Prenatal diagnosis and genetic screening

Community and service implications.

SUMMARY AND RECOMMENDATIONS OF A REPORT OF THE ROYAL COLLEGE OF PHYSICIANS

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1. Introduction

Everyone is at risk for having abnormal offspring. In fact, at some time in their reproductive life about half the world’s women conceive a pregnancy with a chromosomal abnormality. However, most such pregnancies end in a spontaneous abortion and until recently many infants born with serious abnormalities died, often undiagnosed, in early childhood. The purpose of this report is to demonstrate how advances in medical research have created new opportunities in preventive medicine.

Most infants with congenital malformations and chromosomal disorders are born to healthy young women with no identifiable risk factor. There is no evidence that such ‘sporadic’ disorders can be prevented, and neither diagnosis nor intervention is possible before pregnancy is established. Therefore the only means of detecting the disorders is by population-screening during pregnancy using methods that are safe, simple and cheap.

By contrast, 2 to 3% of all couples are at high and recurrent risk of having a child with an inherited disorder. It is becoming increasingly possible to detect these couples by biochemical or DNA tests. Screening for carriers of inherited diseases should whenever possible be offered before pregnancy so that couples at risk can choose from the full range of options available.

The objectives of prenatal diagnosis are:

- To allow the widest possible range of informed choice to women and couples at risk of having children with an abnormality.
- To provide reassurance and reduce the level of anxiety associated with reproduction.
- To allow couples at risk to embark on having a family knowing that they may avoid the birth of seriously affected children through selective abortion.
- To ensure optimal treatment of affected infants through early diagnosis.

Table 1 gives a very general classification of the disorders under consideration in the report, and indicates their relative frequency.

Table 1. Approximate annual incidence of births of infants with congenital and genetically determined disorders in the UK (Total annual births about 700,000).

| Disorder | Annual births per 1,000 | Total annual births in the UK |
|----------|-------------------------|-------------------------------|
| **Congenitally malformed infants:** | | |
| Sporadic abnormalities | 15–20 | 10,500–14,000 |
| Inherited abnormalities | ~ 2 | ~ 1,400 |
| **Chromosomal disorders:** | | |
| Sporadic (parental chromosome non-disjunctions) | 2 | 1,400 |
| Inherited (familial chromosome rearrangements) | 0.6 | 420 |
| **Mendelian single gene defects:** | | |
| Dominant | ~ 4 | ~ 2,800 |
| X-linked | 1–2 | 700–1,400 |
| Recessive | ~ 2 | ~ 1,400 |
| **TOTAL** | 27–33 | 18,600–22,800 |

Total ‘sporadic’ disorders = 17–22 per 1,000; 65% of total. Total inherited disorders = 10–11 per 1,000; 35% of total. ‘Multifactorial’ conditions, other than congenital malformations, are not included.
Table 2. Incidence of some severe inherited diseases and their approximate carrier frequency in the UK

| Disorder and inheritance       | Birth incidence per 100,000 | Incidence of healthy carriers                           |
|--------------------------------|-----------------------------|---------------------------------------------------------|
| Dominant                       |                             | Approximately equal to the incidence of disease; ie few, and mostly relatives of patients |
| Huntington’s chorea            | 7                           | About twice the incidence of the disease; ie relatively few, and most are female relatives of patients |
| Neurofibromatosis              | 3                           | Carriers (% of the population)                          |
| Multiple polyposis coli        | 1                           | 4-5                                                     |
| Adult polycystic kidney disease| 8                           | 1-4                                                     |
| X-linked                       |                             |                                                         |
| Fragile X mental retardation   | ~70                         |                                                         |
| Duchenne muscular dystrophy    | 13                          |                                                         |
| Haemophilia A                  | 5                           |                                                         |
| Recessive                      |                             |                                                         |
| Cystic fibrosis (CF)           | 50                          |                                                         |
| Phenylketonuria (PKU)          | 20-50                       |                                                         |
| In certain ethnic groups:      |                             |                                                         |
| Thalassaemia                   | 30-700                      | 3-17                                                    |
| Sickle cell disease            | 10-2,000                    | 2-25                                                    |
| Tay-Sachs disease              | 20-40                       | 3-4                                                    |

