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A Report of the Royal College of Physicians

PRENATAL DIAGNOSIS AND GENETIC SCREENING

Community and service implications

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September 1989

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Contents

Preface

With very few exceptions, genetically determined and congenital disorders cannot be cured, so the parents of an affected newborn may face many years of caring for a severely disabled child, and they will almost certainly require continuous support from social services, as well as frequent medical attention. Some malformations can be successfully corrected surgically, and a limited number of other disorders can be controlled by lifelong drug treatment or by other therapies, but there is no immediate prospect of effective treatment for the majority of individuals.

Experience has shown that where they understand the risks, the great majority of couples will use whatever means are available to them to avoid the birth of severely affected children. They may choose to remain childless if they cannot ensure that only healthy children are born, but they are unlikely to change their chosen partner. The goal of genetic and prenatal diagnostic provision must be to help these couples make an informed choice, one which they feel is best for themselves and their families. A few will choose to accept a handicapped child, but they may be better able to do so if they are forewarned. Others will refuse testing altogether. These wishes must be respected; nevertheless, it is clear that proper investment in the improvements to the existing services, and the introduction of new ones made possible by scientific advances, could greatly help individuals and couples at risk, and also help to contain the overall budget for health care.

Two to three per cent of couples are at high and recurrent risk of having children with an inherited disorder. It is increasingly possible to detect these carriers by biochemical or DNA methods, and wherever possible this should be done prior to a pregnancy being established so that the couple can choose from the full range of options which could be available.

Most infants with congenital malformations and chromosomal disorders are born to healthy young women with no previously identifiable risk factors. It seems unlikely that these sporadic disorders can be prevented, and neither diagnosis nor intervention is possible before the woman becomes pregnant. Here the only solution is cheap, accurate and safe mass screening of all pregnant women prepared to accept it. As a consequence, some women will face the decision whether or not to abort an affected fetus. The parents will require counselling and support at that time, but it is equally important that proper provision is made for checking and recording the outcome so that the best possible advice can be given if future pregnancies are planned. These developments draw the whole community within the range of genetics services and have important implications for general practice, obstetrics, neonatal paediatrics and community health.

Recent developments such as the increased ease, speed and resolution of real-time ultrasound scanning in obstetrics, the rapid development of DNA technology for diagnosis, and the introduction of chorionic-villus sampling which allows diagnosis in the first trimester of pregnancy, present new opportunities at a time when there is increasing concern about the delivery of even well established techniques such as karyotyping on grounds of maternal age, maternal serum alphafetoprotein screening, and screening the ethnic minority populations for traits of haemoglobin disorders. Difficulties include poor organisation and monitoring, limited professional and public awareness, and severely limited technical, educational and counselling

resources. The problems increasingly reflect missed opportunities for the entire community, but their effects are particularly distressing for couples at risk of having a child with an inherited disorder.

Prenatal diagnostic services therefore fall into overlapping categories: community services based on better methods of population screening which ought to be delivered through the primary health care system and the obstetric and other hospital services, and specialist clinical genetics and fetal medicine services. Both should provide for pre-pregnancy and pregnancy screening. This Royal College of Physicians report reflects a widespread and growing concern over the present and future problems in service delivery, problems which are essentially interdisciplinary. A recent King's Fund Consensus conference addressed the same issues [1], reaching very similar conclusions. The nature of prenatal diagnosis and the requirements for its effective delivery must be better defined if health authorities are to respond appropriately to the existing as well as the new possibilities.

CHAPTER 1 Introduction

The objectives of prenatal diagnosis

1.1 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. Improved primary health care now allows many of these vulnerable affected infants to survive and be diagnosed and also allows some to be treated. As management improves and affected individuals live longer, so their prevalence is rising and their needs are increasingly recognised. At the same time modern technology is increasing the possibilities for early identification of mothers and pregnancies at risk, and for prenatal diagnosis to predict the outcome of pregnancy. Many congenital malformations can be detected by ultrasound scanning and many hereditary disorders, such as chromosomal abnormalities and inherited diseases, can be definitively diagnosed before birth.

1.2 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.

1.3 This chapter broadly outlines the types of congenital and hereditary disorders and establishes the importance of distinguishing betweeen specialist and community genetics services, and between risks that can be identified before pregnancy and those that can be detected only during pregnancy.

Nature and frequency of congenital and genetic disorders

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

1.5 The main types of congenital malformations, their clinical impact and the possibilities for successful surgical correction are summarised in Table 2. Since about 20% of affected infants have multiple malformations, although the total incidence of malformation (shown in Table 2) is about 29 per 1000 births, the actual incidence of affected infants is about 15 per 1000 births.

1.6 The commoner types of chromosomal abnormalities and their clinical consequences are summarised in Table 3. Their incidence is closely related to maternal age (Fig 1) and in developed countries, Down's syndrome (characterised by an additional chromosome 21) is one of the most frequent causes of severe mental retardation.

1.7 In every pregnancy there is a relatively low risk that the fetus has a congenital malformation or a chromosomal disorder. These disorders arise at the time of conception or during early embryonic development. The only realistic method of

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 different types of congenital malformations[a]

System involved	Rate per 10,000 births	Percentage of all malformations	Proportion correctable
Central nervous system	18–50	>10	Very few
Eye	3–12	< 2	Some
Ear	7	2.6	Some (often minor)
Heart	40–96	>20	Many
Respiratory system	4	1.4	Some
Lip and palate	14	4.9	Most
Digestive system	12–38	6.3	Most
External genitalia	11–24	5.9	Most
Urinary tract	9–16	3.5	Many
Limbs			
Reduction deformity	3–9	1.5	None
Other	40–80	20	Many
Abdominal wall	5–6	2	Many
Other	–	19.4	Many not severe
TOTAL	287	100	

[a] Based on EUROCAT Study [52]

detecting them is to screen pregnant women using mass methods such as routine ultrasound scanning, maternal serum alphafetoprotein (AFP) screening or, for older mothers, amniocentesis and fetal chromosome analysis (karyotyping).

1.8 Some of the commoner inherited disorders are listed in Table 4 and their Mendelian modes of inheritance are summarised in Fig 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 McKusicks's *Mendelian inheritance in man* [2] shows on the one hand the collective frequency, and on the other the diversity and individual infrequency of these conditions.

Table 3. Common chromosomal disorders

Chromosome constitution	Name of syndrome + (birth incidence)	Effects
Autosomes		
47 (+21)	Down's syndrome (1/600–1/1000)	Severely mentally retarded Reduced survival Malformations common
47 (+18)	Edward's syndrome (1/3000)	Very severely retarded Growth retarded
47 (+13)	Patau syndrome (1/5000)	Multiple malformations Survival < 1 year
Mosaics (part normal, part abnormal)	—	Often severely affected
Sex chromosomes:		
47 (XXY)	Klinefelter syndrome (1/700 males)	Mild educational handicap Tall, slightly feminised Usually infertile
45 (XO)	Turner's syndrome (1/2500 females)	Short stature Infertile Some congenital malformations
47 (XXX)	(1/800 females)	Mild educational handicap Some infertile Occasional psychiatric problems
47 (XYY)	< 1/800 males	Usually little effect
Mosaics	—	Partial effects

Table 4. 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		
Huntington's chorea	70	Approximately equal to the incidence of disease; ie few, and mostly relatives of patients
Neurofibromatosis	30	
Multiple polyposis coli	10	
Adult polycystic kidney disease	80	
X-linked		
Fragile X mental retardation	~ 70	About twice the incidence of the disease; ie relatively few, and most are female relatives of patients
Duchenne muscular dystrophy	13	
Haemophilia A	5	
Recessive		Carriers (% of the population)
Cystic fibrosis (CF)	50	4–5
Phenylketonuria (PKU)	20–50	1–4
In certain ethnic groups:		
Thalassaemia	30–700	3–17
Sickle cell disease	10–2,000	2–25
Tay-Sachs disease	20–40	3–4

