**QUEEN'S
UNIVERSITY
BELFAST**

Three-stage contingent screening for down syndrome

Wright, D., Bradbury, I., Cuckle, H., Gardosi, J., Tonks, A., Standing, S., & Benn, P. (2006). Three-stage contingent screening for down syndrome. *Prenatal Diagnosis*, 26(6)(6), 528-534. <https://doi.org/10.1002/pd.1451>

Published in:
Prenatal Diagnosis

Queen's University Belfast - Research Portal:
[Link to publication record in Queen's University Belfast Research Portal](#)

General rights

Copyright for the publications made accessible via the Queen's University Belfast Research Portal is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy

The Research Portal is Queen's institutional repository that provides access to Queen's research output. Every effort has been made to ensure that content in the Research Portal does not infringe any person's rights, or applicable UK laws. If you discover content in the Research Portal that you believe breaches copyright or violates any law, please contact openaccess@qub.ac.uk.

Three-stage contingent screening for Down syndrome

Dave Wright^{1*}, Ian Bradbury², Howard Cuckle³, Jason Gardosi⁴, Ann Tonks⁴, Sue Standing⁵ and Peter Benn⁶

¹Department of Mathematics and Statistics, University of Plymouth, UK

²School of Biomedical Science, University of Ulster, Coleraine, UK

³Reproductive Epidemiology, School of Medicine, University of Leeds, UK

⁴Perinatal Institute, Birmingham, UK

⁵Department of Clinical Chemistry, Birmingham Women's Health Trust, UK

⁶Department of Genetics and Developmental Biology, University of Connecticut, Health Center, Farmington, CT, USA

Objective To demonstrate the potential value of three-stage sequential screening for Down syndrome.

Methods Protocols were considered in which maternal serum pregnancy associated plasma protein-A (PAPP-A) and free β -human chorionic gonadotropin (hCG) measurements were taken on all women in the first trimester. Those women with very low Down syndrome risks were screened negative at that stage and nuchal translucency (NT) was measured on the remainder and the risk reassessed. Those with very low risk were then screened negative and those with very high risk were offered early diagnostic testing. Those with intermediate risks received second-trimester maternal serum α -fetoprotein, free β -hCG, unconjugated estriol and inhibin-A. Risk was then reassessed and those with high risk were offered diagnosis. Detection rates and false-positive rates were estimated by multivariate Gaussian modelling using Monte-Carlo simulation.

Results The modelling suggests that, with full adherence to a three-stage policy, overall detection rates of nearly 90% and false-positive rates below 2.0% can be achieved. Approximately two-thirds of pregnancies are screened on the basis of first-trimester biochemistry alone, five out of six women complete their screening in the first trimester, and the first-trimester detection rate is over 60%.

Conclusion Three-stage contingent sequential screening is potentially highly effective for Down syndrome screening. The acceptability of this protocol and its performance in practice, should be tested in prospective studies. Copyright © 2006 John Wiley & Sons, Ltd.

KEY WORDS: Down syndrome; prenatal screening; policy; modelling; sequential

INTRODUCTION

The most commonly used screening tests for Down syndrome use either second-trimester maternal serum biochemical markers or a combination of first-trimester maternal serum markers with ultrasound measurement of nuchal translucency (NT). Recently, screening policies have been introduced where information from both the first- and second-trimester tests is combined. In comparison with screening based on first- or second-trimester markers alone, these policies have great potential for reducing false-positive rates while maintaining or even increasing detection rates. One class of such sequential policies assesses risk on the basis of first- and second-trimester data that are collected on all women. Risk is calculated in the second trimester on the basis of all the data considered together. The 'integrated test' of Wald *et al.* (1999, 2003) is an example of this type of 'nondisclosure' sequential testing.

Another policy is to select women for second-trimester testing on the basis of their first-trimester risk (Cuckle and Arbuzova, 2002, 2004; Wright *et al.*, 2004;

Maymon *et al.*, 2004, 2005; Benn *et al.*, 2005; Cuckle *et al.*, 2005). Such 'contingent' sequential screening can achieve similar performances to nondisclosure screening, while only a fraction of women need second-trimester tests (Wright *et al.*, 2004).

