Institution: Queen Mary University of London

Unit of Assessment: A1 (Clinical Medicine)

Title of case study: Antenatal screening for Down's syndrome

1. Summary of the impact

This research significantly improved the accuracy of antenatal screening for Down's syndrome and the extent to which maternal choices are informed by robust evidence. Tests developed by Professor Nick Wald's team at Queen Mary's Wolfson Institute of Preventive Medicine and validated in the SURUSS (Serum Urine and Ultrasound Screening Study) study were adopted as national UK policy in 2003 and remain an established gold standard worldwide. As a result, most Down's syndrome babies in UK are now born through parental informed choice, and (using age-adjusted figures) approximately 3,000 fewer babies with the syndrome were born between 2008 and 2013. Screening programmes in numerous countries are based on this research.

2. Underpinning research

Down's syndrome is the commonest genetic disorder in the UK. It produces moderate to severe mental impairment with or without physical abnormalities, as well as early-onset dementia. Almost all individuals with this syndrome require lifelong care. Down's syndrome affects one in 500 fetuses in mothers under 20 years' old but rises sharply with maternal age to one in 40 in mothers over 45. Over 90% of couples choose to terminate a pregnancy if they know their fetus is affected. Those who choose not to terminate prefer to know the diagnosis in advance of the birth. No non-invasive test yet allows diagnosis of Down's syndrome at a sufficiently early stage of pregnancy to offer the choice of termination with 100% accuracy. Amniocentesis and chorionic villous sampling, while highly accurate, carry a risk of miscarriage and fetal harm. False negative and false positive tests place significant stress on the couple and have ethical implications.

Since 1993, the Wolfson Institute at Queen Mary has undertaken a series of research studies to find the most effective, safe and cost-effective test for antenatal detection of Down's syndrome and ensure the results are taken up in policy and practice. The challenge in developing any screening test is maximising sensitivity (the proportion of all cases detected), while minimising the false-positive rate, and ensuring that tests are acceptable and feasible to patients and busy clinicians. Each study in this programme has generated a new test or combination of tests that further improved sensitivity for any given false positive rate, reducing the need for invasive tests.

In particular, the multicentre study SURUSS (Serum Urine and Ultrasound Screening Study), was based on data collected from 25 maternity units on 47,053 singleton pregnancies in 1999-2002, including 101 with Down's syndrome, and compared five tests or test combinations, of which the Integrated test (first and second trimester tests combined in a single estimate, which detects over 90% of Down's fetuses with a 2% false positive rate) was the most accurate; but the first-trimester Combined test (involving only a single visit) had better feasibility and cost-effectiveness [1].

Results from SURUSS were independently corroborated on a large cohort of pregnancies in USA (FASTER study [2]). This built on work carried out at Queen Mary since 1998, including studies to develop and validate Triple, Combined and Quadruple screening tests [1,3-5]. Subsequent work by other groups has built on the SURUSS findings to improve screening performance further (eg combining first and second trimester blood tests with ultrasound scan), achieving detection rates of around 95% for false positive rates of 2%. A team at Queen Mary have demonstrated the efficacy and acceptability of these screening methods in a national audit of almost 11,000 pregnant women through the National Down Syndrome Cytogenetic Register: 98% of women accepted the Integrated test and of these, 94% completed both stages of the test [6].

The SURUSS HTA research programme began in 1999 and the initial results were published in 2003; related work continues. The key researchers were Nicholas Wald, Allan Hackshaw and Jocelyn Walters (Wolfson Institute), and Charles Rodeck, Lynn Chitty and Ann-Marie Mackinson (from UCLH). Funding was from the NHS Health Technology Assessment Group. Audit work on implementation and uptake was led by Joan Morris (Wolfson).

3. References to the research

Six papers selected of 35 publications from this stream of research (also see reference 15 in s.5 below describing a major national audit by Morris *et al* under 'Sources to corroborate the impact'):