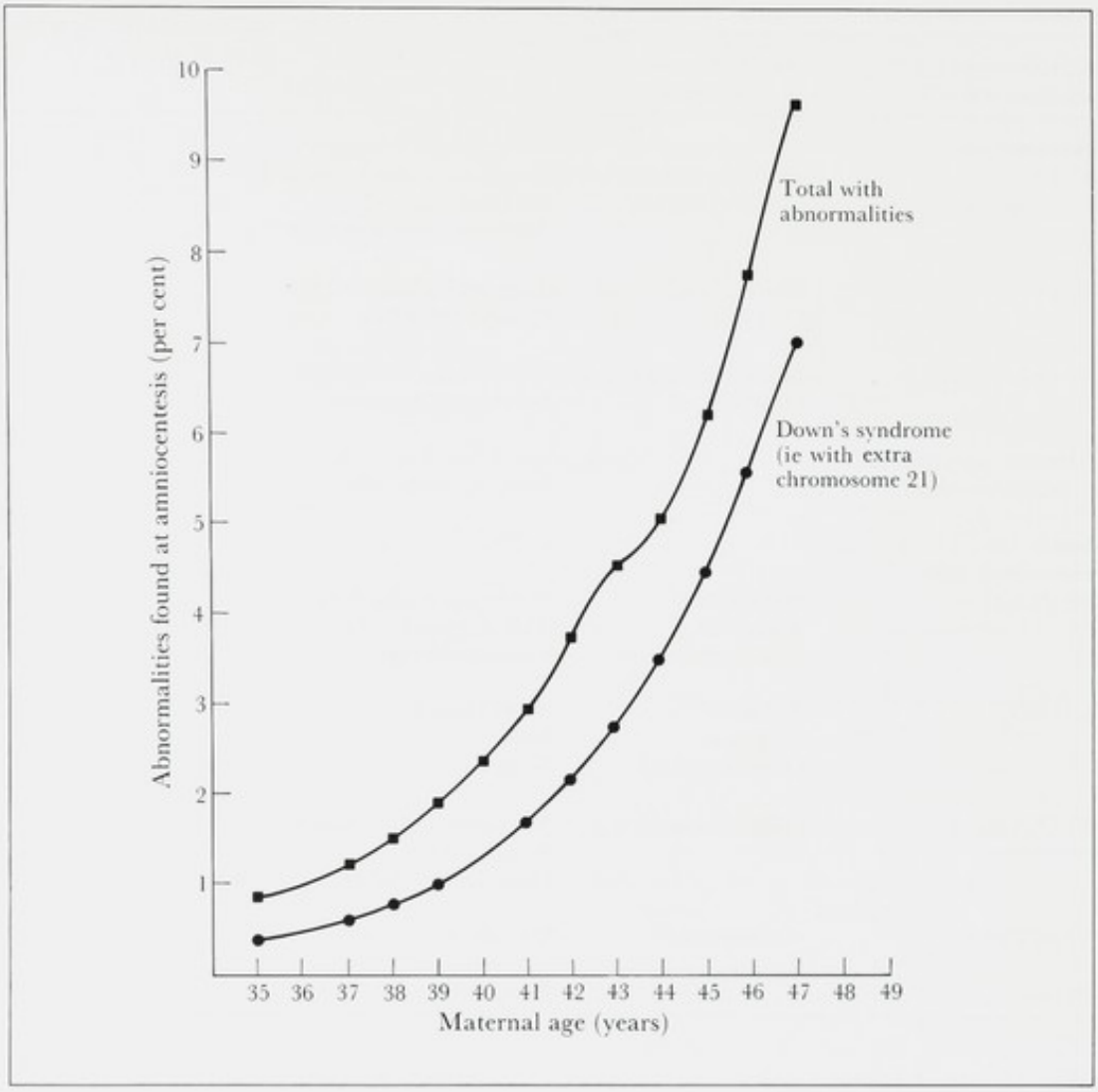
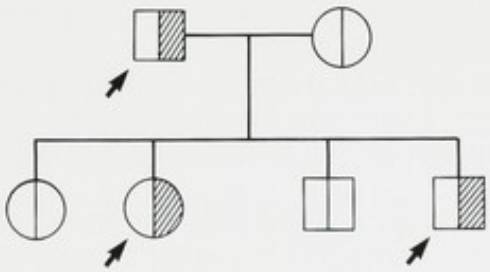


Fig 1. The risk of carrying a fetus with a chromosomal abnormality increases with maternal age. Data for Down's syndrome, the commonest abnormality, are shown separately. The figure is based on a large collaborative European study of results of amniocentesis [64]. About one third of chromosomally-abnormal fetuses abort spontaneously between 16 weeks and term, so the risk of actually delivering a live-born chromosomally-abnormal child is about two thirds that shown in the figure.

Fig 2. Patterns of inheritance.
a *Dominant inheritance.* The disorder usually manifests itself in all carriers of a single dose of the abnormal gene. The arrows indicate individuals who have or will develop, the disease.
b *X-linked inheritance.* The disorder manifests itself in males who carry a single dose of the abnormal gene on their only X-chromosome. Female carriers are usually protected by their second, normal X-chromosome. In males, the X-chromosome is always inherited from the mother, so if she is a carrier her sons have a 50% chance of being affected. Daughters inherit one maternal and one paternal X-chromosome: if their mother is a carrier, they have a 50% chance of being carriers, while if their father is affected they are all carriers. The diagnosis of an affected male suggests that his mother is a carrier and that most female relatives are at risk for being carriers. X-linked disorders may be transmitted unnoticed in the female line for several generations (see lower part of Figure).
c *Recessive inheritance.* The disorder occurs only when an individual inherits the abnormal gene from both parents, ie is a homozygote. In fact carriers usually marry non-carriers, so the vast majority of carriers do not have affected children and recessive genes are transmitted undetected in most families for many generations. When by chance two carriers marry, there is a 1-in-4 chance in each pregnancy of an affected child (arrow), so most people with recessively-inherited diseases do not have a family history.

a Dominant inheritance



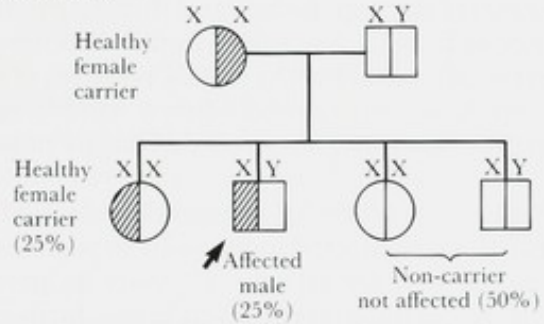
= male

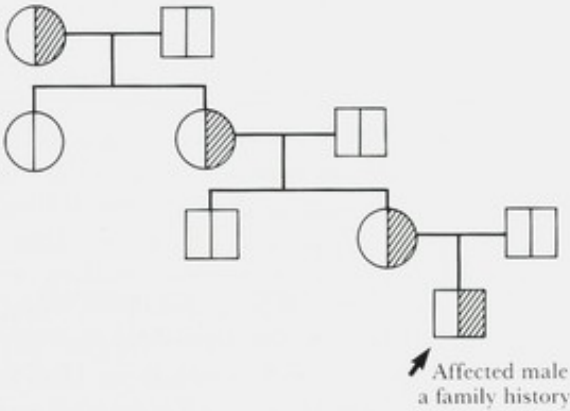
= female

= abnormal gene

= affected individuals

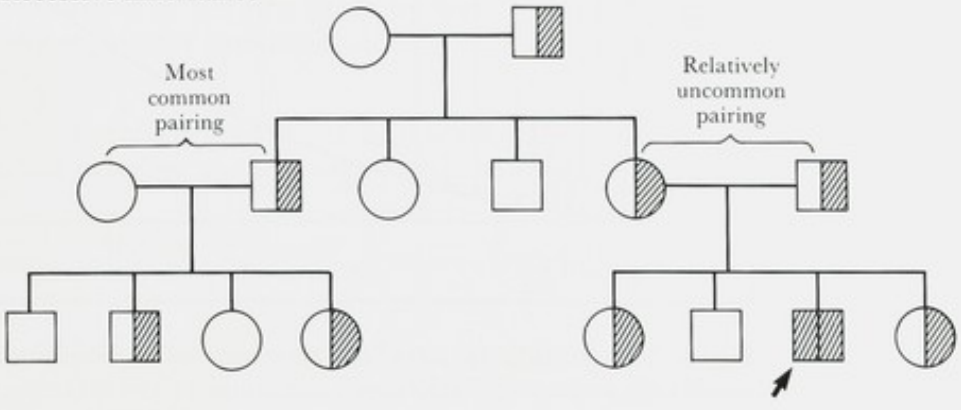
b X-linked inheritance





Affected male born without a family history of the disorder

c Recessive inheritance



1.9 Dominant genetic disorders which become manifest relatively late in life usually have a strong family history, unless affected ancestors died from another cause before the onset of the disorder. Early-onset dominant disorders such as achondroplasia are frequently due to a new genetic mutation and thus have no family history. The diagnosis of a dominant disorder in one individual implies a risk for all first-degree relatives of carrying the same pathological gene and of developing the same disease and transmitting it to their offspring (Fig 2a).

1.10 Classically, X-linked (or sex-linked) disorders show a typical family history of symptomless (healthy) female carriers giving birth to affected males. However, there may be no family history if the disorder is transmitted only in the female line for several generations or has arisen as a new mutation; this is relatively common in severe X-linked disorders (Fig 2b). The commonest of the severe X-linked disorders is fragile-X mental retardation. This is a severe disability often, but not always, associated with a visible 'fragile site' on part of the X-chromosome. It affects 1 in 1,000–2,000 of the population, and therefore is almost as common a cause of mental deficiency as Down's syndrome. In this disorder a proportion of female carriers may be severely affected. Healthy female relatives of males with X-linked disorders have a high reproductive risk, and when a reliable carrier test is available many can be identified by screening the extended family of known affected individuals.