In a previous article (Benn *et al.*, 2005), we proposed a contingent screening protocol in which all pregnant women received first-trimester NT and serum biochemical tests (pregnancy associated plasma protein-A (PAPP-A) and either free β - or total human chorionic gonadotropin (hCG)), and approximately 20% of women with intermediate risks would be tested in the second trimester for 'triple' or 'quadruple' markers (α -fetoprotein (AFP), free β -hCG or total hCG, unconjugated estriol (uE₃), with or without inhibin-A). Applied to the United Kingdom, this approach could achieve approximately 91% detection with a 2.1% false-positive rate. Because NT measurement is expensive or otherwise limited in its availability in some locations, it has been suggested that the provision of the first-trimester ultrasound could also be offered on a contingency basis (Christiansen and Larsen 2002; Larsen *et al.*, 2005; Wright *et al.*, 2005). In this article, we evaluate the effectiveness of such a three-stage screening policy.

*Correspondence to: Dave Wright, Department of Mathematics and Statistics, University of Plymouth, Plymouth PL4 8AA, UK. E-mail: dave.wright@plymouth.ac.uk

METHODS

Policies

The three-stage policies considered here are defined in terms of four risk cutoffs (Figure 1). Except where specifically stated, modelling is based on the following tests and gestational ages:

Stage 1

PAPP-A and free β -hCG are measured at 10 weeks. The risk based on maternal age and these markers is assessed and women with very low risk are screened negative. No pregnancies are screened positive at this stage. The first stage risk cutoff $1/b$ determines the proportions of pregnancies that go on to have NT measurements in the second stage. Increasing the cutoff (lower value for b) reduces the proportion of pregnancies for which NT is measured. The proportion of Down syndrome pregnancies with risk below this cutoff determines a first stage false-negative rate, which is a lower bound on the overall false-negative rate. The choice of b thus involves a compromise between the earliest reassurance of women and the limit placed on overall detection.

Stage 2

NT is measured at 11 weeks and the risk, based on maternal age, NT and the first-trimester biochemical

markers is assessed. Women with very low risk are screened negative and those with very high risk are screened positive. For a given first stage cutoff $1/b$, the second upper stage cutoff $1/c_1$ determines the early detection and early false-positive rate, while the lower cutoff $1/c_2$ determines the proportion of women who continue to the third stage and have second-trimester biochemical markers.

Stage 3

The 'quadruple' markers (α -fetoprotein, free β -hCG, unconjugated estriol and inhibin-A) are measured in the second trimester. The information from maternal age is combined with both the first- and second-trimester markers to assess risk. On the basis of this risk, the pregnancy is screened negative or positive according to the final cutoff $1/d$.

Modelling

For each outcome considered (Down syndrome and unaffected), $\log_{10}$ transformed marker values are assumed to follow multivariate Gaussian distributions. Following our earlier work (Wright *et al.*, 2005), the means, standard deviations and correlation coefficients defining these distributions were obtained from the SURUSS study (Wald *et al.*, 2003, 2004). These first- and second-trimester statistical parameters are based on pregnancies that are expected to be viable in the second trimester and assume no correlation between marker values and *in utero* survival. SURUSS truncation limits were applied in risk calculations. Unless specifically stated, all modelling was based on the sets of parameters obtained when gestational age was measured by ultrasound (with maternal weight correction).

The various rates were estimated using Monte-Carlo methods. Samples of 500 000 observations were drawn. Likelihood ratios were computed for each set of markers at each stage. These were then combined with the maternal age distribution of Down pregnancies or unaffected pregnancies, as appropriate, to derive maternal age-specific detection and false-positive rates.

Rates and cutoffs

The probability of a Down syndrome term pregnancy, conditional on maternal age, was taken from Wright and Bray (2000). The maternal age distribution was based on data from England and Wales in 2002 (Office of National Statistics, 2002). To illustrate the performance of the policies for different maternal ages, women were stratified into five groups; 25 and under, 26 to 30, 31 to 35, 36 to 40 and 41 or over.

Initially, the efficiency of three-stage screening was evaluated from the standpoint of either the false-positive rate achievable for a fixed 85% detection rate or, alternatively, the detection rate corresponding to a fixed 1% false-positive rate. For this part of the analysis, we selected risk cutoffs corresponding to second stage

Figure 1—Schema showing the design of a three-stage contingent sequential screening policy

sampling rates of 15, 20, 30 and 40%. We fixed the third-stage sampling rate at half of that in the second stage. The cutoffs were selected to achieve first-trimester detection rates of 50, 60 and 70%.