Some of the commoner inherited disorders are listed in Table 2. Almost everyone carries one or more recessively inherited genetic defects and about 3% of couples have a high and recurrent risk of bearing a child with a specific inherited disorder. The fact that about 4,000 such ‘single gene disorders’ are listed in McKusick’s Mendelian inheritance in man shows on the one hand the collective frequency, and on the other the diversity and individual infrequency of these conditions.

People who carry inherited diseases require time both to come to terms with their carrier status and to make informed decisions. It is therefore important, whenever possible, to identify carriers before pregnancy. There is an important planning difference between risks that can be identified before pregnancy and those that can be detected only during the course of pregnancy.

So far, our improved understanding of the molecular basis for single gene defects has proved much more valuable for diagnosis than for treatment.

Intrauterine treatment of the affected fetus is of limited value, though intrauterine diagnosis may allow more effective treatment of the newborn child. Neonatal diagnosis allows a few well defined disorders to be treated satisfactorily, and many congenital malformations can be corrected surgically, but the remainder of these disorders result in either death in infancy or prolonged chronic illness with premature death in adolescence or adult life. There seems little prospect of radical change in this general picture.

Prenatal diagnosis services must operate at two levels. At one level are specialist clinical genetics and fetal medicine services, which must be supported on another level by genetics services in the community. The community service involves population screening delivered through the primary health care system and obstetric and other hospital services. In both specialist and community-based services it is important to distinguish between pre-pregnancy and pregnancy screening.

Equitable delivery of these services requires that they be integrated into all levels of the maternal and child health system. Their multidisciplinary implications mean that explicit planning and organisation as well as funding are now essential.

2. Scope of prenatal diagnosis

Although it will never be possible to identify everyone at risk, with present technology the potential exists for a great reduction in births of infants with severe congenital and genetically determined disorders.

Prenatal diagnosis involves an invasion of many seemingly normal pregnancies in the search for uncommon abnormalities, and so must be practised to the highest possible standard.

The following important recent developments extend the range of prenatal diagnosis, sometimes increase its speed and often allow tests to be performed earlier in pregnancy:

i The rapid development of obstetric ultrasound has greatly increased the feasibility of directly detecting congenital malformations and has made possible improved fetal sampling methods.

ii The introduction of chorionic villus sampling (CVS) allows genetic diagnosis in the first trimester of pregnancy, thus increasing the acceptability, and in some cases the speed, of prenatal diagnosis.

iii The development of molecular genetics means that:

- an increasing range of inherited disorders can be detected in fetal cells, including chorionic material;
- improved carrier diagnosis is possible in families at risk;
- conditions in which the genetic abnormality is still unknown are open to diagnosis.

However, the usefulness to the community of these new diagnostic methods depends on:
- the extent to which the population is informed, so that individuals and couples can request testing, and pregnancies at risk can be identified;
- the level of popular demand for prenatal diagnosis;
- adequate service provision.

Because of the possibility of error or unexpected natural variation, both screening and prenatal diagnosis must be practised to the highest possible standard according to the following general principles:

1. The methods used must be capable of giving a clear result with a minimum of false positives and negatives, and their safety should be defined.
2. Staff must be suitably trained and must work within a professional code of practice.
3. In case of the slightest doubt, the diagnosis should, as far as possible, be confirmed by an independent approach.
4. Prenatal diagnoses should, whenever possible, be confirmed in aborted fetuses, and in babies born following diagnosis. The services of an expert in fetal pathology are essential.
5. Results should be subjected to regular audit, with particular emphasis on false positives and false negatives. National and regional monitoring should be established.
6. The genetic, obstetric and laboratory aspects of prenatal diagnosis are closely related and optimal results require close collaboration. Ideally, the obstetric scanning and sampling procedures, counselling, and laboratory analysis should be practised side-by-side in the same institution.
7. Women with a continuing pregnancy in which a fetal abnormality has been diagnosed require expert support from the neonatologist and neonatal surgeon.