1.11 Genes for autosomal recessively-inherited disorders are very common but the birth incidence of affected individuals depends on the frequency with which carriers of the same disorder select each other as partners (Fig 2c). Although this is a relatively uncommon event, even a low birth-rate of affected individuals (homozygotes) indicates a sizeable reservoir of carriers of the gene (heterozygotes) (Fig 3),

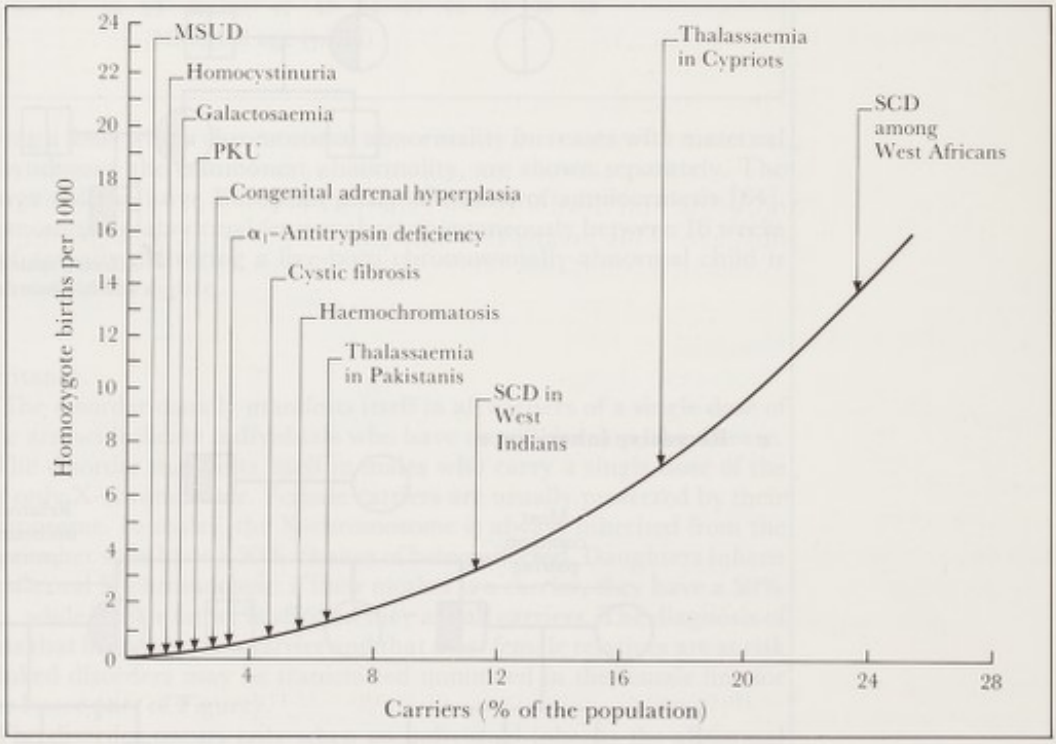


Fig 3. Relationship between the birth-rate of homozygotes with recessively-inherited conditions, and carrier frequency. The examples show that even relatively few births indicate a large number of carriers in the population. MSUD—maple syrup urine disease; PKU—phenylketonuria; SCD—sickle-cell disease.

and most affected infants are born apparently sporadically, ie without a family history. The vast majority of abnormal genes carried in human populations are recessive and most people carry at least one such potentially-lethal gene.

1.12 It is becoming increasingly possible by using biochemical or DNA methods to detect healthy carriers of single-gene defects. The diagnosis of an individual with a dominant or X-linked condition identifies an entire family at high risk; where carrier testing is possible, the relatively small numbers involved make carrier testing for the family very worthwhile. By contrast, for common recessively-inherited disorders the relatively large numbers of carriers and the rarity of a family history of a disorder make population-screening the only realistic way to identify them. At present, in the absence of a family history, sufficiently accurate methods for carrier detection are available only for the haemoglobin disorders and Tay-Sachs disease, but it is probable that new DNA technology will permit carrier testing for cystic fibrosis and other recessively inherited disorders.

1.13 In practice, 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. As mentioned earlier, 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.

Limitations of treatment

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

1.15 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. Support services for children with chronic physical and/or mental disability are generally good, and have led to improved survival to adult age. This means that although, for several reasons, the birth-rate of infants with some conditions is falling the cumulative number who survive and require care is increasing. However, provision for disabled adults is inadequate and the quality of life of older patients and their families often deteriorates [3].

Primary prevention and social and environmental factors

1.16 The objective of primary prevention is to stop non-inherited congenital disorders arising in the first place by identifying and avoiding causative factors. Examples of primary prevention are:

- prevention of Rhesus haemolytic disease of the newborn by postnatal injection of Rhesus negative mothers with anti-D immunoglobulin;
- immunisation of young girls against rubella infection;
- careful control of maternal diabetes in pregnancy;
- improved diet to avoid neural tube defects.

1.17 Social change has in itself important 'primary' effects. For instance, between 1950 and the mid-1970s the proportion of mothers in the UK over 35 years old fell from around 20% to less than 6%, although it has since risen to over 10%. Since older mothers are particularly at risk for Down's syndrome, this resulted in a fall of almost 50% in the incidence of Down's syndrome, and a change to the present situation in which most affected infants are born to younger mothers. Non-selective abortion accounted for about half this decrease because in the UK, as in most of Europe, more than 40% of pregnancies in women over 35 years old are aborted for social reasons.

1.18 Partly because of such social changes, most infants with congenital malformations and chromosomal disorders are now born to healthy young women with no identifiable risk factor. There is no evidence that such rare sporadic disorders can be detected or prevented prior to pregnancy. Primary prevention does not assist in preventing inherited diseases, because the genetic carrier status of the parents cannot be changed. As medical science is highly unlikely to be able to eradicate reproductive risk, there will always be a need for prenatal diagnosis and the option of selective abortion.

Organisation of prenatal diagnosis

1.19 From an operational point of view, prenatal diagnosis services must be provided at both specialist and community level (Fig 4). Specialist services are centred on the existing network of clinical genetics centres (Appendix 1) where

COMPONENTS OF PRENATAL DIAGNOSIS SERVICES		
	Specialist services	Community services
BEFORE PREGNANCY	**Clinical geneticist** Detection of familial disorders Diagnosis of propositus Risk evaluation Carrier diagnosis Counselling *(The above are also carried out by specialists in single diseases or organ systems)*	**Primary care team** Rubella immunisation Screening for recessively inherited diseases Maternal age – risk identification Maternal disease (e g diabetes) Referral to specialist for: familial conditions infertility or recurrent abortion previous abnormal child Information and counselling
DURING PREGNANCY	**Clinical geneticist** As above, if not carried out before pregnancy Counselling Prenatal diagnosis Laboratory diagnosis **Fetal medicine specialist** Tertiary ultrasound Fetal sampling Termination of pregnancy Fetal treatment Counselling and information	**Antenatal clinic** As above, if not carried out before pregnancy Pregnancy screening (Rh, rubella, etc) Prevention of Rh haemolytic disease Ultrasound – anomaly scan Maternal serum screening Information and counselling **Obstetrician** Secondary ultrasound Amniocentesis Termination of pregnancy Information and counselling
AFTER PREGNANCY	**Neonatologist** Treatment of affected infants **Neonatal pathologist** Diagnosis of birth defects Examination of aborted fetuses	**Midwives and health visitors** Neonatal screening

Fig 4. Components of prenatal diagnosis services. A very large part of the responsibility for delivering these services falls on the primary health care and maternal and child health services.

people with a known or suspected genetic risk are seen mainly by referral. The specialists involved are:

i Clinical geneticists and specialists in specific disorders who are concerned primarily with differential diagnosis, identification and counselling of families at high genetic risk, and management of some disorders;

ii Specialists in laboratory diagnostic services;

iii Obstetricians specialising in fetal medicine, expert in ultrasound and fetal sampling techniques;

iv Neonatologists;

v Paediatric pathologists.

1.20 To date, community genetics services are not well-recognised as an entity. They involve population screening, counselling before, during or after pregnancy, and the management of abortion for fetal abnormality. Figure 5 shows that, in

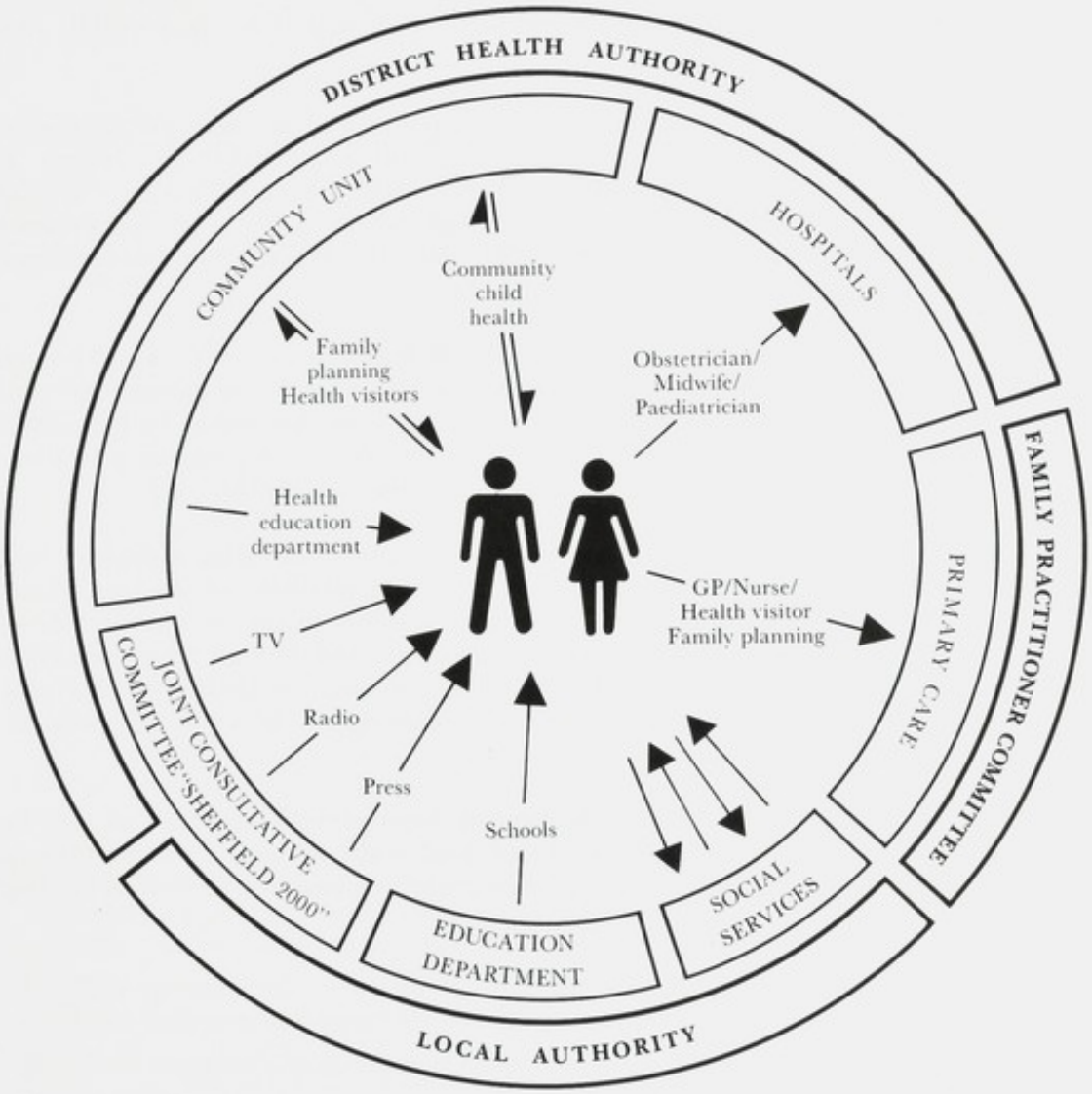


Fig 5. Model showing health workers at the district level (based on 'Sheffield 2000'). Any of the medical services may refer the couple on to regional clinical genetics units or, if indicated, a specialist in fetal medicine.