To assess the practical impact of three-stage screening in a population, we set the term risk cutoffs $1/c_1$ and $1/c_2$ at $1/20$ and $1/2000$ respectively, consistent with our previous proposal for two-stage contingency screening (Benn *et al.*, 2005). The value for $1/d$ was set at the widely used $1/250$ level. Various values for $1/b$ were considered. We also considered the impact of a number of modifications from this basic protocol, as described in the Results.

RESULTS

Performance based on fixed detection or false-positive rates

Table 1 shows detection rates and false-positive rates for various levels of stage 2 and stage 3 sampling. For comparison, Table 1 also gives results for the case in which 100% of all pregnancies go through all stages.

Of the contingent sampling strategies presented in Table 1, the strategy in which 40% continue to stage 2 and 20% continue to stage 3 is the most intensive strategy as far as testing is concerned. With this strategy, 60% of screening is completed with first-trimester PAPP-A and free β -hCG alone and 80% is completed in the first trimester. For an 85% overall detection rate, the false-positive rates are only marginally higher than if all screening were completed in the second trimester on the basis of all marker information. For first-trimester detection rates of 50, 60 and 70%, the marginal increase in false-positive rate is 0.1, 0.2 and 0.4% respectively. For a first-trimester detection rate

of 70%, the marginal increase is 0.4%. If the overall false-positive rate is fixed at 1%, then the marginal reductions in detection rate compared to 100% sampling are 1.1, 1.4 and 2.9% for 50, 60 and 70% first-trimester detection rates respectively. For a population of 100 000 pregnancies, these reductions in detection rate would account for an expected 2.3, 2.9 and 6.1 missed cases respectively. On the other hand, 40 000 NT scans and 80 000 second-trimester samples would be avoided.

Performance for a population

The risk cutoff implicit in Table 1 is determined by the rates of second and third-stage sampling, and by the first-trimester detection rate. They are unlikely to be acceptable for implementation against a background where policy is based on a fixed $1/250$ risk cutoff. We therefore present in Table 2 the results achievable using practically based risk cutoffs as proposed in Benn *et al.* (2005) for the UK population. Data is presented for different values of $1/b$.

Following NT measurement (stage 2), the detection rate for affected pregnancies is approximately the same for each of the $1/b$ values evaluated (Table 2). Similarly, $1/b$ has little effect on the first-trimester false-positive rate even though the proportion of women receiving NT measurement varies from 12.4 to 64.7%. Although the choice of $1/b$ has little effect in the first trimester, it does affect the subsequent second-trimester detection that declines from 28.6% when $1/b = 1/8000$ to 20.4% for $1/b = 1/500$.

Of the various choices for $1/b$ considered, $1/2000$ may be preferred (see Discussion). For $1/b = 1/2000$, less than one-thirds of patients need a NT measurement, and less than one-sixth require second-trimester screening. The overall detection rate is only 2.7% lower, and the false-positive rate is only 0.2% higher,

Table 1—Detection rates and false-positive rates for various three-stage contingent screening policies^a

Patients receiving NT (%)	Patients receiving both NT + second-trimester biochemistry (%)	First-trimester detection rate (%)	Detection rate for a 1% false-positive rate (%)	False-positive rate for an 85% detection rate (%)
100	100	0	88.5	0.5
15	7.5	50	82.6	2.9
20	10	50	84.5	1.1
30	15	50	86.5	0.7
40	20	50	87.4	0.6
15	7.5	60	82.4	2.9
20	10	60	84.3	1.2
30	15	60	86.2	0.8
40	20	60	87.1	0.7
15	7.5	70	81.1	3.0
20	10	70	83.1	1.4
30	15	70	84.9	1.0
40	20	70	85.6	0.9

^a PAPP-A and free β -hCG at 10 weeks, NT measured contingently at 11 weeks and AFP, uE₃, free β -hCG and inhibin measured at the second trimester.

