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Prenatal Diagnosis in the United Kingdom – An Overview

Abstract

Prenatal diagnosis is now a well-established part of health care in the UK. Cytogenetic or molecular diagnostic analysis following amniocentesis, chorionic villus sampling or cordocentesis is in routine practice and identification of 'at risk' pregnancies using biochemical screening or ultrasound is widespread. Professional guidelines have been established covering both sampling procedures and diagnostic testing, and legislation is in place regarding termination of pregnancy and pre-implantation diagnosis. The close liaison of the various groups of professionals involved has led to well-developed prenatal diagnostic and screening services within the UK. These links have been the major contributory factor to the current state of prenatal diagnosis and have been of great benefit to patients undergoing prenatal testing.

Key Words

Prenatal diagnosis
United Kingdom
Organisation
Overview

Introduction

Genetic services in the UK have developed over many years to a highly integrated network of diagnostic testing and clinical counselling. The services have been organised and funded on a regional basis, with clinicians and laboratories serving the various health boards within designated regions. In general, the number of laboratories in each of the regions is related to the population served, with most laboratories serving a population of between 1 and 3 million.

The number of live-births for 1994 in the UK was 726,382 out of a population of 58,394,616 with a breakdown of 664,726 live-births for England and Wales and 61,656 for Scotland [1]. A total of 33 UK laboratories participate in the cytogenetics National External Quality Assessment Scheme (NEQAS) for prenatal diagnosis, with all 33 submitting data on amniotic fluid sampling (AFS) and 28 for chorionic villus sampling (CVS).

A total of 35,769 pregnancies (4.9%) underwent diagnostic karyotyping (figures for the 12-month period 01/04/94–31/03/95), with 31,887 being diagnosed by AFS (4.38%) and 3,882 (0.53%) by CVS.

The laboratories providing a molecular genetics service have in the main developed where cytogenetic services existed in the first place. At present there are 42 laboratories listed in the most recent edition of the Clinical Molecular Genetics Society (CMGS) handbook [2].

Laboratories providing a serum screening service are rather more difficult to quantify as they are not organised, throughout the UK, on a regional basis, and many small laboratories serve subregional populations.

Biochemical laboratories providing specialised diagnosis for conditions such as the inborn errors of metabolism are dispersed throughout the country on a loose 'consortium' basis, with different laboratories specialising in the diagnosis of different diseases.

There are 256 departments in the UK undertaking obstetric scanning [Royal College of Obstetricians and Gynaecologists (RCOG) and Royal College of Radiologists (RCR) survey, 1994, currently unpubl.]. The majority (around 80%) of routine scans are undertaken by radiographers, with few obstetricians being involved in performing ultrasound. No databases exist which give an accurate insight, but the recent unpublished survey suggested that about 80% of women were offered an anomaly scan at 18–20 weeks gestation.

Within the UK, the overwhelming majority of prenatal diagnostic testing is funded through the National Health Service, with less than 1% of testing being paid for privately.

Note: The following information has been collated from several sources, official data, previously published data, personal communications and as a result of a questionnaire distributed to all the known genetic centres in the UK performing prenatal diagnosis.

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Sources of Information

Local

As all the cytogenetic laboratories providing a prenatal service participate in the UK NEQAS, they routinely collect the following data (usually on a monthly basis and at least on an annual basis): numbers of samples processed, reporting times, success/failure rates, abnormality rates, and QA scores (a measure of the quality of the cytogenetic results). One of the recommendations of the NEQAS is to send out an 'Outcome of Pregnancy' form, along with the cytogenetic results. This is returned after delivery to the genetic centre and forms a part of the internal quality control audit.

Regional

The funding arrangements for prenatal diagnosis are generally on a 'block contract' basis with the referring health boards. This necessitates constant monitoring of workloads and means that in the majority of centres, monthly volumes of samples are monitored and the figures used as a basis for establishing or updating new block contracts.

Some regions have also developed their own registers in which they collate their own data on the impact of screening for Down's syndrome or have regional malformation/fetal abnormality databases.