addition to the specialists listed above, the entire maternal and child health team is involved in screening and prenatal diagnosis, and these services must be delivered through the obstetric and other hospital services and the primary health care system. At both levels it is important to distinguish between pre-pregnancy and pregnancy screening. Community-based support Groups (see Appendix 2) play a particularly important role in improving the delivery of information and screening at community level.

1.21 In the following chapters, the specialist and community services are often discussed separately because of their different service implications but the need for parallel development and integration of these services is a central theme of this report.

Summary

S1.1 One to two per cent of all newborns have a major congenital or genetically-determined disorder. These conditions are disproportionately important because of their life-long implications and the heavy burden they place on the individuals and families concerned as well as on society as a whole. Although a few such disorders can be treated satisfactorily, for most management when possible at all is burdensome, expensive and unsatisfactory. Because treatment is so often unsatisfactory, prenatal diagnosis and selective abortion are options that should be available to couples at risk.

S1.2 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.

S1.3 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.

S1.4 Prenatal diagnosis services must therefore 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.

S1.5 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.

CHAPTER 2 The scope of prenatal diagnosis

2.1 This chapter reviews the general principles and techniques of screening and prenatal diagnosis, their practical application for the main groups of disorder, and their potential for reducing the total burden of disease. Subsequent sections show that in practice for several reasons, they fall far short of their potential.

2.2 The established methods for screening and prenatal diagnosis, summarised in Fig 6, have some important limitations. For example, until recently fetal sampling was possible only in the second trimester of pregnancy (after 16–18 weeks' gestation) and abortion, if requested, could be carried out only at around 20 weeks' gestation. Biochemical diagnosis of inherited diseases depends on measuring protein gene-products and calls for diverse laboratory methods. It requires that the relevant gene be expressed in an accessible source of fetal cells, and as there is usually extensive overlap between normal and carrier ranges, biochemical methods can be used only rarely to identify carriers. 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.

General principles

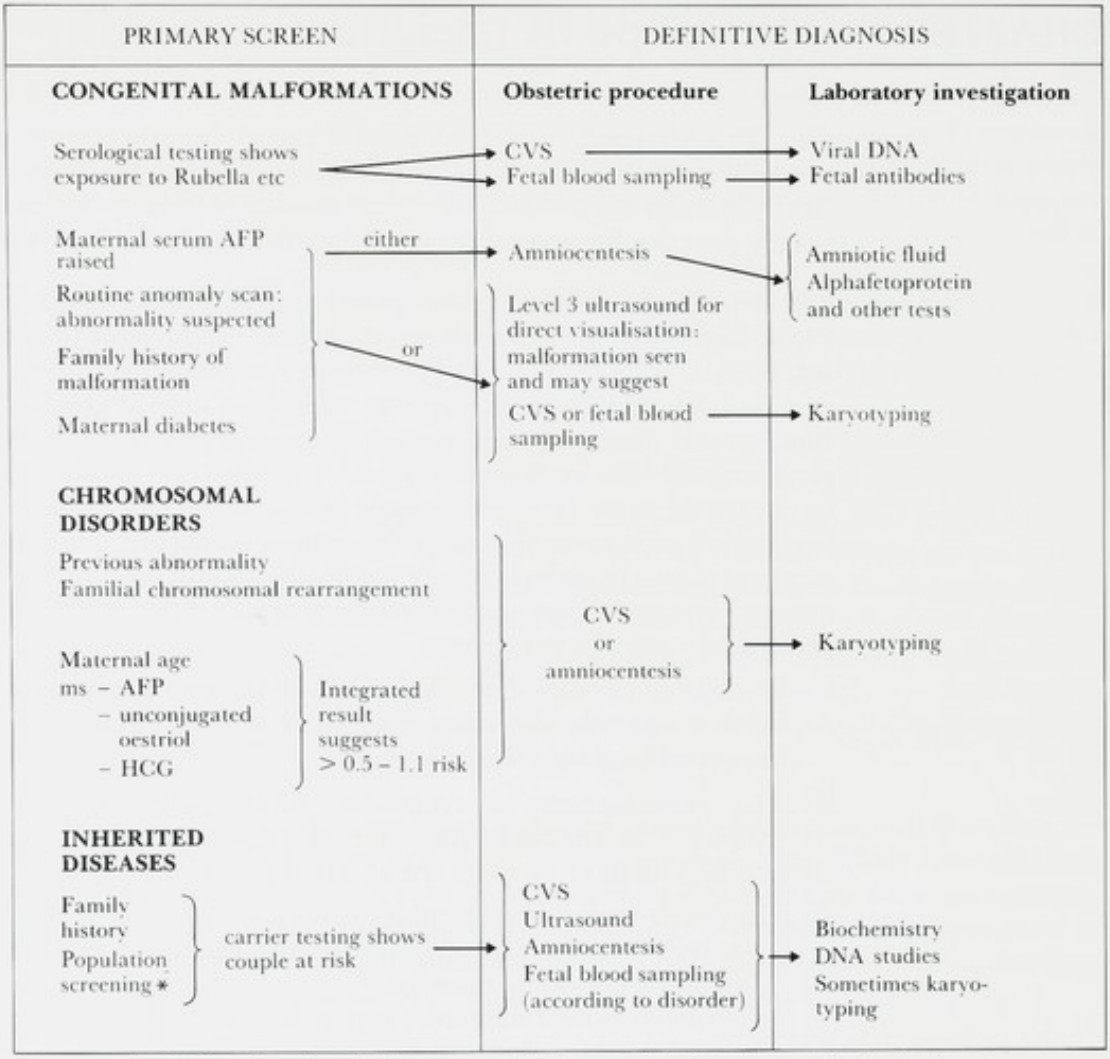
2.3 Prenatal diagnosis may involve testing many seemingly normal pregnancies in the search for uncommon abnormalities, and the techniques used for definitive fetal diagnosis are often invasive, relatively costly, and carry some risk. Figure 6 shows that in practice the strategy for prenatal diagnosis consists of initial 'primary screening' of the whole population to identify individuals or couples at increased risk, who are then offered prenatal diagnosis as a separate step.

2.4 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:

i 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.

ii Staff must be suitably trained and must work within a professional code of practice.

iii In case of the slightest doubt, the diagnosis should, as far as possible, be confirmed by an independent approach.



*At present limited to selected populations, screened for haemoglobin disorders or Tay-Sachs disease

Fig 6. Summary of present strategies for screening and prenatal diagnosis.

iv 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.

v Results should be subjected to regular audit, with particular emphasis on false positives and false negatives. National and regional monitoring should be established.

vi 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.

vii Women with a continuing pregnancy in which a fetal abnormality has been diagnosed, require expert support from the neonatologist and neonatal surgeon.

Primary screening

2.5 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) [4]. Whenever possible, screening should be carried out before pregnancy. Table 5 shows that many present methods fall short in one or more of these requirements.

Table 5. Criteria for screening methods and the extent to which they are met for prenatal diagnosis

Screening method	Safe	Simple	Cheap	Reliability	
				False +ve	False −ve
For maternal infections:					
Blood tests	+	+	+	Few	Few
For congenital malformations:					
msAFP[a] for NTD[b]				Many	
anencephaly	+	+	+	clinically	Nearly 0
spina bifida	+	+	+	relevant	20–30%
Detection of maternal diabetes	+	+	+	0	0
Ultrasound	+[c]	0	0	Dependent on skill of operator and equipment	
For chromosomal disease:					
Maternal age	+	+	+	> 90%	65%
Maternal age + serum factors	+	+	+	> 90%	< 50%
For inherited disease:					
Family history	+	0	0	Many	Many
Selection by ethnic group	+	+	+	Few	Is increasing[d]
Population screening for haemoglobin disorders and Tay-Sachs disease	+	+	+	Often clinically relevant	0

[a] Maternal serum AFP;
[b] Neural tube defects;
[c] Safety depends on training and supervision of operator;
[d] The proportion of carriers of haemoglobin disorders or Tay-Sachs disease who are not identifiable as members of ethnic minorities is rising as population mixing progresses.