1. **Wald NJ**, **Rodeck C**, **Hackshaw AK**, **Walters J**, Chitty L, Mackinson AM. First and second trimester antenatal screening for Down's syndrome: the results of the Serum, Urine and Ultrasound Screening Study (SURUSS). *Journal of Medical Screening* 2003; 10: 56-104. *A longer version of this paper was published as Health Technology Assessment report: Wald NJ, Kennard A, Hackshaw AK, McGuire A. Antenatal Screening for Down's Syndrome. London: NHS R&D Health Technology Assessment Programme; 1998. Report No: Vol 2: no.1.*
2. Malone FD, Canick JA, Ball RH, Nyberg DA, Comstock CH, Bukowski R, Berkowitz RL **et al** [**Hackshaw**, **Wald**]. First- and Second-Trimester Evaluation of Risk (FASTER) Research Consortium. First-trimester or second-trimester screening, or both, for Down's syndrome. *New England Journal of Medicine* 2005; 353: 2001-11.
3. **Wald NJ,** Huttly WJ, **Hackshaw AK**. Antenatal screening for Down's syndrome with the quadruple test. *Lancet* 2003; 361: 835-6.
4. **Wald NJ**, Huttly WJ, Rudnicka AR. Prenatal screening for Down syndrome: the problem of recurrent false-positives. *Prenatal Diagnosis* 2004; 24: 389-92.
5. **Wald NJ**, Rudnicka AR, Bestwick JP. Sequential and contingent prenatal screening for Down syndrome. *Prenatal Diagnosis* 2006; 26: 769-777.
6. **Wald NJ**, Huttly WJ, Murphy KW, Ali K, Bestwick JP, Rodeck CH. Antenatal screening for Down's syndrome using the Integrated test at two London hospitals. *Journal of Medical Screening* 2009; 16: 7-10.

4. Details of the impact

4a: Rapid and widespread incorporation into national policy in UK

The findings from this research were rapidly adopted in official guidelines, for example:

- The National Screening Committee Model of Best Practice (MOBP) for England 2003 (still current) was based largely on the results of the SURUSS study [7];
- UK National Screening Committee in 2007 summarised the above and recommended a flexible strategy with patient choice based on SURUSS [8]; update in 2012 endorsed the 2003 MOBP recommendations with some changes in cutoff levels [9]
- Genetics White Paper 2003 'Our inheritance, our future' incorporated the recommendations from the SURUSS study (this policy is still current) [10];
- NICE Guidance 2008 (updated from 2003): recommendations were based on SURUSS and subsequent work undertaken by Queen Mary researchers and others, and recommended Combined test for women presenting before 15 weeks and Triple or Quadruple test for those presenting at 15-20 weeks, and also that patients should be given accurate information about detection and false positive rates based on SURUSS results [11].

4b: Change in practice

The SURUSS study prompted most UK antenatal centres to introduce one of the recommended combination of tests for Down's routinely [12]. The Genetics White Paper Review 2008 found almost all NHS maternity units in the UK offer at least one of the screening tests shown in the SURUSS study to have acceptable detection and false positive rates for detection of Down's syndrome [10].

4c: Improved information for parents

Information for patients provided by the NHS, other public bodies and third-sector organisations is

based predominantly on results of the SURUSS study [13].

4d: Staff training

Training and professional development for midwives has been provided by the Wolfson Institute at Queen Mary in the form of study days A total of 34 study days have been held from 2008 to 2013, with over 500 midwives attending [14].

4e: Improved outcomes: antenatal diagnoses and terminations

The proportion of Down's cases diagnosed antenatally in UK rose from 30.6% in 1989-90 to 60.3% in 2008-9 and has remained at over 60% in 2008-13 [15]. While the proportion of antenatally diagnosed cases which were terminated remained constant at 91.5% throughout this period, the number of Down's fetuses terminated annually rose from 307 in 1989-90 to 1,032 in 2008-9 [15].

4f: Cost savings to the NHS and beyond

The advances in screening practice have been shown to be cost effective and led to overall economic savings. A cost analysis in the SURUSS report [1] showed, for example, that to screen 100,000 women, the second trimester double test was estimated to cost £5.8 million at a 90% detection rate, compared with £4.6 million for the Combined test and £3.0 million for the Integrated test; the cost of measuring extra markers in the latter two tests being more than offset by the reduction in the number and associated cost of performing diagnostic procedures. These relatively modest costs clearly outweigh the economic costs of long-term care and support for the Down's syndrome individuals that would otherwise have been born (not to mention the human cost).

4g: Influence on professional knowledge and further research by others

The research is highly cited by fellow academics, with the main outputs being cited hundreds of times. They have taken this work forward in a number of policy-relevant directions. Uptake outside UK, and particularly in north America, was accelerated by the confirmatory results of the FASTER study on which we collaborated with US colleagues (reference 2 above). The SURUSS dataset was used by research teams in several countries to develop statistical and economic models intended to inform national policy decisions. For example researchers in:

- the *USA* used SURUSS data to show the superiority of Quadruple over Triple test in a Californian population and introduce the Integrated test in statewide programmes [16,17];
- *Canada* used SURUSS data to justify using the Integrated test [18];
- *Saudi Arabia* used SURUSS data to model a national screening programme and recommended the Quadruple test [19]; and
- *China* used SURUSS data to produce ROC curves and economic models to inform national screening policy and recommended the Triple test as most cost-effective [20].