National

As previously described, laboratories performing prenatal diagnosis submit data to the NEQAS. This organisation collects total data for the UK laboratories and (anonymously) allows interlaboratory comparison. The data collected are supplemented by independently assessing a random selection of microscope slides and reports issued from each laboratory. Detailed individual laboratory performance is then commented on in an individual report re-submitted to the participating laboratory.

Within England and Wales there is a Down's Syndrome Register which collects and publishes data concerning the diagnosis of Down's syndrome pregnancies and live-births and in Scotland a similar data collection is made covering all trisomic conceptions (Scottish Trisomy Register).

Most cytogenetic laboratories also submit details of abnormal cases to the Chromosome Abnormality Database (CAD) which provides a national collection of cytogenetic abnormalities reported to it. The database currently holds some 65,000 records of constitutional and acquired abnormalities, and holds a sub-set of data about each case and thus acts as a first point of contact for tracing samples, clinical information and potential sources for collaborative or epidemiological studies. The database is available to cytogeneticists, clinical geneticists and those involved in human genome research. This is accessible to all laboratories in the UK.

The professional organisation covering cytogenetics, the Association of Clinical Cytogeneticists (ACC), has a scientific sub-committee which periodically surveys the UK laboratories and collects data relevant to all aspects of the profession. Such recent data collections (resulting in publications available to members) include: 'Chorionic Villi in Prenatal Diagnosis 1987–89' (in the process of being updated to include 1987–1993), Solid Tissue Culture in Clinical Cytogenetics (1995) and 'UK Collaborative Study on Early Amniocentesis' (1996).

The RCOG along with the RCR documents ultrasound practice within the UK.

European

All the UK laboratories performing prenatal diagnosis by CVS now contribute their data to European Collaborative Research on Mosaicism in Chorionic Villus Sampling (EUCROMIC).

Scientific Meetings

The ACC and the CMGS hold annual scientific meetings which are now linked with the British Society of Human Genetics (BSHG) meetings. The BSHG annual meeting covers clinical genetics, cytogenetics, molecular genetics and the genetic nurses groups, and so provides a wide forum for scientific exchange. In addition to this, regional meetings of cytogeneticists take place (usually every 6 months) where more informal exchange of information takes place.

Impact of Prenatal Diagnosis

Down's Syndrome

It has been shown that the introduction of a biochemical screening programme using maternal serum α-fetoprotein (AFP) and human chorionic gonadotrophin (hCG) has made an impact on the birth incidence of Down's syndrome in the west of Scotland [3]. A potential detection rate of 70% has been calculated for the year 1991–1992, with an actual detection rate of 57% (the uptake of diagnostic testing was only 70% in the women placed in the high-risk group) in the screened population and an overall prenatal detection rate in the total population of 48%.

This then compares favourably with the 30% detection rate possible using maternal age 35 as the cut off (and assuming 100% uptake of diagnostic testing).

Neural Tube Defects

The overall incidence of neural tube defects in the west of Scotland for the years 1987–1990 was 2.2/1,000 pregnancies and the birth incidence (liveborn and stillborn) 0.52/1,000. This contrasts with a rate of over 5/1,000 livebirths in this region in the mid 1970s the decline being attributable to a downward secular trend and the contribution of prenatal diagnosis using maternal serum AFP, amniotic fluid AFP and detailed ultrasonography [D. Aitken, pers. commun.].

Ultrasound Diagnosis

There are no data covering the overall detection rates for structural abnormalities and karyotypic abnormalities in the UK as a whole. Only one database exists in the UK and that is in the Northern Region [4]. It indicates that ultrasound may be effective for conditions such as neural tube defects but not particularly good for other anomalies particularly involving the cardiovascular system. A further analysis of the data [5] indicated that when a termination was done on the basis of a scan that autopsy showed concordance with regard to prognosis in 99.5% although the exact diagnosis was refined in 35%. This suggests that overall ultrasound is better at estimating severity rather than providing absolute diagnostic accuracy. Average detection rates, drawn from the literature [6–13] for very serious conditions (anencephaly and bilateral renal agenesis) may approach 95–100% but spina bifida may be nearer 80–85%, and for cardiac anomalies about 20–30%. A fetal anomaly register has just been established in the West Midlands but data are not yet available and a database from Scotland is in the process of publication. More research and collaboration is required.