2.6 The family history is a primary screen that allows clusters of people at increased risk for inherited disease to be identified and referred to a clinical geneticist. The family history is not easy to interpret because other factors, such as a shared environment, can cause familial clustering, while recessively-inherited diseases and new genetic mutations occur without a family history (See Fig 2b). In addition to a possible genetic disorder in the family, a positive family history includes recurrent abortions, delivery of a malformed or otherwise abnormal infant, and sometimes infertility. Most disorders manifest at birth are not inherited, but the parents always need expert diagnosis and counselling about the recurrence risk and the value of prenatal diagnosis in future pregnancies. Information is increasing about the relevance of factors such as number of affected relatives, severity of expression of the defect, and sex of the patient, so that an empiric recurrence risk can often be given. At present, the value of the family history as a primary screen is restricted by the limited education in genetics of most doctors.

2.7 Some high risk groups can be identified by characteristics such as ethnic group, parental age, diabetes, rhesus negativity and lack of immunity to rubella infection. Screening for such factors is well established in obstetric practice, but much should also be done before pregnancy. However, offspring of identifiable high-risk groups contribute only a small fraction of abnormalities.

2.8 In population screening, the aim is to identify individuals at increased risk by reviewing all members of a population by means of routine tests (such as ultrasound scanning, maternal serum AFP estimation, or carrier screening for a recessively-inherited disease). This form of screening has very great potential but at present in the UK it is limited to the antenatal clinic.

Screening for congenital malformations

Infectious causes

2.9 The Rubella virus is the main recognised infectious cause of congenital malformations. Maternal immunity should always be ensured before pregnancy, but in practice this is not always the case. Positive evidence of maternal infection in early pregnancy often leads directly to therapeutic abortion, although only about 20% of exposed fetuses are severely affected. Definitive prenatal diagnosis of affected fetuses is possible by measuring the appropriate antibodies in fetal blood, but only at about 22 weeks' gestation when the fetal immune system is sufficiently mature [5]. In future it may be possible to diagnose or exclude fetal rubella infection in the first trimester of pregnancy by testing for virus DNA in chorionic villus samples [6].

Maternal serum alphafetoprotein estimation

2.10 Alphafetoprotein (AFP) is a fetal plasma protein. When a malformation such as a neural tube defect allows it to leak into the amniotic fluid, some also passes into the maternal circulation. In many areas maternal serum AFP estimation is now offered routinely to all pregnant women between 16 and 18 weeks of gestation in order to identify a risk group that includes all fetuses with anencephaly and most with spina bifida.

2.11 The service is usually organised from the antenatal clinic, but AFP screening can be carried out in collaboration with general practitioners. Information and counselling for the women who are tested and evaluation of outcome are essential. Results of maternal serum AFP assay are expressed quantitatively as deviations from a median value, and vary with the assay method used, the population studied and gestational age. Laboratories participate in a quality-control programme and regularly monitor their results. Ultrasound is an important adjunct to maternal serum AFP screening.

2.12 A raised maternal serum AFP should lead to expert (level 3) ultrasound examination for a fetal malformation, with or without amniocentesis for confirmatory biochemical tests, or else directly to amniocentesis for assay of the amniotic fluid AFP. It is important to note that in about 50% of pregnancies with a raised maternal serum AFP, no cause can be found, either pre- or post-natally [7]. Maternal serum AFP estimation is likely to remain an important screening test because the expert routine ultrasound scanning for fetal abnormalities, which some think could replace it, is not generally available and because when integrated with maternal age a low maternal serum AFP is a useful screen for fetal chromosomal abnormality (see para 3.3).

Ultrasound scanning

2.13 Ultrasound scanning is now a basic part of obstetric practice. There is a continual increase in the range and capabilities of the best equipment and a decrease in the size and cost of basic machines. The use of ultrasound in screening and prenatal diagnosis will be discussed together here, because essentially the same methods are used for both, though practised at different levels of clinical expertise.

2.14 There is good evidence that with an appropriately organised obstetric ultrasound service, most major structural malformations could be detected in the second trimester of pregnancy (at about 19 weeks' gestation), allowing parents the option of termination of pregnancy. These findings need confirmation in larger studies.

2.15 There is no evidence for a harmful physical effect of diagnostic obstetric ultrasound [8]. Its main limitations are the dependence on the skill and experience of the operator and the quality of the equipment, and its main risk is misinterpretation of the image leading to failure to detect abnormalities (false negatives) or to abortion of a healthy fetus (false positives).

Table 6. Levels of obstetric ultrasound

Level	Instrument	Time required (min)	Uses in prenatal diagnosis
1	Basic real-time	5–10	Only fetal number, viability and gestational age
2	Good real-time	15–20	Fetal anomaly scan (with a check-list) Amniocentesis
3	Very high quality	Over 15	1st trimester observations Fetal movements Diagnosis of fetal anomalies Fetal sampling (amniocentesis, CVS, fetal blood etc) Fetal operations Research Teaching

2.16 Inevitably, when an abnormality is suspected the pregnant woman perceives that something is wrong. Intense anxiety is aroused and must be dealt with immediately; the findings must also be integrated with other information, including the family history. It is not sufficient to write a report to be discussed at her next visit to the obstetrician. Scanning during pregnancy should be done whenever possible in the obstetric department, and always under clinical supervision. Full information, advice and support, rapid obstetric back-up and expert counselling should be available on the spot. Obstetric ultrasound scanning requires appropriate training, a high standard of supervision and a clear code of practice.

2.17 At present, ultrasound is used for detecting fetal anomalies at three stages of pregnancy (see below) and at three levels of expertise (Table 6). Only *level 1* scanning, which confirms gestational age and fetal viability and number, is available to most pregnant women in the UK. Because only a few gross malformations are detectable by level 1 scanning, it does not constitute a primary screen for congenital malformations. It is essential to correct the common misunderstanding that it can exclude fetal abnormality.

2.18 *Level 2* 'fetal anomaly scanning' (see Table 6) does constitute a primary screen, but is routinely offered to pregnant women at only a few centres. In most areas it is available only for recognised risk groups. Most operators at levels 1 and 2 are not doctors and do not have the training or authorisation to discuss their findings with the mother. When an abnormality is suspected by screening at this level, it may be advisable to refer the woman to a recognised level 3 centre for confirmation of the diagnosis.

2.19 *Level 3* scanning is performed by experts at some centres. An expert with good equipment can visualise the first and second trimester fetus, observe fetal anatomy and movement, define the majority of major congenital malformations, study cardiac function by measuring blood flow, and guide fetal sampling and operative instruments with precision (see Table 6). Such 'fetal medicine' centres should be physically associated with clinical genetics units, but at present this is rarely the case in the UK.

2.20 Scanning in the first trimester (at booking) is very effective in detecting non-viable pregnancy and is recommended as a routine, at least for women over 35 who run a more than 20% risk of a spontaneous abortion.

2.21 A basic level 1 scan, in association with maternal serum AFP screening, is usually routine at about 16 weeks' gestation; but the best time for detailed anomaly scanning is at around 19 weeks when the fetus is larger and the organ systems are more differentiated. At this stage, a level 3 expert can detect over 90% of major congenital malformations in risk groups, with very few false positives [9]. However, 90% of congenital malformations occur in pregnancies not recognisably at risk, and the only way to detect more of these is by offering routine, skilled level 2 anomaly scanning to every pregnant woman. It has been shown that at some expert centres where systematic level 2 anomaly scanning is performed by trained and supervised midwives, radiographers or technicians with suitable equipment and adequate time, 80% of major structural anomalies can be detected [9].

2.22 A major malformation detected before 24 weeks of pregnancy is associated in up to 30% of cases with an underlying chromosomal anomaly [10]. Knowledge of the fetal karyotype can be crucial to the parents' decision whether or not to continue the pregnancy. Therefore, when there is any uncertainty about management, malformed fetuses detected in time for induced abortion should be referred to a level 3 centre for rapid karyotyping on fetal blood or a placental biopsy [11].

2.23 Ultrasound is often routinely used at around 32 weeks to confirm normal fetal growth and progress of the pregnancy. At present, congenital malformations are most likely to be detected at this stage, when selective abortion is no longer an option.

Screening for chromosomal disorders

2.24 The diagnostic method used for detecting fetuses with chromosomal disorders is amniocentesis, or CVS for collecting fetal cells, followed by karyotyping (chromosomal analysis). This method of testing would have to be offered to all pregnant women if all affected fetuses were to be detected. However, because there are obstetric risks and karyotyping is a highly-skilled and labour-intensive procedure, prenatal testing for fetal chromosome anomalies is usually offered only to women at more than 0.5–1% risk of bearing an infant with Down's syndrome*. Until recently, this applied only to older mothers (over 35–37 years of age), or to women who had already born an affected child, and to couples where one partner carries a chromosomal anomaly. However, karyotyping limited only to these groups can reduce affected births by one third at most, because most Down's syndrome infants are now born to younger mothers (see paras 1.17 and 1.18). Better primary screening methods for detecting mothers at risk are needed, and promising new developments are described in Chapter 3.

Screening for inherited diseases

2.25 The feasibility of carrier detection is an important limiting factor in screening for inherited disease. The ideal is to detect carriers before they embark on a pregnancy (prospective carrier diagnosis). This is possible at present only for relatives of patients with a limited number of dominant or X-linked disorders, and for the recessively-inherited haemoglobin disorders and Tay-Sachs disease (See Chapter 4). However, the possibilities for carrier detection using DNA methods (see 2.41) are steadily increasing.

