NDSCR

The National Down Syndrome Cytogenetic Register (NDSCR)

E Alberman

New cytogenetic diagnoses of Down's syndrome in England and Wales

THE REGISTER

Since January 1989 the National Down Syndrome Cytogenetic Register (NDSCR)[1 2] has recorded new cytogenetic diagnoses of Down's syndrome (DS) made in England and Wales. The register was established by the Medical Research Council with three main objectives: (*a*) to monitor the DS antenatal screening and diagnostic services; (*b*) to provide data on annual numbers of affected births to help those planning for their health, educational, and social care; and (*c*) to provide a database for aetiological studies.

Down's syndrome remains one of the leading causes of severe learning difficulties, often associated with other disabling congenital defects. It is caused by the presence of an extra chromosome 21, and its diagnosis, whether antenatal or postnatal, is virtually always confirmed cytogenetically. This makes both the definition of the condition and the collection of data relatively straightforward. From the outset the Association of Clinical Cytogeneticists has collaborated with the NDSCR; every laboratory in England and Wales providing data for all new diagnoses.

Notification is by a simple three part self copy form. The top copy is sent to NDSCR, the second copy is usually attached to the laboratory report to the referring physician for completion. The laboratory retains the third copy. The data have been kept anonymous, but include sufficient patient identifiers to eliminate duplicates, and allow the follow up of missing information, through the laboratories and clinicians. No contact is made, or could be made, with the parents except through the referring clinicians. Data collected include stage at diagnosis, the karyotype, parental age and place of residence, the indication for antenatal diagnosis where this has been done, and the outcome of the pregnancy. Annual checks for completeness are made with the national statistics congenital anomaly system, regional anomaly registers, and the notifying laboratories.

The register now comprises over 15 000 cases, and capture-recapture studies with the national statistics congenital anomaly system, which is acknowledged to be incomplete,[3] suggests that the NDSCR is over 94% complete. The answer to the most basic questions are over 90% complete, karyotypes for all cases being available, maternal age for 97%, full post code for 81%, and partial postcode for another 10%.

USES OF THE REGISTER

The monitoring of antenatal screening and diagnosis

Results from the NDSCR are regularly published. Findings include time trends in rates of antenatal detection and screening methods,[4–9] and show the steady increase in diagnosed pregnancies. Over 90% of these are legally terminated, and there has been a consequent small fall in numbers of affected live births (fig 1), despite a steady increase in mean maternal age.

The birth prevalence is currently of the order of 1/1000 livebirths. This level is determined by the maternal age distribution, and the availability and take up of offers of antenatal diagnosis and termination of affected pregnancies.

Probably over 70% of recognised conceptions with this anomaly are spontaneously lost during pregnancy. Publications on trends over time produced by the NDSCR team, with their collaborators, have taken a lead in showing the importance of taking into consideration the natural fetal loss in the absence of antenatal diagnosis and termination of pregnancy. The NDSCR data were the basis of papers by Hook *et al*[10] and Morris *et al*,[11] which produced estimates for natural fetal loss after chorionic villus sampling (early in pregnancy) and amniocentesis (in mid-pregnancy). Morris *et al* analysed the time elapsing between antenatal diagnosis and birth, miscarriage, or legal termination in 4148 affected pregnancies, and combined their results with published corresponding studies. The resulting estimates were that 43% (95% confidence interval (95% CI) 31% to 54%) of affected pregnancies undergoing chorionic villus sampling, and 23% (95% CI 19% to 28%) of those who had undergone amniocentesis, ended as a miscarriage or stillbirth. These are the estimates now commonly used to adjust the numbers prenatally diagnosed for naturally occurring fetal loss.

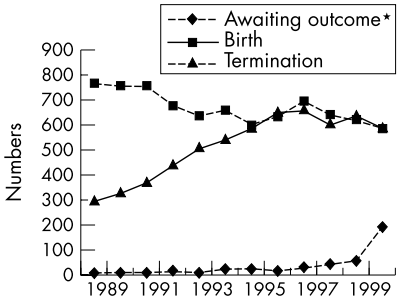

Figure 1 Down's syndrome trends: England and Wales 1989–2000. *(Prenatally diagnosed: outcome not yet available >90% likely to be terminations.

Audit of the genetic services

The national confidential enquiry into counselling for genetic disorders made use of the NDSCR for the audit of services for DS.[12] The register was also used to select families for a study of parental attitudes to children with DS born after false negative screening.[13] The NDSCR is also being used to estimate trends in false positive results—that is, the number of antenatal invasive tests carried out for the detection of one case of DS. The denominator for this has been derived from the United Kingdom national external quality assessment scheme control system reports for clinical cytogenetics [14] to which all antenatal diagnostic tests (but no results) are notified. A preliminary report showed that although the antenatal detection rate has been increasing since 1989 the number of invasive tests per case of DS has been falling.[15] This shows the increasing sensitivity of screening tests developed in the past decade. The NDSCR has also been used to help identify all DS outcomes for local areas evaluating their own results; and by the serum, urine, and ultrasound screening study (the SURUSS project, now completed and awaiting publication), which is expected to guide future screening practice.