Table 2—Disposition of Down syndrome and unaffected pregnancies for various screening policies

Policy ^a		Stage 1		Stage 2		Stage 3		Overall	
		Continue (%)	Negative (%)	Positive (%)	Continue (%)	Negative (%)	Positive (%)	Negative (%)	Positive (%)
Three stage 1/b = 1/8000	Down	99.0	1.0	62.6	32.9	3.5	28.6	4.3	91.2
	Unaffected	64.7	35.3	0.3	18.7	45.8	1.8	16.9	2.1
Three stage 1/b = 1/4000	Down	97.7	2.3	62.6	32.2	2.9	28.1	4.1	90.7
	Unaffected	48.2	51.8	0.3	18.0	29.9	1.7	16.2	2.0
Three stage 1/b = 1/2000	Down	95.2	4.8	62.6	30.6	2.0	26.9	3.7	89.5
	Unaffected	33.0	67.0	0.3	16.6	16.2	1.7	14.9	1.9
Three stage 1/b = 1/1000	Down	91.2	8.8	62.6	27.5	1.0	24.4	3.1	87.0
	Unaffected	21.0	79.0	0.3	14.2	6.5	1.5	12.7	1.8
Three stage 1/b = 1/500	Down	85.5	14.5	62.4	22.8	0.3	20.4	2.4	82.8
	Unaffected	12.4	87.6	0.3	10.8	1.4	1.2	9.5	1.5
Two stage	Down	100.0	0.0	62.5	33.4	4.1	28.9	4.4	91.4
	Unaffected	100.0	0.0	0.3	19.1	80.7	1.8	17.3	2.1
Nondisclosure	Down	100.0	0.0	0.0	100.0	0.0	92.2	7.8	92.2
	Unaffected	100.0	0.0	0.0	100.0	0.0	2.1	97.9	2.1

^a Cutoffs: stage 1, 1/b; stage 2, low risk 1/2000, high risk 1/20; stage 3, 1/250.

Table 3—Disposition of Down syndrome and unaffected pregnancies by maternal age

Maternal age Outcome No.			Stage 1		Stage 2		Stage 3		Overall	
			Continue (%)	Negative (%)	Positive (%)	Continue (%)	Negative (%)	Positive (%)	Negative (%)	Positive (%)
25 or under	Down	23	86.4	13.6	44.2	38.6	3.7	34.1	4.4	78.3
	Unaffected	30 294	19.8	80.2	0.1	8.0	11.7	0.6	7.4	0.7
26–30	Down	29	89.5	10.5	48.2	38.0	3.3	33.5	4.5	81.7
	Unaffected	28 077	25.2	74.8	0.1	10.8	14.2	0.9	9.9	1.0
31–35	Down	56	94.4	5.6	56.6	35.3	2.5	30.9	4.4	87.5
	Unaffected	27 981	38.8	61.2	0.3	18.9	19.6	1.7	17.2	2.0
36–40	Down	68	98.5	1.5	68.9	28.3	1.2	24.8	3.6	93.7
	Unaffected	11 732	64.8	35.2	0.9	39.1	24.8	4.4	34.7	5.3
41 and over	Down	37	99.9	0.1	82.2	17.4	0.3	15.5	1.9	97.7
	Unaffected	1 703	91.0	9.0	3.2	69.3	18.5	11.0	58.3	14.2
Overall	Down	214	95.2	4.9	62.5	30.7	2.0	27.0	3.7	89.5
	Unaffected	99 786	33.0	67.0	0.3	16.6	16.3	1.6	14.9	1.9

than that obtained when all patients receive all tests (nondisclosure approach).

Maternal age

Table 3 shows that the use of the three-stage protocol can be advantageous for women of all ages. Data is shown for the expectation when the screening is applied to 100 000 women who are subdivided into five age categories. In the highest age group (46 and older), the group risk for fetal Down syndrome is 1 in 45. For these women, approximately 9% would not require a NT measurement, and 22% would complete their screening in the first trimester. In the youngest age group (25 and under), the group risk for fetal Down syndrome is 1 in 1321. For these women, approximately 80% would not require a NT measurement, with 92% completing their screening in the first trimester.

Variant screening protocols

Table 4 summarizes estimates for the screening when alternative screening policies, cutoffs, populations or other changes in variables are taken into consideration.

Since a substantial proportion of women referred for screening at the first stage may not have received an ultrasound, we first considered the detection rate and false-positive rates when the statistical parameters for first stage biochemical markers were based on gestations derived from the last menstrual period. Assuming the parameter estimates from SURUSS, the overall performance of the screening was found to be similar to that modelled using ultrasound based parameters, but slightly more pregnancies reach the second stage of the sequential test. Assessment of overall performance fails to reflect the fact that errors in gestational age may have large impact on individual screening results. For

example, pregnancies with true gestations of 8 weeks with erroneous menstrual gestations of 10 weeks would tend to have inflated first stage risks and over 80% of unaffected pregnancies would continue to the second stage. Compared to the general population, the overall detection rate and false-positive rate would improve for these pregnancies as a result of the additional tests. On the other hand, pregnancies with true gestational ages of 12 weeks with erroneous gestational ages of 10 weeks would be assigned erroneously low risks at the first stage. The effect of this would be a reduction in the proportion continuing to the second stage (to 7%) and a reduced detection rate to 75% overall. In our modelling, we assume no systematic error in over- or under-assessment of gestational age by menstrual dating, and therefore the net effect of these errors is relatively small.