In addition to being safe, simple and cheap, screening methods should be reliable. They should have a high detection rate (a high proportion of affected individuals should yield a positive result) and a low false-positive rate (few unaffected individuals should yield a positive result). Whenever possible, screening should be carried out before pregnancy.

Assuming continuing progress in methods of prenatal diagnosis, the birth prevalence of dominant and X-linked severe disorders might be reduced by up to 50%, while population screening for carriers of common recessively inherited disorders may drastically reduce the birth prevalence of affected infants.

Prenatal diagnosis is now possible in the first trimester of pregnancy (before the 12th week of gestation) by chorionic villus sampling (CVS). This increases the importance of identifying mothers at risk prior to pregnancy or very early in pregnancy. More information on the short- and long-term risks of CVS is awaited from randomised controlled comparisons with amniocentesis, now under way.

3. Future developments in prenatal diagnosis

Technical innovations of many kinds are continually broadening the scope of prenatal diagnosis with important service implications. Particularly important are the development of DNA technology, progress in obstetric ultrasound, and improved possibilities for screening for Down’s syndrome in pregnancy.

Although the precise techniques that will eventually be used are still uncertain, the implications in terms of medical training, community education and service provision for prenatal diagnosis and genetic screening are already obvious. It is now essential for health care planners to participate in these developments.

In view of the rate of progress, it is unwise to wait until the details of the laboratory methods have been settled before making the decision to set up the service. Workers and laboratories should be supported, and rapid evaluation and development of methods and flexibility in their application should be promoted. Improved undergraduate and postgraduate medical education in genetic methods, and technical training of medical and non-medical staff, are equally important.

4. Ethnic minorities

In England at present about 5.5% of the population and 9% of births are in ethnic groups with specific genetic risks. People of Jewish origin are at increased risk of carrying Tay-Sachs disease, and many ethnic groups originating outside northern Europe are at high risk of the haemoglobin disorders. It is cheap and easy to detect carriers of these disorders, and prenatal diagnosis, which is freely available at several national centres, is in high demand from informed couples at risk. The haemoglobin disorders in particular provide a good model of screening at the community level for inherited disease.

The fact that the haemoglobin disorders affect particular ethnic minorities is often thought to be a useful ‘primary screen’, but in reality it is a major difficulty. There has been considerable resistance to the requirement to develop a selective approach to the groups at risk, partly because of anxiety about attracting attention to ethnic minorities and fear that focusing on their genetic problems will be considered racist. But such fears cause real racial discrimination when they result in failure to provide a necessary medical service.

Approaches to the haemoglobin disorders have been local initiatives. There has been much wasteful duplication of effort, and though a consensus view on the best approaches can be developed only by pooling experience, information is still not integrated at a regional or national level. In particular, the education-
al component of a community approach and the production of educational aids cannot be organised effectively on a district basis. These problems lead to failure to inform, misinformation, anxiety, waste of resources and unnecessary duplication of testing.

The requirements for an adequate screening programme for haemoglobin disorders include the recognition of specialist centres which should have associated ethnic genetic counsellors to act as a focus for a community service.

The DoH has now issued haemoglobinopathy cards to be given to people who have been screened. Though the information provided is still inadequate, it is to be hoped that this is the first step in better central recognition of this problem, which would include advice to regions on funding for special services.

Among ethnic minorities, many older mothers are not being counselled because it is assumed that they will not want karyotyping, and because of language difficulties.