Psychosocial Aspects

In order to see the above data in context, it must be realised that the vast majority of prenatal diagnosis provides reassurance to couples at risk of delivering a child with some form of congenital abnormality. Without such reassurance, they may not otherwise be able to contemplate embarking upon a pregnancy. In only a small percentage of cases (estimated at some 4% of chromosomal diagnoses) will an abnormality be detected. These will be in patients who have received pre-test counselling, and receive further counselling once the result is known in order to arrive at an informed decision as to how to proceed. Whether termination or continuing with the pregnancy is chosen, there are many national and local support agencies and groups to offer either bereavement counselling or support in caring for a handicapped child. These include (amongst many others) such organisations as a National Down's Syndrome Society, the Association for Spina Bifida and Hydrocephalus and the Scottish Association for Care and Support after Diagnosis of Fetal Abnormality (CARE).

Diagnostic Procedures Available

Fetal Karyotyping

Fetal chromosome diagnosis is available nationally within the UK, with the majority of diagnoses being made by amniocentesis (89%) and only some 11% by CVS. The number performed by chordocentesis is less than 1%.

Amniocentesis is widely available, and sampling takes place in the majority of maternity units. The predominant referral reason for a diagnostic procedure is the patient being placed in the 'high-risk' group following serum screening, with referrals for advanced maternal age being the next largest category. Some centres report the use of 'early amniocentesis' as a diagnostic procedure ($\leqslant$15 weeks gestation), with the laboratories performing the greatest number of early amniocenteses accounting for some 30% of their amniotic fluid samples. Other reasons for referral for sampling include, previous or family history of chromosome abnormality, parent a carrier of a chromosome rearrangement, abnormalities seen on ultrasound scan and maternal anxiety.

Chorionic villus sampling in contrast to amniocentesis, tends to be restricted to one or two centres in each region which are competent to perform the sampling. Other patients, however, who may have an indication for prenatal diagnosis by CVS may be referred to the appropriate sampling centres.

Within the UK as a whole, 63% of CVS are performed at $\leqslant$12 weeks gestation and 37% at >12 weeks. This figure is however slightly biased by one or two centres who use CVS extensively as a mid-trimester procedure following a biochemical screen. In general, however, CVS is reserved as a sampling procedure for pregnancies at high risk of being abnormal such as in cases of previously identified carriers of structural rearrangements.

Cordocentesis like CVS is restricted to particular sampling centres which have the expertise to perform the sampling. Something less than 1% of fetal karyotypes are performed using cordocentesis and these are often restricted

to cases where an abnormality has been identified following an ultrasound scan.

Ultrasound. Virtually every expectant mother in the UK has at least one ultrasound examination in pregnancy. 77% have a scan at their first hospital visit and about 80% will have an 'anomaly' scan at 18–20 weeks [RCOG/RCR survey, 1994, unpubl.]. Most scans are undertaken in district hospitals, with regional units being available for tertiary referrals.

Biochemical Screening

Biochemical screening is widely (but not universally) available in the UK. There is, however, considerable variability as to both the analytes used and intraregional cover of the different screening methodologies. This is probably due to the fact that there are often several centres within each region providing the screening service. The majority of screening is carried out using AFP/age/hCG. Both the 'triple test' and age/AFP screening are also used, but much less widely. Only 9 out of the 24 centres responding to the question reported that the screening policy was the same throughout their region. Other replies included 'policy varies considerably', 'two districts do not offer Down's screening', 'hCG assayed only if AFP is low' and '50% offer a restricted service on demand only'.