Use of the second-trimester 'triple' test instead of the 'quadruple' test (omitting inhibin) also has a very small effect on the overall performance of three-stage screening. A second-trimester 'double' test (omitting unconjugated estriol) would also be associated with very good overall screening performance.

Lower false-positive rates, at some cost in detection, can be achieved by using a higher second-trimester cutoff. For example, setting $1/d = 1/100$ provides an overall detection rate of 87% for a 1% false-positive rate.

We also considered the performance of the three-stage screening protocol applied to the US pregnant population (National Center for Health Statistics, 2004). For this analysis, we used second trimester rather than term risks, cutoffs of $1/1300$ or $1/2600$ for $1/b$, $1/30$ for $1/c_1$, $1/1300$ for $1/c_2$, $1/270$ for $1/d$, total hCG instead of free β -hCG in both the first and second trimester, first-trimester serum testing at 12 weeks, and NT measurement at 13 weeks (Benn *et al.*, 2005). Primarily because of the differences in sampling times during the first trimester, the screening performance is somewhat worse overall than in the UK but the relative merits of the three-stage policy are similar to those for the United Kingdom.

DISCUSSION

This study demonstrates that three-stage contingent sequential screening has the potential to considerably reduce NT scanning and second-trimester sampling with little impact on overall screening performance when compared to a policy of nondisclosure screening where all markers are measured on all women. A benefit of this approach is that it allows screening to be completed in the first trimester for most women and early detection of most Down syndrome pregnancies. Although a high proportion of advanced maternal age women would require testing in addition to first-trimester serum biochemical markers, the three-stage protocol does appear to be potentially advantageous for pregnant women of all ages. The protocol provides a logical approach to allocate NT ultrasound examination in situations where, owing to limited resources, it cannot be made available to all women.

The three-stage screening protocol requires the selection of four risk cutoffs, each of which will affect the overall performance of the screening. Furthermore, the choice of a particular cutoff can affect the efficiency of screening downstream from the point that the cutoff is applied. This is illustrated with the first stage $1/b$ cutoff that affects the number of affected pregnancies detected in the second trimester (Table 2). Selecting an appropriate set of cutoffs is therefore relatively complex. In practice, cutoffs are likely to be largely determined by those currently in use in first- and second-trimester protocols, availability of resources for NT measurement and biochemical testing, existing patterns of patient screening, and simplicity in the implementation of the protocols. It is also desirable to select cutoffs that do not lead to perceived inequities in patient management. For example, it would be difficult to justify the restriction of NT measurement to women whose risks were greater than $1/1000$ on the basis of first-trimester serum tests but also to provide second-trimester screening to women with lower risks. Similarly, it would be problematic to restrict second-trimester screening to women with risks greater than $1/1000$ based on first-trimester NT and serum tests when existing second-trimester protocols provide the testing for young women who do not receive first-trimester screening and who, on the basis of their age alone, have risks less than $1/1000$. On the basis of these considerations, our estimates for the efficiency of three-stage screening, and our previous suggestions for cutoffs (Benn *et al.*, 2005), we would propose that the low risk cutoff $1/b$ be equal, or lower, than $1/c_2$. A term risk of $1/b = 1/c_2 = 1/2000$ for the United Kingdom and second-trimester values of $1/1300$ for these cutoffs in the United States are associated with highly efficient screening protocols (Tables 2 and 4).

Women who enter a three-stage screening protocol may receive up to four estimates for their risk for fetal Down syndrome; risk based on *a priori* maternal age alone, risk after first-trimester serum testing, risk following the NT exam, and a further estimate following the second-trimester serum test. It would therefore be essential to emphasize to patients that only the most recent risk figure is an accurate assessment of their risk. The psychological impact of these multiple risk figures on patients is unknown and this may be an important consideration in the acceptability of three-stage screening. Because the time interval between first-trimester serum testing and NT measurement is small, the additional patient anxiety associated with the three-stage protocol should not be substantially more than that associated with two-stage contingency screening. In fact, overall stress may be reduced because many women will be able to avoid referral to a maternal-fetal medicine unit for the NT scan.