British Pakistanis have a strong tradition of consanguineous marriage. It would be inappropriate to try to interfere with this custom on genetic grounds. However, as a group, British Pakistanis do have special genetic counselling needs.

5. Genetic counselling and education

Couples at risk for bearing an abnormal child, and pregnant women who discover they are carrying an abnormal fetus, have to choose among several options and must live with the decision for the rest of their lives. They need information and support through the process of genetic counselling. Three core ethical principles are recognised for genetic counselling:

i. The autonomy of the individual or the couple.
ii. Their right to full and complete information.
iii. The preservation of the highest standard of confidentiality.

Although counselling should be non-directive, this does not mean simply telling people the facts and leaving them to make their own decision. Counselling is a special skill that depends on training and the ability to communicate, and involves actively helping couples to reach decisions in the context of their unique medical, moral and social situation.

To meet the requirement for autonomy, it is essential to communicate the diagnosis and the implied risks effectively. Because genetic disease is diverse and in some cases unpredictable, and the language, culture and social level of those counselled covers such a wide range, communication can represent a major challenge.

Couples at high risk for having children with inherited diseases rarely see separation and finding another partner an acceptable alternative to having their own (genetic) children. If they modify their reproductive behaviour, prenatal diagnosis is most often their method of choice. Such couples need information and the support of a trained genetic counsellor who should possess good communication skills.

6. Genetic counselling and education

Now that genetic screening and prenatal diagnosis are accepted components of medical practice, audit is essential for their effective service delivery. Although audit is still very underdeveloped, such audit as exists points to inadequate delivery of existing services.

Some data are collected and recorded, but usually not on a regular basis. Data collection should be organised on a regional and national level in order to monitor the impact of prenatal diagnosis. It is particularly necessary to develop ways of monitoring the impact of routine ultrasound scanning.

There is a strong medical and socio-economic case for rational planning and adequate funding of prenatal diagnosis services but most existing economic analyses of such services are highly unsatisfactory, and underestimate their true benefits.

The economic dilemma of modern medicine arises partially from the fact that many medical advances improve the survival of people with chronic disabilities, and so lead to increasing service needs. Largely because of this, in the absence of prevention, the cost of treating patients with the inherited diseases listed in

Table 3. Estimated minimum annual cost to the NHS in the UK of treating patients with selected inherited disease, and projected future figures if there were no prevention

| Disease                  | Estimated number of patients | Per patient (\textdollar{}) | All (£ millions) | Effectiveness score for treatment | Minimum expected survival with treatment (year) | Expected final number of patients on treatment | Multiples of present number |
|--------------------------|------------------------------|-----------------------------|------------------|----------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------|
| Cystic fibrosis          | 360                          | 4,600                       | 36               | 3                                | 25                                           | 12,000                                        | x2                          |
| Sickle cell disease      | >100                         | 2,500                       | 10               | 2                                | 250                                          | 6,000                                         | x1.5                        |
| Phenylketonuria          | 75                           | 2,080                       | 2.7              | 1                                | 70                                           | 5,250                                        | x4                          |
| Haemophilia              | >70                          | 7,800                       | 33.5             | 1                                | 70                                           | >4,900                                       | x1.5                        |
| Thalassaemia             | 60                           | 5,500                       | 2.0              | 3                                | 35                                           | 1,800                                        | x3                          |
| Huntington's chorea      | 50                           | 1,560                       | 1.3              | 5                                | 16 from diagnosis                            | 800                                          |                              |
| **TOTAL**                | **815**                      | **5,100**                   | **-86**          |                                  |                                               | **30,850**                                   | **x1.9**                    |

* Effectiveness score is a rough indicator of the effectiveness of treatment in controlling the disease. 1 = completely effective; 5 = ineffective. The score indicates that when treatment is effective, costs can be high and tend to rise because of improved patient survival. When there is no effective treatment, as for Huntington’s chorea, costs to the NHS can be modest and are not expected to increase with time, unless a more effective treatment is found.
Table 3 will double in the next 20–30 years. Unlike many other branches of medicine, medical genetics has a built-in means through genetic counselling and prenatal diagnosis for limiting its own expansion.