Molecular Diagnosis

The organisation of molecular genetics within the UK is based on a 'consortium' system, whereby laboratories are grouped together with each laboratory offering a more limited range of diagnostic testing, but the consortium as a whole offering a fuller range of tests. This allows for economies of scale and particular expertise to be established in particular centres.

The most widespread molecular diagnoses in the UK are for the X-linked muscular dystrophies, cystic fibrosis, fragile-X syndrome, Huntington's disease, myotonic dystrophy, and the haemoglobinopathies. Other commonly diagnosed conditions, though less widely available, include Prader-Willi-Angelman syndrome, spinal muscular atrophy, mitochondrial myopathy, familial adenomatous polyposis coli, and neurofibromatosis.

The professional organisation for those involved in molecular diagnosis in the UK is the CMGS; and as well as organising scientific meetings, they publish a Laboratory Directory [2, 3rd edition 1993, 4th edition in press] listing all the diagnostic testing and research interests of the contributing centres. This facilitates the availability of testing for the rarer diseases.

Current Methods in Use for Prenatal Diagnosis

Amniocentesis is the 'gold-standard' prenatal test performed in the UK, and accounts for 89% of the prenatal tests (31,887 tests for the 12-month period 01/04/94–31/03/95). For the majority of tests, the referral reason is the identification of a pregnancy at risk of Down's syndrome following biochemical screening. This means that most AFS is performed at mid-trimester. However, several cytogenetic laboratories reported performing early amniocentesis, usually comprising about 10% of their prenatal samples. The number of amniocenteses performed in the UK has seen a gradual rise over the last 5 years.

The samples are routinely taken at antenatal clinics by experienced operators using ultrasound guidance and are transported to the genetics laboratories either by taxi, courier, or first-class post.

The average success rate (as reported to the 94/95 NEQAS) is 99.2%, and 89.3% of samples are reported within the NEQAS guideline time (currently 21 days, but under review).

Chorionic villus sampling is widely available as a laboratory technique, but less so as a sampling procedure, necessitating patients travelling to centres with clinicians who are experienced in performing the procedure. About 11% of prenatal diagnoses are made by CVS (3,882 tests in the period 01/04/94–31/03/95) and the majority of laboratories will report following analysis of cultured cells. Some, however, will report the preliminary results of 'direct' analysis depending on the referral reason. The success rate for CVS in the UK is 98.5%, with 81.1% of samples being reported within the national guideline time (currently 21 days, but under review).

Although CVS was developed as a first-trimester technique, several hospitals now also perform CVS in the mid or even third trimester as a means of rapid diagnosis (using 'direct' preparations and usually following an abnormal ultrasound finding) for pregnancy management.

Sampling is performed by a limited number of clinicians who regularly sample patients (see below).

Cordocentesis (accounting for less than 1% of diagnostic procedures) is limited by sampling centre rather than laboratory and in general is restricted to pregnancies where a rapid diagnostic result is needed and CVS is not an option. This highly specialised technique does not have separate cytogenetic NEQAS data collected.

Professional guidelines for cytogenetics are (as already described) generated by the NEQAS [14] and cover such issues as: use of appropriate techniques, numbers of cells to examine, laboratory problems, checking and authorisa-

tion, acceptable success rates, acceptable limits of microscopic resolution, reporting, making risk assessments, reporting time guidelines, and recommended minimum quality. In addition, each laboratory receives an individual report following their annual submission to NEQAS, which comments on, and may make recommendations regarding their performance.

Professional guidelines for sampling procedures are such that most of the operators would comply with the guidelines produced by the European Association of Perinatal Medicine 1993 [15]. This report suggests that before being admitted to a clinical programme, clinicians' tissue sampling success rate should approach 95% for chordocentesis and 100% for amniocentesis and CVS. The RCOG has recently published recommendations on the taking of amniocentesis samples [16] which suggests that at least 30 amniocenteses should be performed under supervision, with a successful tap on each occasion before the operator is deemed as competent. It also suggests that a minimum number of 20 procedures per annum would be reasonable in order to maintain competence.