A further set of practical considerations arises over the logistics of delivering a coordinated set of maternal serum and ultrasound examinations within relatively narrow gestational age windows. Our modelling is based on the assumption that, at each stage, all high-risk women will receive the appropriate additional testing. In practice, it is likely that not all women will receive the

recommended set of tests. For example, some women may not present until the second trimester. A realistic expectation for sequential contingency screening would therefore be based on detection rates and false-positive rates that fall between those presented here and those based on either first- or second-trimester screening alone. Other practical issues that need to be considered are the availability of first-trimester screening tests and second-trimester screening for open neural tube defects using AFP.

In summary, under the assumption that three-stage contingency screening can be effectively delivered, we have demonstrated that this can be associated with highly effective screening while minimizing the testing offered. Trials are needed to confirm or refine the values for the statistical parameters used, demonstrate the validity of the modelling and to assess the ability to provide the service.

REFERENCES

- Benn P, Wright D, Cuckle H. 2005. Practical strategies in contingent sequential screening for Down's syndrome. *Prenat Diagn* **25**: 645–652. DOI: 10.1111/j.1471-0528.2005.00560.x.
- Christiansen M, Larsen SO. 2002. An increase in cost-effectiveness of first trimester maternal screening programmes for fetal chromosome anomalies is obtained by contingent testing. *Prenat Diagn* **22**: 482–486.
- Cuckle H, Arbuzova S. 2002. The efficiency and clinical practicality of multi-modality screening strategies. In *Early Prenatal Diagnosis, Fetal Cells and DNA in the Mother: Proceedings of the 12th Fetal Cell Workshop*, Macek M, Bianchi D, Cuckle H (eds). Charles University Press: Prague; 387–397.
- Cuckle H, Arbuzova S. 2004. Multianalyte Maternal serum screening for chromosomal defects. In *Genetic Disorders and the Fetus: Diagnosis, Prevention and Treatment* (5th edn) Milunsky Aubrey (ed.). Johns Hopkins University Press: Baltimore.
- Cuckle H, Benn P, Wright D. 2005. Down syndrome screening in the first and/or second trimester: model predicted performance using meta-analysis parameters. *Semin Neonatol* **29**: 252–257.
- Maymon R, Betser M, Dreazen E, Padoa A, Herman A. 2004. A model for disclosing the first trimester part of an integrated Down's syndrome screening test. *Clin Genet* **65**: 113–119.
- Maymon R, Cuckle H, Jones R, Reish O, Herman A. 2005. Predicting the result of additional second trimester markers from a woman's first trimester marker profile: a new concept in Down's syndrome screening. *Prenat Diagn* **25**: 1102–1106.
- Larsen SO, Christiansen M, Norgaard-Pedersen B. 2005. Which contingent sequential screening protocol? (Letter). *Prenat Diagn* **25**: 1168–1169.
- National Center for Health Statistics. 2004. *Vital Statistics of the United States. 2002. Natality Data Set, CD ROM, Series 21*: Hyattsville, MD; 16.
- Office of National Statistics. 2002. *Birth Statistics, Series FM1*, The Stationary Office: London; vol 30.
- Wald N, Watt HC, Hackshaw AK. 1999. Integrated screening for Down syndrome based on tests performed during the first and second trimesters. *N Engl J Med* **341**: 461–467.
- Wald NJ, Rodeck C, Hackshaw AK, Walters J, Chitty L, Mackinson AM. 2003. First and second trimester antenatal screening for Down's syndrome: the results of the Serum, Urine and Ultrasound Screening Study (SURUSS). *J Med Screen* **10**(2): 56–104.
- Wald N, Rodeck C, Rudnicka A, Hackshaw A. 2004. Nuchal translucency and gestational age. *Prenat Diagn* **24**(2): 150–151.
- Wright DE, Bray I. 2000. Estimating birth prevalence of Down's syndrome. *J Epidemiol Biostat* **5**(2): 89–97.
- Wright D, Bradbury I, Benn P, Cuckle H, Ritchie K. 2004. Contingent screening for Down's syndrome is an efficient alternative to non-disclosure sequential screening. *Prenat Diagn* **24**: 762–766.
- Wright D, Bradbury I, Benn P, Cuckle H, Ritchie K. 2005. Which contingent sequential screening strategy (Letter). *Prenat Diagn* **25**: 520–521.