i For many couples, the relatively small cost of a prenatal diagnosis represents the price of a healthy child, since without prenatal diagnosis they might not dare to undertake a pregnancy.

ii A proportion of couples at risk (25% in the case of X-linked and recessively inherited diseases) find the pregnancy is affected. Most of those at risk for severe disease choose to terminate the pregnancy, and soon undertake another in the hope of replacing the aborted fetus with a healthy one.

iii If the costs of the whole programme are aggregated, it is cheaper to screen and counsel the whole population than it is to treat affected children who would otherwise be born to unprepared couples.

iv When prospective carrier screening is possible, a primary-health-care-based policy of community information, screening and counselling provides by far the best medical service to the groups at risk and also leads to the greatest short- and long-term savings.

v Most analyses agree that screening and prenatal diagnosis programmes are wanted by the population and offer major financial advantages. The investment required is relatively modest and will conserve NHS resources for other uses.

7. Organisation of services

There is now a national network of clinical geneticists and a clinical genetics unit in most NHS regions. Most are associated with an academic centre, but few have adequate staff or counselling or diagnostic resources, and very few bring together all the relevant services on one site. In addition, prenatal diagnosis services are falling short of their potential because of conspicuous inadequacies of medical education and community information, absence of educational aids, and inadequate counselling associated with screening and prenatal diagnosis. Monitoring of the impact of prenatal diagnosis is almost non-existent. To improve the situation, planning is needed at national, regional and district levels.

Policy formulation, development and distribution of education materials, and service monitoring should be organised at a national level.

Each region should develop an organisation, involving genetics and fetal medicine centres, neonatologists and paediatric pathologists, obstetric and paediatric consultants, primary care physicians, community physicians, health workers involved in family planning, health visitors, midwives, nurses and experts in health education and community medicine. A designated co-ordinator (who may often but not always be a clinical geneticist) should be responsible for bringing these people together on a regional basis to improve delivery of both specialist and community genetics services.

For the prenatal diagnostic service to be delivered effectively, the regional organisation must be reflected at the district level and involve general practitioners, maternal and child health workers and antenatal clinics.

8. Ethical aspects of prenatal diagnosis

The central ethical obligations of prenatal diagnosis are those of good medicine. Bad science, sloppy medicine, insensitive communication and misinformation can cause at least as much harm as failure to enunciate ethical principles or minor deviation from them.

The choice of option and outcome following prenatal diagnosis should be made by informed couples; they are the best judges of what should be done. The same objective situation may lead to different decisions by different couples or individuals, depending on their attitudes and beliefs—particularly those of the mother. But their decision will also depend on the advice available to them, in terms of both its scientific quality and the manner in which it is given.

Prenatal diagnosis should be undertaken within the general principles of informed consent, including the possibility that, after testing, the question of terminating the pregnancy may have to be faced. Women must therefore have the right to refuse testing, even at a fairly preliminary stage, and must understand the implications of their decision.

While prenatal tests should not be pressed upon anyone, they should be made available, even to women who are completely opposed to abortion, since testing may provide welcome reassurance, or an informed choice to care for a child with a known handicap, or allow the option of abortion to be reconsidered on the basis of known facts.

Though it is important to consider financial costs and benefits in order to ensure that these services are made available, couples should never be pressed to choose termination of an affected pregnancy on grounds of cost. Any decision should arise exclusively from the moral perceptions of the couple themselves.

A doctor does not have the right to deprive pregnant women of the possibility of prenatal diagnosis because of his or her own opposition to abortion. If, in conscience, a doctor cannot offer information and access to the service, it is obligatory to refer the woman or the couple to someone who will do so.