2.26 Carrier detection and prenatal diagnosis for dominant disorders involve some unique problems. For example, in Huntington's chorea, knowledge of risk leads many family members to remain childless (see ref 46), even though half of them are not carriers. Testing for carrier status would allow non-carriers to reproduce normally, while with prenatal diagnosis, known carriers could reproduce without

* This risk level numerically matches the risk of the obstetric procedure causing a spontaneous abortion, but the risks are not comparable. Either may outweigh the other depending on a couple's obstetric history and social situation. The real limiting factors in the offer of prenatal diagnosis for chromosomal anomalies are associated with the expense (and tedium) of karyotyping.

fear of handing on the undesirable gene. However, carrier detection in dominant disorders amounts to preclinical diagnosis for the person at risk, and in the absence of effective treatment the major psychological implications of such a diagnosis mean that it must always be undertaken by experts. So far, there has been a very cautious uptake of carrier detection for Huntington's chorea. Prenatal diagnosis, seemingly impossible if the parents' carrier status is unknown, can be done in many cases by 'exclusion testing' using DNA analysis methods to confirm that a fetus is unaffected [12].

2.27 The diagnosis of a male with an X-linked disorder, for example haemophilia, places several female relatives at recognised risk of being carriers. Since healthy (ie symptomless) female carriers are not themselves at risk for the disorder, such women are often interested in carrier testing. DNA analysis methods, especially useful for detection of Duchenne muscular dystrophy and haemophilia, provide more reliable prediction than the classical biochemical methods. One of the main advantages of the DNA method has proved to be the restoration of reproductive confidence to women with a family history of an X-linked disorder who are shown not to be carriers.

2.28 The potential of carrier detection and prenatal diagnosis for reducing the incidence of dominant and X-linked diseases is restricted by the limitations of the family history and by the relatively high incidence of new mutations in some groups of disorders. For example, only about two-thirds of cases of Duchenne muscular dystrophy could be prevented in this way. However, taking the above factors into account, and assuming steady progress in developing genetic services, prenatal diagnosis might reduce the incidence of all severe dominant and X-linked disorders by up to 50%.

'Retrospective' carrier diagnosis

2.29 Cystic fibrosis is the most common recessively-inherited disease in the UK. Prenatal diagnosis for this condition is now possible by assay of amniotic fluid alkaline phosphatase at about 19 weeks' gestation [13], or by DNA analysis in the first trimester [14]. Although there is an increasing demand for this service, it can have only a small effect on the birth-rate of affected children. This is because no carrier testing yet exists and prenatal diagnosis can be offered to couples only after the birth of their first affected child, ie 'retrospectively'. However, because final family size is small, most families will contain only one affected child. Prenatal diagnosis can make a major numerical impact on cystic fibrosis only when reliable direct carrier detection is possible.

'Prospective' carrier diagnosis

2.30 When a carrier test exists for a common recessively-inherited disease, as it does at present for the haemoglobin disorders and Tay-Sachs disease, couples at risk can be identified by screening the whole population before they have children, ie 'prospectively'. When most prospectively-detected couples at risk request prenatal diagnosis, as is the case for thalassaemia, there can be a drastic fall in the birth-rate of affected infants (see Fig 7). This is why the development of carrier testing for cystic fibrosis is so urgently required.

2.31 Techniques for screening for inherited disease are evolving rapidly. When questions arise of whether carrier testing or prenatal diagnosis is possible for a particular condition, it is essential to seek up-to-date information from the local clinical genetics centre.

2.32 The birth-rate of infants with inherited disorders will fall steadily over several generations if adequate resources are provided for population-screening, meticulous establishment of genetic registers, conscientious pursuit of family studies, and for genetic counselling including the offer of prenatal diagnosis.

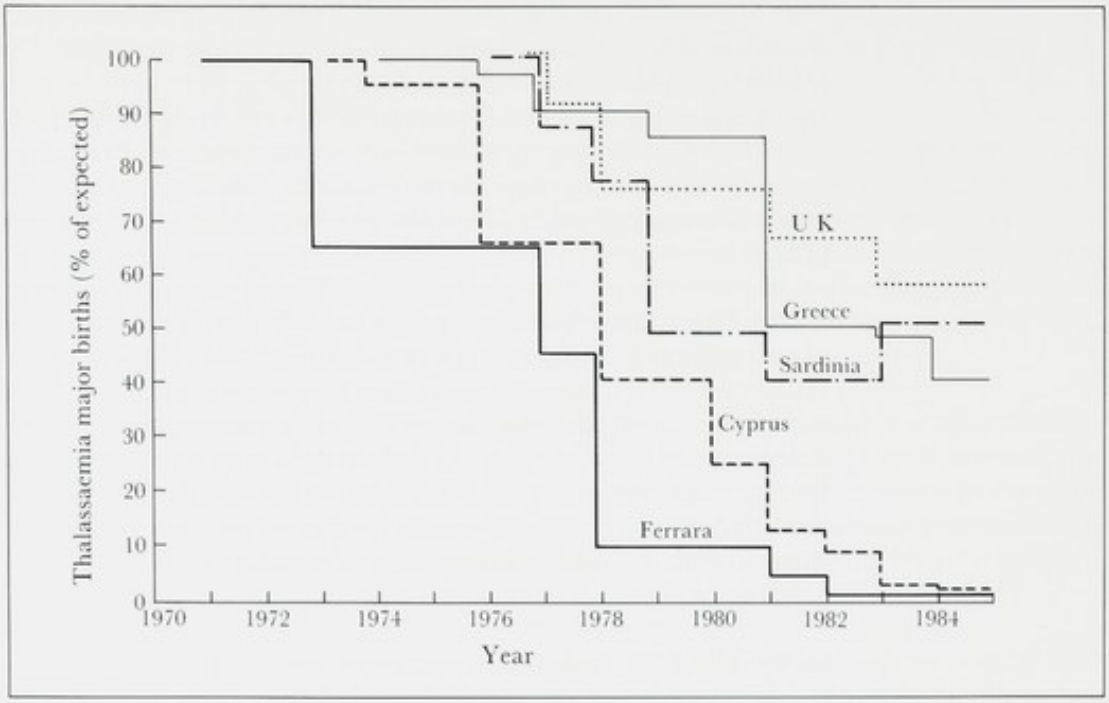


Fig 7. Fall in the birth-rate or infants with thalassaemia major associated with several thalassaemia control programmes [32].

Table 7. Present fetal sampling procedures, risks and time required to obtain a diagnosis

Obstetric aspects			Time to diagnosis					
			Karyotyping		Biochemistry		DNA	
Sampling procedure	Weeks' gestation	Risk to pregnancy (%)	Culture	Rapid	Culture	Direct	Culture	Direct
Amniocentesis	14–17	0.5–1	2–4wk	—	2–4wk	—	5wk	>10d[a]
Fetal blood sampling	>18	1–7	—	3d	—	2–7d	—	10d
Chorionic villus sampling	>9	2–4	2wk	2d	2wk	1d	—	10d
Ultrasound	~ 9	+[b]	Time to a definitive ultrasound diagnosis depends on many variables. Rapid karyotyping may be required.					

[a] New DNA methods promise to reduce the time to diagnosis to 1–2 days.
[b] The risk is of false positive diagnosis leading to abortion of a healthy fetus.

Methods of prenatal diagnosis

2.33 Present methods of obtaining fetal material for analysis, with their advantages and disadvantages, are listed in Table 7.

Amniocentesis

2.34 Amniocentesis should be carried out under real-time ultrasound guidance by an experienced obstetrician. It is usually carried out at around 16 weeks of pregnancy and although it is a relatively simple technique, it continues to evolve, with better ultrasound monitoring and the use of disposable needles.

2.35 There is still some uncertainty about the exact risk to the pregnancy from amniocentesis [15] largely because the risk is so low that it is extremely difficult to measure. The best studies suggest a 1% excess risk of spontaneous abortion following amniocentesis and a slightly increased incidence of mild respiratory problems in the newborn. One study suggested an increased incidence of club-foot,

but the balance of evidence is against this. The problems identified with amniocentesis represent only a slight statistical increase in recognised complications in the newborn, all are correctable and there is no evidence that they are anything but transient. The figure now commonly quoted to pregnant women is a 0.5–1% risk of miscarriage following the procedure; the exact figure given being influenced by the personal experience of the operator.

Fetal blood and tissue sampling

2.36 Fetal blood sampling is used for diagnosis of the haemoglobin disorders and haemophilia when DNA diagnosis is not possible, for immunological diagnosis of combined immune deficiency syndromes or intrauterine infections, and for rapid karyotyping of fetal lymphocytes when a malformation has been detected by ultrasound. It can be performed safely only after the 17th week of pregnancy and only by experts. Initially, fetal blood sampling was done by fetoscopy, a highly specialised procedure with a 3–7% risk of fetal loss [16]. This is now being replaced by the safer and less specialised technique of ultrasound-guided transabdominal needle puncture of the fetal cord insertion [17]. Fetal skin and liver biopsies, selective feticide of one affected twin, and intrauterine transfusion may also be performed [18].

Chorionic villus sampling (CVS)

2.37 Chorionic villus sampling is a relatively new procedure whereby a small sample of chorionic (placental) tissue is removed for prenatal diagnosis [19]. CVS can be carried out in the first trimester of pregnancy with only minimal discomfort and often allows a genetic diagnosis to be achieved before 12 weeks' gestation. This means that termination of pregnancy, when requested, can be carried out simply, painlessly and in privacy under general anaesthesia. First trimester testing may greatly reduce the emotional and some of the ethical conflicts involved in prenatal diagnosis, especially for high-risk pregnancies.