Areas of Research and Development

A total of 17 laboratories (out of 24 respondents to the question) indicated that they were developing interphase fluorescence in situ hybridisation (FISH) techniques, the most commonly used probes are for chromosomes 21, 18, X, Y, and 13.

Three centres reported that they were investigating the recovery of fetal cells from maternal circulation, with a further 4 expressing some sort of interest in it.

There were several reports of the development of first-trimester serum screening.

One centre was investigating uterine lavage, another coelocentesis.

(As the questionnaires were distributed to primarily diagnostic, cytogenetic laboratories, the above levels of activity in development are likely to be underestimates.)

Funding Arrangements for Prenatal Diagnosis

The vast majority of prenatal diagnosis within the UK is publicly funded and is provided for by the National Health Service. Something less than 1% of the diagnoses made are provided under private arrangements.

Genetics laboratories, as previously described, provide regional or subregional services. As such, the funding arrangements are on a purchaser/provider basis. Health boards contract for a particular number of tests on an annual basis and are charged accordingly. This charging is usually according to an estimated volume of work based on previous uptake. Once the contracted volume of work has been achieved, then extra work may be charged as an 'extra-contractual referral'.

Current Legislation Surrounding Prenatal Diagnosis

Termination of Pregnancy

Following the 1992 Abortion Act (Amendment), a pregnancy may be terminated at any gestational age when there is a significant risk that the baby will have serious mental or physical disability.

The doctor making the diagnosis completes a 'Certificate A' which is countersigned by the parents, which gives legal permission to terminate the pregnancy under section 1(1) of the 1967 Abortion Act. Two clinicians must complete, and sign the certificate of opinion before treatment commences. The wording is such that 'there is substantial risk that if the child were born it would suffer from such physical or mental abnormalities as to be seriously handicapped'. This certificate must then be kept for 3 years.

If clinicians are unable to give impartial advice (on moral, ethical or religious grounds) they should refer the patient on in a non-judgmental way.

A clinician making a diagnosis must state in the report what investigations are needed to confirm the original diagnosis. All abnormal cytogenetic reports should state that post mortem samples are required in order to confirm the diagnosis (NEQAS recommendation).

It is also a statutory requirement that all terminations of pregnancy are registered with the Chief Medical Officer at the Department of Health.

The Stillbirth (Definition) Act of 1992 has reduced the minimal age by which a stillbirth is defined from 28 weeks to 24 weeks. After 24 weeks then a stillbirth certificate must go to the Registrar of Births and Deaths within 42 days (21 in Scotland) who then issues a certificate for burial or cremation. Before 24 weeks, there is no requirement to register the death though a letter or certificate is required by the funeral directors stating that the baby 'was born before the age of viability and showed no signs of life'.

Advice from the RCOG [17] suggests that when a termination of pregnancy is contemplated after 21 weeks that prior fetocide should be considered.

Pre-Implantation Diagnosis

Pre-implantation diagnosis is covered by the Human Fertility and Embryology Act of 1990 and in particular section 26 which forms a Code of Practice.

Under this act, all research involving the 'creation, keeping or using of human embryos outside the body must be licensed by the Authority' (Human Fertilisation and Embryology Authority). The Authority grants licences for research projects for among other things 'to develop methods for detecting the presence of gene or chromosome abnormalities in embryos before implantation'. The licence will only be granted if the Authority is satisfied that the use of human embryos is essential for the purposes of the research.

The Act prohibits by law (amongst other things) the 'altering of the genetic structure of any cell while it forms part of an embryo' and 'will not license research projects involving embryo splitting with the intention of increasing the number of embryos for transfer'.

Problems Faced and What of the Future

As can be seen, prenatal genetic diagnosis in the UK is well established and has benefited not only from regional organisation, but also from the good communications network developed between the various groups in the professions dealing with prenatal diagnosis.

The main problems to be faced are probably not those of the organisation or delivery of the services themselves but rather those to be confronted by all workers in the field of genetics. These problems are due to the rapid expansion in the molecular testing and diagnostic field. The possibility of pre-symptomatic testing in utero for the presence of late onset disease or the detection of predisposition to disease throws up new ethical issues which will need to be resolved.