Counselling should be non-directive. Information, not direction, is given in such a way as to help the parents to make the decision that is right for them. The counsellor should as far as possible be ethically neutral, and the long-term ethical presuppositions must be those of the parents.

The most likely outcome of prenatal testing is reassurance, requiring no further choices. If, however, the tests suggest that a handicapped child is likely, the degree of likelihood should be explained, and also the extent of the burden which the child and family may
have to carry
The ethical case has already been made for carrying out genetic counselling prior to marriage or pregnan-
cy, when possible. For moral reasons, every effort should be made to develop and evaluate earlier meth-
ods for prenatal diagnosis.

RECOMMENDATIONS

1. Genetic screening and prenatal diagnosis services should be equally available to the whole community. They should be recognised as an intrinsic component of maternal and child health services.

2. A policy advisory structure should be set up to facilitate decision making in the future.

3. Although there is clear majority support for the principles of prenatal diagnosis, some serious ethical issues are involved. A professional code of practice governing genetic screening should be developed. It should be widely publicised to reassure the public that:
   a. prenatal diagnosis will not be used for a positive eugenic policy;
   b. prevention programmes will not detract from the appreciation of, and provision for, people with disabilities.

4. Resources should be made available:
   a. to ensure equitable delivery of existing services;
   b. to support the development, evaluation and early application of new approaches.

5. Professional training in medical genetics and the principles of genetic counselling should be provided for all maternal and child health workers (GPs, obstetricians, paediatricians, family planners, health visitors and midwives). Official contact should be made with the relevant professional bodies to develop the genetic component of the training curriculum and to organise updating courses for existing practitioners.

6. Because of the large numbers involved, and the relative simplicity of some issues in large-scale screening programmes, genetic information and counselling must be provided at the community level. The ideal professionals to provide information and counselling would be specially trained health visitors and midwives, who are already the point of first and most frequent contact with mother and child. The suggestion is consistent with current proposals to train nurse specialists, who in this case would act as reference and training resources for MCH workers in general.

7. Specialist genetic counsellors already work with clinical geneticists and with specialists in particular disorders. Equivalent specialist counsellors should be attached to each obstetric unit practising pre-
natal diagnosis. It is urgent to define a career struc-
ture for such specialist counsellors, who may have differing professional backgrounds, and carry out a wide range of activities.

8. a. Policy formulation, defining a career structure for genetic counsellors, development and distribution of educational materials and service monitoring, should be organised at national level.

b. Each region needs to develop an organisation for ensuring delivery of genetic screening and prenatal diagnosis. This organisation should include clinical genetics and fetal medicine centres, neonatologists and paediatric pathologists, obstetric and paediatric consultants, primary care physicians, community physicians, health workers involved in family planning, health visitors, midwives, nurses, and experts in health education and community medicine.

c. For the service to be delivered effectively, the regional organisation must have roots at the district level, in the antenatal clinics and among general practitioners and other maternal and child health workers.

9. Because of their multidisciplinary nature, prenatal diagnosis services should be under the overall supervision of designated district and regional co-ordinators who may often, but not always, be clinical geneticists. The co-ordinator’s responsibility should be to ensure that the services are provided to the recommended standard and co-ordinated and monitored throughout each region.

10. Though monitoring should be organised on a regional basis, a national centre is needed to develop appropriate methods, co-ordinate information nationally, and stimulate equal service delivery throughout the country.

11. Face-to-face counselling and written information are complementary rather than alternative sources of information for an educated population; one should not be given without the other. Information packages need to be directed to schools, young couples and pregnant women, and individuals with defined genetic risks. Because of the wide range and different levels of educational resources needed to cover the spectrum of potential abnormalities, a National Genetic Health Education Unit is needed to generate, store and disseminate information.

12. These proposals should be implemented through working groups and supported by the DoH.

This is a very abbreviated summary of the full report which is available from the Royal College of Physicians, price £10.00.