2.38 One of the main dangers of CVS is that although it appears simple, it requires first-class ultrasound and an expert and well-trained team. Transcervical CVS is most successful and has fewest complications between 9 and 11 weeks of gestation. Transabdominal CVS can be done at any stage of pregnancy provided that the placenta is in an accessible position. As some pregnancies are more suitable for transcervical and some for transabdominal sampling, both techniques are practised at many centres.

2.39 The presence of chorionic villi in the sample taken is confirmed microscopically at the bedside. Usually about 20–50 mg of tissue is needed for a genetic diagnosis. If villi are absent or insufficient the procedure is repeated, but no more than twice on any one occasion. Table 7 shows why the time taken for a diagnosis ranges from 3 days to 3 weeks, depending on the laboratory method involved.

2.40 The rapid spread of CVS testing presents a real challenge in evaluation of risk because the high spontaneous abortion rate in the first trimester of pregnancy, particularly among older women, confuses the evaluation of losses due to the procedure. A WHO-sponsored registry showed a total fetal loss rate of less than 4% in over 10,000 cases reported from 1982 to the end of 1986, while some large expert centres report a total fetal loss rate of 2–3%, estimated to be about 1% in excess of expectation at this stage of pregnancy [20]. There is thus already considerable evidence that CVS is a suitably safe procedure for prenatal diagnosis of high-risk genetic disease. However, more information is needed on its short- and long-term risks [21]. The first report from the randomised controlled comparisons of CVS with amniocentesis, now under way, tend to be reassuring [21A]. These randomised studies also have the important advantage that they generate matched cohorts of children, one exposed to amniocentesis and one to CVS, who can be followed-up and examined in the future should questions arise about possible subtle long-term effects.

Table 8. Inherited diseases that have been diagnosed prenatally using DNA methods

Adrenoleukodystrophy	Myotonic dystrophy
α1-Antitrypsin deficiency	Norrie disease
Congenital adrenal hyperplasia (21-hydroxylase deficiency)	Ornithine transcarbamylase deficiency
X-linked choroideremia	Osteogenesis imperfecta Type IV
X-linked chronic granulomatous disease	Phenylketonuria
Cystic fibrosis	Predisposition to hereditary retinoblastoma
Dihydropteridine reductase deficiency	Adult polycystic kidney disease
Duchenne/Becker muscular dystrophy	Sickle cell disease
Fragile X mental retardation[a]	α-Thalassaemia
Haemophilia A	β-Thalassaemia
Haemophilia B	Tuberose sclerosis
Huntington's chorea	Fetal sexing for X-linked conditions

[a] Linkage data is still contradictory and considerable caution is necessary in this condition.

DNA methods

2.41 Methods for the examination and analysis of DNA are greatly increasing the range and accuracy of prenatal and carrier diagnosis for inherited diseases, and can be used on any tissue at any stage of embryonic development. The principles and methods have been reviewed by Weatherall [22]. The possibility of prenatal diagnosis using DNA techniques usually depends on family studies, and especially analysis of DNA from an affected relative. It is therefore of the utmost importance to ensure that DNA (eg from a blood sample) from individuals with confirmed or even suspected severe inherited diseases is stored, whether the disease concerned can be diagnosed at present or not, for the future benefit of other family members.

2.42 Inherited diseases that have been diagnosed prenatally using DNA methods are listed in Table 8. However, progress is so rapid that the list will lengthen between the writing and publication of this report.

Twin pregnancies

2.43 All multiple pregnancies in which prenatal diagnosis is contemplated should at the onset be referred to expert centres. With modern ultrasound guidance it is usually possible to obtain material from each fetus, but sampling multiple pregnancies requires a very high level of skill. Counselling prior to prenatal diagnosis in twin pregnancies must include the possibility of discordant results in the two fetuses, and of failure to obtain a diagnostic sample from one fetus and the choices that will then have to be made.

2.44 In the past, when results were discordant, couples had to choose between aborting both fetuses even though one was healthy or continuing a pregnancy that was certain to produce one seriously affected infant. Most couples at risk for really severe abnormalities chose to terminate the pregnancy, but there can be few more distressing outcomes. Selective feticide of an affected fetus is now possible in both the second and first trimester of pregnancy [23, 24] and often allows the healthy fetus to come to term. However, such techniques should be attempted only at expert fetal medicine centres.

Timing of prenatal diagnosis

2.45 Prenatal diagnosis should be carried out as early in pregnancy as possible for both pragmatic and moral reasons. Therefore, general practitioners need to be sufficiently aware of the indications to refer at-risk women early in the first trimester, and women should be encouraged to contact their GP early in pregnancy.

2.46 However, even with the best standard of practice it is not possible at present, and probably never will be possible, to complete all prenatal diagnoses before the 20th week of gestation. The reasons for this are as follows:

i Because the organ-systems must be adequately developed before abnormalities can be seen, many congenital malformations cannot be diagnosed before the 19th week of gestation.

ii Some diagnoses (eg of fetal infections and immune deficiencies) depend on measuring products of the fetal immune system. Since the fetal immune system is not always functional before 20 weeks' gestation, these diagnoses cannot be made before this stage.

iii Women are sometimes slow to recognise that they are pregnant, or may present relatively late at the antenatal clinic. The high-risk ones among them will therefore be recognised relatively late.

iv Even with early recognition of risk and early fetal sampling, laboratory diagnosis sometimes takes several weeks.

2.47 As a rule, prenatal diagnosis can be completed by 24 weeks of pregnancy. Pressure to complete all prenatal diagnoses earlier, eg before 20 weeks of pregnancy, would exclude many people who need it and would lead to inequity in service delivery. The pressure generated would also militate against the high standard of practice recommended at the beginning of this chapter and would lead to avoidable errors.

Summary

S2.1 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.

S2.2 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.

S2.3 Existing evidence indicates that with an appropriate obstetric ultrasound service, many major congenital malformations can be detected during the second trimester of pregnancy.

S2.4 Obstetric ultrasound and its applications are important parts of the emerging sub-specialty of fetal medicine. Obstetric ultrasound is an integral part of good obstetric care at all levels, and full information, advice and support, and rapid obstetric back-up must be available on the spot. Expert fetal medicine centres should be associated with clinical genetics centres.

S2.5 If all mothers over 35 were to undergo fetal karyotyping and consequent selective abortion, the birth-rate of infants with severe chromosomal abnormalities would be reduced by only 35%. Better methods of primary screening to predict more accurately the presence of a fetus with Down's syndrome are described in Chapter 3.

S2.6 Developments in DNA analysis are constantly increasing the range and accuracy of prenatal and carrier diagnosis for inherited diseases, and can be used at any stage of embryonic development. Since prenatal diagnosis using DNA often depends on analysing DNA from an affected relative, it is now essential to obtain and store DNA from individuals with major inherited diseases, for the future benefit of other family members.

S2.7 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.

S2.8 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.

CHAPTER 3 Future developments in prenatal diagnosis

Congenital malformations

3.1 Further technical development of obstetric ultrasound will allow improved diagnosis of congenital malformations, and DNA analysis will help to detect the minority of malformations that are inherited. However, the most important future development will be the organised application, supervision and teaching of obstetric ultrasound.

Chromosomal anomalies

3.2 There are two possibilities for improving the detection of fetuses with chromosomal abnormalities—better primary screening for mothers at risk, and better selection of samples for detailed karyotyping.

3.3 Fetuses with Down's syndrome are relatively retarded in their development, and it seems that this is often reflected in lower than average maternal serum AFP and unconjugated oestriol levels, and a higher than average maternal serum human chorionic gonadotrophin level at a given gestational age [25]. Since routine maternal serum AFP screening is already widespread in the UK, in many areas maternal serum AFP results are already integrated with maternal age to identify pregnant women at more than 0.5% risk [26]. Using AFP screening and maternal age alone, it should be possible to identify about 30% of mothers with a Down's syndrome fetus, who could then be offered amniocentesis for definitive diagnosis. However, by combining all four indicators, it may be possible to identify a risk group constituting about 5% of all pregnancies and including over 50% of Down's syndrome fetuses [25]. These findings need to be verified in further studies. The value of integrated maternal serum screening for detecting other chromosomal abnormalities and for detecting chromosomal abnormalities in the first trimester is still uncertain.

3.4 It has also been proposed that if fetal samples could be screened by a simple DNA-based method for abnormalities of chromosome number, more women could be offered amniocentesis or CVS. Only positive samples would then go for full karyotyping. However, the potential of DNA methods for screening for chromosomal abnormalities is unknown at present.

3.5 Methods of karyotyping are needed that are less labour intensive and faster because rapid results are very important to parents. Although there is no definitive simplication of methods for karyotyping, short (48 hours) tissue culture techniques after CVS can greatly reduce the time to diagnosis.

Inherited diseases

3.6 The new methods for human DNA analysis promise radical advances in the prevention of inherited disorders. The chromosomal locations of defective genes that cause about 600 single-gene disorders, including the most important ones, have now been identified. Once the chromosomal location is known, it is only a matter of time to define the gene that carries it, and the nature of the defect or defects causing the disease. This has already happened with Duchenne muscular dystrophy [27]. It is safe to predict that in the next decade specially constructed genetic probes to detect carriers and provide prenatal diagnosis will be available for the commonest inherited diseases. Major simplifications in DNA-based diagnosis, for example the use of the polymerase chain reaction (PCR) [28] to amplify selected sections of DNA, will make DNA diagnosis not only much easier, but also much cheaper. Using this method, population-screening will be possible using single hairs, or cells from mouth washings, thus saving the time and expense of taking blood samples [29]. But however 'user-friendly' DNA methods become, prenatal genetic diagnosis should only be carried out at specialised centres. This is because of the need (a) to know the precise genetic mutation involved; (b) to integrate other genetic and family history information when making a diagnosis; and (c) to provide expert genetic counselling.