The arrival of serum screening in the first trimester of pregnancy may result in a re-emergence of CVS as a method of sampling, with a diagnosis being made on interphase cells using FISH techniques. This would allow greater numbers of women to be offered diagnostic testing, but of course the type of testing would be different, with only particular chromosomes being tested for and not whole karyotyping performed. This would require a change in the philosophy of prenatal testing and a public re-education programme to be undertaken. This being said, financial constraints may prove the overriding deciding factor in the way in which prenatal diagnosis evolves.

The dismantling of the previous regional structure of the National Health service in the UK with the development of Trust Hospitals may destabilise the successful referral pattern seen from former district hospitals to regional centres. This would be a major disadvantage to patient care and a change which will hopefully be strongly resisted.

References

1 Office for National Statistics, St. Catherine's House, 10 Kingsway, London WC2B 6JP, 1996.
2 Clinical Molecular Genetics Society: Laboratory and National Consortium Handbook, 1993.
3 Crossley JA, Aitken DA, Berry E, Connor JM: Impact of a regional screening programme using maternal serum alpha fetoprotein (AFP) and human chorionic gonadotrophin (hCG) on the birth incidence of Down's syndrome in the west of Scotland. J Med Screening 1994;1:180–183.
4 Northern Region Survey Steering Group: Fetal abnormality: An audit of its recognition and management. Arch Dis Child 1994;67:770–774.
5 Brand IR, Kaminopetros P, Cave M, Irving HC, Lilford RJ: Specificity of antenatal ultrasound in the Yorkshire region: A prospective study of 2261 ultrasound detected anomalies. Br J Obstet Gynaecol 1994;101:392–397.
6 Chitty LS, Hunt GH, Moore J, Lobb MO: Effectiveness of routine ultrasonography in detecting fetal structural abnormalities in the low risk population. Br Med J 1991;303:1165–1169.
7 Crane JP, LeFevre ML, Winborn RC, Evans JK, Ewigman BG, Bain RP, Frigoletto FD, McNellis D and the RADIUS Study Group: A randomized trial of prenatal ultrasonographic screening: Impact on the detection, management and outcome of anomalous fetuses. Am J Obstet Gynecol 1994;171:392–399.
8 Goncalves LF, Jeanty P, Piper JM: The accuracy of prenatal ultrasonography in detecting congenital anomalies. Am J Obstet Gynaecol 1994;171:1606–1612.
9 Levi S, Schaaps JP, DeHavay P, Defoort P: End-result of routine ultrasound screening for congenital anomalies : The Belgium Multicentre Study 1984–1992. Ultrasound Obstet Gynaecol 1995;5:366–371.
10 Luck C: Value of routine ultrasound scanning at 19 weeks: A four-year study of 8,849 deliveries. Br Med J 1992;304:1474–1478.
11 Rosendahl H, Kivinen S: Antenatal detection of congenital malformation by routine ultrasound. Obstet Gynaecol 1989;73:947–951.
12 Shirley IM, Bottomley F, Robinson VP: Routine radiographer screening for fetal anomalies by ultrasound in an unselected low risk population. Br J Radiol 1992;65:564–569.
13 Stoll C, Dott B, Alembik Y, Roth MP: Evaluation of routine prenatal diagnosis by a registry of congenital anomalies. Prenat Diagn 1995; 15:791–800.
14 National External Quality Assessment Scheme: Guidelines for Clinical Cytogenetics, ACC, UK NEQAS, PO Box 401, Sheffield, S5 7YZ.
15 Recommendations and Protocols for Prenatal Diagnosis. Report of the European Study Group on Prenatal Diagnosis, Barcelona, 1993.
16 Royal College of Obstetricians and Gynaecologists: Amniocentesis, 1996.
17 Royal College of Obstetricians and Gynaecologists: Termination of pregnancy for fetal abnormality, 1996.