4h: Change in screening policy beyond UK

SURUSS data, either directly or via further modelling work in the countries concerned (see previous point) influenced advice from professional bodies and/or national screening policy in numerous other countries. For example:

- The American College of Obstetricians and Gynecologists, and US National Institute of Child Health and Human Development (NICHD) and US Society for Maternal-Fetal Medicine proposed first-trimester screening for Down's syndrome (flexibly depending on circumstances and patient choice) based on SURUSS data [21];
- The European Union EUROCAT (European Surveillance of Congenital Abnormalities) programme report 2010 suggests that SURUSS findings have influenced current antenatal screening policy in Croatia, Denmark, Finland, France, Italy, Netherlands, Spain, and Switzerland [22]. Most other European countries have no systematic screening programme and/or have significant legal or religious bars to termination of pregnancy.

5. Sources to corroborate the impact

See reference 6 in section 3 above, plus:

7. National Screening Committee Model of Best Practice (MOBP) for Down's syndrome screening in England 2003.
8. UK National Screening Committee. Fetal Anomaly Screening Programme: Screening for Down's syndrome. In: NSC Policy Recommendations 2007-2010: Model of Best Practice. London, Department of Health, 2008.
9. UK National Screening Committee. Fetal Anomaly Screening Programme: Screening for Down's syndrome. In: NSC Policy Recommendations 2011-2014: Model of Best Practice. London, Department of Health, 2012.
10. Genetics White Paper 2003 'Our inheritance, our future: Realising the potential of genetics in the NHS' (still current). See page 13. www.geneticseducation.nhs.uk/downloads/0070DH_White_paper_review.pdf
11. NICE Guidance 2008: Antenatal care: Routine care for the healthy pregnant woman (CG62, updated from 2003). See Section 1.7.2, page 29. www.nice.org.uk/CG62
12. Ward P. From *ad hoc* Down's syndrome screening to a functional uniform national screening programme. *Ultrasound* 2011; 19: 151-153.
13. Information for NHS patients/parents based on SURUSS (examples):
    Example of NHS hospital website explaining Down's screening using SURASS data:
    www.bartsandthelondon.nhs.uk/our-services/maternity-service/for-women-and-families/your-pregnancy
    NHS Choices patient advice on screening for Down's syndrome
    www.nhs.uk/Planners/pregnancycareplanner/Pages/Downsscreening.aspx
    Patient UK leaflet on screening for Down's syndrome:
    www.patient.co.uk/doctor/Antenatal-Screening-for-Down%27s-Syndrome.htm
14. Wolfson Institute website (includes patient information site and details of study days for clinicians). www.wolfson.qmul.ac.uk/epm/screening
15. Morris JK, Alberman E. Trends in Down's syndrome live births and antenatal diagnoses in England and Wales from 1989 to 2008: analysis of data from the National Down Syndrome Cytogenetic Register. *BMJ* 2009; doi: 10.1136/bmj.b3794.
16. American College of Obstetrics and Gynecology Practice Bulletin No.77. *Screening for Fetal Chromosomal Abnormalities Obstetrics and Gynecology* 2007; 109: 217-227.
17. Kazerouni NN *et al*. Detection rate of quadruple-marker screening determined by clinical follow-up and registry data in the statewide California program, July 2007 to February 2009. *Prenatal Diagnosis* 2011; 31: 901-906.
18. Okun N, Summers AM, Hoffman Bet al. Prospective experience with integrated prenatal screening and first trimester combined screening for trisomy 21 in a large Canadian urban center. *Prenatal Diagnosis* 2008; 28: 987-992.
19. Habib FA. Antenatal Screening Strategies for Down Syndrome: Analysis of Existing Protocols and Implications in the Kingdom of Saudi Arabia. *British Journal of Medicine and Medical Research* 2011; 1: 105-121.
20. Hong Q *et al*. A perspective study and financial analysis of different protocols of second trimester maternal serum screening for Down's syndrome. *Chinese Journal of Reproductive Medicine* 2010 (19): z2. http://d.wanfangdata.com.cn/periodical_szyxzz2010z2003.aspx
21. Reddy U, Mennuti M. Incorporating First-Trimester Down Syndrome Studies Into Prenatal Screening: Executive Summary of the National Institute of Child Health and Human Development Workshop. *Obstetrics & Gynecology* 2006; 107: 167-173. See also statewide recommendations operationalizing these eg California Department of Public Health www.cdph.ca.gov/programs/PNS/Pages/default.aspx
22. EUROCAT report on prenatal screening policies in Europe www.eurocat-network.eu/content/Special-Report-Prenatal-Screening-Policies.pdf