ORIGINAL PAPER

First and second trimester antenatal screening for Down's syndrome: the results of the Serum, Urine and Ultrasound Screening Study (SURUSS)

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CONTENTS

	Executive summary	56
1	**Introduction**	57
2	**Methods**	57
3	**Results**	62
4	**Discussion**	78
5	**Conclusions**	86
	Acknowledgements	86
	Author Affiliations	87
	List of investigators	87
	Glossary	87
	Abbreviations	88
	References	88
	Appendix	89

EXECUTIVE SUMMARY

Objectives

To identify the most effective, safe and cost-effective method of antenatal screening for Down's syndrome using nuchal translucency (NT), maternal serum and urine markers in the first and second trimesters of pregnancy, and maternal age in various combinations.

Design

A prospective study of women who booked for their antenatal care at about 8–14 weeks of gestation, with follow-up to identify pregnancies with Down's syndrome ascertained through second trimester screening or at birth.

Setting

Twenty-five maternity units (24 in the UK and one in Austria) offering second trimester Down's syndrome serum screening that agreed to collect observational data in the first trimester.

Participants

The results were based on 47,053 singleton pregnancies, including 101 pregnancies with Down's syndrome.

Measurements and tests

NT measurements were included if obtained between 9 and 13 weeks of pregnancy; serum and urine samples were also taken and stored. Another pair of serum and urine samples was collected in the second trimester and included if obtained between 14 and 20 weeks. Urine and serum samples from each affected pregnancy and five matched controls were tested for:

Serum:
- alphafetoprotein (AFP)
- total human chorionic gonadotrophin (hCG)
- unconjugated oestriol (uE_3)
- pregnancy associated plasma protein A (PAPP-A)
- free β-hCG
- dimeric inhibin-A.

Urine:
- invasive trophoblast antigen (ITA)
- β-core fragment
- total hCG
- free β-hCG.

The matching criteria were gestation (using an ultrasound crown–rump length or biparietal diameter measurement), duration of storage, and centre. Screening performance of the individual markers and combinations of markers together with maternal age was assessed using standard methods. In addition pairs of first and second trimester serum samples from 600 controls were tested to secure a larger set in which screening performance could be determined using distribution parameters based on dates (time since first day of the last menstrual period).

Main outcome measures

The following were determined for different combinations of markers:
- efficacy (by assessing screening performance, focusing on the false-positive rate (FPR) for an 85% detection rate (DR))
- safety (focusing on the number of fetal losses due to amniocentesis (or chorionic villus sampling) in 100,000 women screened)
- cost-effectiveness (focusing on the cost of screening 100,000 women and the cost per Down's syndrome pregnancy diagnosed).

Test (all include maternal age)	Measurements	FPR for 85% DR (%)	95% confidence interval (%)
Integrated test	NT and PAPP-A at 10 completed weeks AFP, uE_3, free β-hCG and inhibin-A at 14–20 completed weeks	1.2 (1.3[a])	1.0–1.4 (1.2–1.4[a])
Serum integrated test	Integrated test without NT. PAPP-A at 10 completed weeks	2.7 (4.9[a])	2.4–3.0 (4.4–5.4[a])
Combined test	NT, free β-hCG and PAPP-A at 10 completed weeks	6.1 (6.0[a])	5.6–6.5 (5.5–6.5[a])
Quadruple test	AFP, uE_3, free β-hCG, inhibin-A at 14–20 completed weeks	6.2	5.8–6.6
Triple test	AFP, uE_3, free β-hCG at 14–20 completed weeks	9.3	8.8–9.8
Double test	AFP and free β-hCG at 14–20 completed weeks	13.1	12.5–13.7
NT measurement	NT at 12–13 completed weeks	20.0	18.6–21.4

[a] NT and/or serum measurements at 12 completed weeks of pregnancy

Results

Efficacy (screening performance)

The false-positive rates for an 85% detection rate for the main screening tests are shown in the above table, in decreasing order of screening performance:

With the serum integrated test, 10 weeks is the preferred time in pregnancy for the PAPP-A measurement. For the integrated test and the combined test, the timing of the measurement of the first trimester markers is less critical.

Safety

The lower false-positive rate with the integrated test compared with other tests means that at an 85% detection rate there would be nine diagnostic procedure-related unaffected fetal losses per 100,000 women screened compared with 44 using the combined test or 45 with the quadruple test.

Cost-effectiveness

Screening using the integrated test is less costly than might be expected because the extra screening costs tend to be offset by savings in the cost of diagnosis arising from the low false-positive rate. It was estimated that to achieve an 85% detection rate the cost to the UK NHS would be £15,300 per Down's syndrome pregnancy detected. The corresponding cost using the second trimester quadruple test would be £16,800 and using the first trimester combined test it would be £19,000.

Conclusions

Implications for healthcare

The results showed that screening performance in the first trimester of pregnancy was virtually the same as that in the second trimester, and in either it was much less effective than integrating screening measurements from both trimesters into a single test. In applying these results to screening practice several conclusions can be drawn. The following tests offer the most effective and safe method of screening:

- overall: the integrated test
- if an NT measurement is not available: the serum integrated test
- for women who do not attend for antenatal care until the second trimester of pregnancy: the quadruple test
- for women who choose to have a screening test in the first trimester: the combined test.

At a constant detection rate, the cost-effectiveness of these four tests is broadly similar, any extra screening costs tending to be offset by fewer diagnostic costs. The evidence presented in this report does not support retaining the double test, the triple test, or NT measurements on their own (with or without maternal age) because each would lead to many more women having invasive diagnostic tests, without increasing the proportion of Down's syndrome pregnancies detected.

1 INTRODUCTION

We here report the results of the Serum Urine and Ultrasound Screening Study (SURUSS), a large collaborative study of antenatal screening for Down's syndrome, funded as part of the UK Health Technology Assessment (HTA) Programme, to help determine best screening practice.

Antenatal screening for Down's syndrome has developed rapidly over the last 15 years. In 1988, maternal age screening was improved by the second trimester triple test.[1] Some centres adopted the double test. (A glossary of definitions of the various screening tests and a key to abbreviations used are included at the end of this report.) The triple test was later improved by the addition of maternal serum inhibin-A to form the quadruple test. At the same time, three first trimester markers, serum pregnancy-associated plasma protein A (PAPP-A), free β-human chorionic gonadotrophin (β-hCG) and the ultrasound marker nuchal translucency (NT; see glossary) were shown to be useful in screening. A systematic review of antenatal screening for Down's syndrome published in 1997 recommended that the second trimester triple or quadruple test should be the test of choice.[2] In 1999 the integrated test was described,[3] which combined markers from the first and second trimesters to yield a screening performance better than from either trimester alone. Several urinary markers have been proposed as screening tests, notably β-core fragment[4] and invasive trophoblast antigen (ITA).[5]

The value of SURUSS is that it provides a large dataset on women seen in both the first and second trimester of pregnancy (it is the largest such dataset yet reported), without planned intervention in the first trimester. This allows a direct examination of the screening performance of all individual screening markers – NT and first and second trimester serum and urine markers. The strength of SURUSS is that it can do this in a single large unselected group of pregnant women with data collected in both trimesters, in a collaborative study from 25 centres that together reflect the provision of routine antenatal care.

2 METHODS

The study was based on women attending 25 maternity centres (24 in the UK and one in Austria). Most centres began recruiting in September 1996, following a pilot study started in January 1995 at one centre. Recruitment to the study ended in April 2000, and follow-up of pregnancy outcome was carried out to 31 May 2001.