Use of the NDSCR for epidemiological studies of possible causes and outcome of DS

No cause for the anomaly has been established apart from increased maternal age, although there have been unconfirmed suggestions that maternal preconceptional radiation, or exposure to

Abbreviations: DS, Down's syndrome; NDSCR, the National Down Syndrome Cytogenetic Register

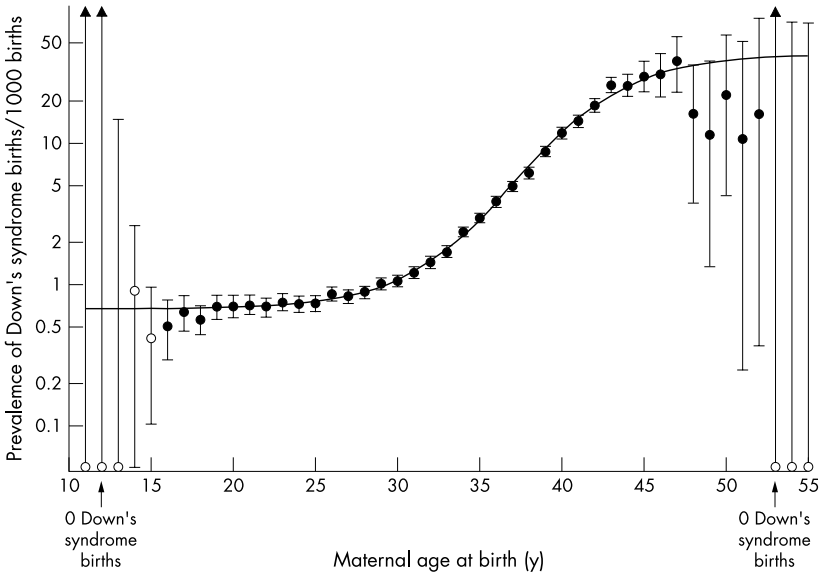

Figure 2 Observed (dots) and predicted (line) maternal age related risk of a Down's syndrome birth (95% CI).

other environmental hazards may play a part. The register data have been used to produce what are probably the most precise estimates of maternal age specific risk to date.[16] These show that the maternal age related risk does not continue to rise at an increasing rate with age above 45, as was previously assumed (fig 2). This may lead to changes in the basis of calculating risk in DS screening programmes, but may also lead to further studies of the condition at very advanced maternal ages.

Other studies have been of possible time-space clustering which would be evidence of environmental influences.[17] A recent paper, which included NDSCR data for two districts only, suggested that there may be a small excess risk of DS in births occurring near hazardous waste landfill sites.[18] This possibility will be investigated further by the Small Area Health Statistics Unit using NDSCR data.

Associated defects

An early study based on register data was of mortality and morbidity in a small but representative subsample.[19] Its findings included the confirmation of the well known association of DS with leukaemia, particularly in young children. The NDSCR records have subsequently been linked with the national childhood cancer register to produce improved risk estimates for childhood leukaemia and other malignancies in DS.[20] Another well known association is with congenital heart disease. A study has been started, but is unfinished, to link the NDSCR records with those relating to paediatric surgery for heart defects.

The large numbers of cases in the NDSCR provide samples of the rarer karyotypes associated with DS, and a report has been published of the epidemiology of specific cytogenetic subgroups.[21] An original and unexpected finding was a female excess in mosaic DS, subsequently confirmed with data from the United States,[22] which may lead to new basic research. The continuation of the register will increase the numbers of these rare subgroups, including certain translocations, which may be particularly valuable for genetic research.

Evaluation of the register

The core cost of running the NDSCR has been about £50 000 a year, about the overall cost of antenatal detection of one to two cases of DS. The Register has provided the basis of numerous studies of national and international importance relating to risk, effects of maternal age, and associated defects, which have helped to advance knowledge and improve medical care. Its achievements arise from the size of the population covered; the generous collaboration of the many people who provide the data; and the expertise of colleagues who have helped with their analysis and interpretation.

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Author's affiliations

E Alberman, *Director of Register,* Wolfson Institute of Preventive Medicine, Department of Environmental and Preventive Medicine, Barts and The London Queen Mary's School of Medicine and Dentistry, University of London, Charterhouse Square EC1M 6BQ, UK; kenevalb@aol.com

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