of the crown rump length (CRL) to estimate fetal gestational age (dating scan), measurement of the nuchal translucency (NT) space at the back of the fetal neck and maternal blood to quantify maternal serum markers (pregnancy associated plasma protein (PAPP-A), free β hCG hormone. An appointment slot of 20 minutes is recommended to undertake all the ultrasound aspects of the process.

The sonographic measurements of CRL and NT require the skills of a trained ultrasound practitioner (sonographer or clinician) who has the minimal qualifications to undertake ultrasound and specialist training in NT scanning. Without these credentials the potential to either under or overestimate the NT can happen and generate unnecessary maternal anxiety because of an inaccurate result.

ⁱⁱⁱ Clinicians providing either procedure should be trained to the competencies expected of the RCOG Fetal Medicine Advanced Training Skills Module (ATSM) or other internal equivalent. Where clinicians are providing amniocentesis and / or CVS outside of a tertiary fetal medicine centre, then referrals should be 'pooled' so that clinical expertise and competency is maintained by undertaking an adequate number of procedures.

^{iv} For T21 alone, equal to, or greater than $\geq 90\%$ DR, for equal to, or less than $\leq 2\%$ SPR