3.7 Important advances are now pending for cystic fibrosis, the gene for which is carried by about 5% of the UK population. When a DNA-based method for carrier screening becomes available, the high incidence of carriers implies that screening should be offered to all people prior to reproduction.

3.8 One of the most potentially important future developments would be a reliable DNA marker for fragile-X mental retardation. Present methods of prenatal diagnosis are not entirely reliable and are not able to predict whether females carriers will be affected. A reliable method for detecting carriers and affected fetuses would make a major impact on the incidence of mental retardation.

Obstetric methods

3.9 In the search for an absolutely safe fetal sampling method, one remote possibility would be to extract cells of fetal origin from the maternal circulation for testing. However, recent work in this area has proved disappointing, and it seems more likely that the existing techniques of CVS will be developed to a very high level of safety.

3.10 Another approach to earlier diagnosis is early amniocentesis. With modern ultrasound guidance it is possible to obtain amniotic fluid as early as 10 weeks' gestation; but it cannot be assumed that amniocentesis will be safe and reliable in the first trimester simply because it is so in the second. Early amniocentesis needs rigorous evaluation.

Pre-implantation diagnosis

3.11 Though CVS reduces the stresses of prenatal diagnosis, couples at high genetic risk would really like to know the genetic make-up of the fertilised ovum before implantation. Pre-implantation diagnosis may be possible by obtaining a few cells from the fertilised ovum or early blastocyst *in vitro*, for genetic diagnosis before returning it to the mother [30]. It is already technically possible to karyotype a single cell, and to diagnose single gene defects on the DNA from a very few cells. However, we know little about the resilience of the pre-embryo under such manipulation, and research on human pre-embryos will be necessary to allow this important new development.

Common diseases

3.12 Environmental and genetic components interact in many common disorders of middle life, such as coronary heart disease, diabetes, some malignancies, manic-depressive disorders and schizophrenia. Gene probes that can identify some people at high risk for such disorders are becoming available, but it is not at present expected that people will use prenatal diagnosis for conditions that can be avoided by changes in personal or community lifestyle (as by not smoking, or by working in a pollution-free environment). However, there are already some borderline situations, such as the carrier state for familial hypercholesterolaemia or the emphysema-producing form of α-1 antitrypsin deficiency, or a strong predisposition to diabetes. The possibilities for accurate prediction of risk for multifactorial diseases will increase, and ultimately the attitudes, experience, and wishes of parents and society at large will determine their application for prenatal diagnosis.

Resource implications

3.13 Genetic screening and prenatal diagnosis will become more common as the services are demanded by the population. They enhance the cost effective potential for avoiding serious disability, but existing resources are already overstretched. It is necessary to start planning now to provide adequate resources, to train staff, to improve public and professional education and to involve Primary Health Care teams.

3.14 Consultants in clinical genetics have now been appointed in most NHS Regions, but there remains a shortfall.

3.15 The Royal College of Obstetricians and Gynaecologists has recently recognised the subspeciality of fetal medicine. However, there are so far very few fetal medicine centres in the country, and in most places obstetric ultrasound is still officially a branch of radiology.

3.16 Certainly, there will soon be a substantial and increasing need for clinicians trained in molecular pathology who can understand the implications and potential of molecular genetics; for laboratory scientists who can translate new research techniques and resources quickly to clinical practice; and for technicians who can understand and carry out the assays. The Royal College of Pathologists now has a Diploma in Molecular Genetics but as yet neither the NHS nor the Universities are addressing the financial, service and training implications of the new technology.

Summary

S3.1 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.

S3.2 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.

S3.3 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.

CHAPTER 4 Ethnic minorities

4.1 The numbers of the main ethnic minorities in the UK (in 1984) are summarised in Table 9. Many of these groups have a high incidence of the haemoglobin disorders (thalassaemia and sickle-cell disease), some have a tradition of consanguineous marriage, and many older women are relatively fertile. Partly because of the young age-structure of these groups in England and Wales about 5.5% of the population and 9% of all births are in groups at risk for haemoglobin disorders [31]. The proportion of births gives the relevant figure for planning perinatal services. In most areas of England and Wales more than 1% of births are in these ethnic groups. They are particularly concentrated in industrial conurbations and 'inner city' areas, so that in Greater London and some other cities, more infants are born annually with major haemoglobin disorders (>0.8 per 1,000) than with cystic fibrosis (about 0.5 per 1,000).

4.2 Screening for haemoglobin disorders provides a particularly clear model of the requirements for community genetic counselling. World Health Organisation recommendations for screening for haemoglobin disorders [32] are summarised in Appendix 3. In Southern Europe comprehensive thalassaemia control programmes are organised on these lines. The associated fall in the birth-rate of thalassaemic children (Fig 7, p. 18) shows that a community-based approach can lead to near eradication of this common and severe inherited disease.

4.3 By contrast, in North-West Europe (including the UK), there has been a relatively disappointing reduction in the birth-rate of thalassaemic infants because of the difficulties of establishing population-screening only for disorders that affect diverse and unevenly distributed ethnic minorities.

Table 9. Approximate numbers of ethnic minorities in the UK (1984) with specific genetic risks [66, 67]

Group	Approximate numbers
Afro-Caribbean	746,000
West African	98,000
Indian	872,800
Pakistani	369,300
Bangladeshi	87,150
East African Asian	220,800
Greek and Turkish Cypriot	179,900
Italian	202,000
Chinese	109,000
Arab	63,000
'Mixed'[a]	205,000
Jewish	>350,000
Total	3,503,350
Total UK population	54,084,000
Minorities with specific genetic risks =	6.5%

[a] Descendants of marriages between members of white and other groups or between other groups.

Haemoglobin disorders in the UK

4.4 The thalassaemias are carried by from 3–17% of people of Mediterranean or Asian origin, and the sickle-cell disorders are carried by from 8–25% of people of African or Afro-Caribbean origin. However, because most groups carry both classes of genes, unified social and laboratory strategies are required for diagnosis and prevention of both groups of disorder. It is estimated that about 100 infants with sickle-cell disease are born annually in the UK, and that the birth-rate of infants with thalassaemia major has been reduced from about 60 to less than 30 per year by screening, counselling and prenatal diagnosis.

4.5 People of African, Cypriot and Pakistani origin are at particularly high risk of haemoglobin disorders. Carriers who choose a partner within their own ethnic group have a high (3–20%) chance of forming an at-risk couple, so all carriers should be informed and advised to have their partner tested. Prenatal diagnosis has been most effectively delivered to British Cypriots living in and around London.

4.6 It is cheap and easy to detect healthy carriers of the haemoglobin disorders, and prenatal diagnosis in either the first or the second trimester of pregnancy is freely available at several national centres. Most informed couples at risk for thalassaemia and up to 50% of couples at risk for sickle-cell disease request prenatal diagnosis [33, 34]. Prenatal diagnosis is markedly more acceptable for some groups, such as British Pakistanis, in the first than in the second trimester of pregnancy, so carrier screening and counselling should be provided before pregnancy. Neonatal screening is also recommended for infants with sickle-cell disease [36]. Technical recommendations have now been published by the British Society for Haematology [35].

4.7 The fact that the haemoglobin disorders affect particular ethnic minorities is often thought to be a useful 'primary screen', but in reality 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.

4.8 Because the ethnic groups at risk for haemoglobin disorders are concentrated in industrial cities, with different groups predominating in different places, administrators preferred until very recently to perceive their needs for diagnosis and counselling as a multiplicity of local problems rather than as a regional or national problem. Approaches to the haemoglobin disorders have perforce 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 educational 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.

4.9 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.

Carrier screening

4.10 Antenatal clinic screening, with all the disadvantages listed in para 5.13, is by far the most common approach to detecting carriers of haemoglobin disorders. Pregnant women are rarely informed that they will be tested, the carriers detected are rarely given adequate written or verbal information, and at-risk couples receive

expert counselling only if they are referred to a specialist unit. Cypriots, Afro-Caribbeans and Africans may have access to a community counselling resource, but few Indians, East African Asians, Chinese, Pakistanis or Bangladeshis are aware of haemoglobin disorders, and most have no access to appropriate counselling. Information should be more widely disseminated and screening should be provided before as well as during pregnancy.

4.11 Incidental screening is possible because most haematology laboratories use automated equipment to measure the red cell indices, and so unavoidably and at no additional cost screen every blood sample for the typical microcytosis of thalassaemia. When patients with an African or Afro-Caribbean background present for any surgical reason, including pregnancy, it is also routine for clinical and medico-legal reasons to perform a test for sickle-cell disease. However, the benefit of incidental testing is largely wasted, because the genetic implications are rarely explained to the patient. The opportunity could be better exploited if cards and counselling booklets, now both freely available (Appendix 3), were issued by haematology laboratories at the time of diagnosis.

4.12 Community-based screening and counselling is the ideal and is possible. Haemoglobinopathy centres and a core of specialist ethnic counsellors (similar to the genetics counsellors recommended for prenatal diagnosis centres in Chapter 5) are a necessary resource for reaching the ethnic minorities. In London, the Brent sickle-cell centre provides training for haemoglobinopathy counsellors working in primary health care and in several cities sickle-cell centres associated with existing specialist haemoglobinopathy services are being set up (see Appendix 4).

4.13 There are good reasons for counselling of ethnic minorities to be carried out by members of the communities involved. First, the ideal specialist ethnic counsellors should be people 'of the two cultures' [37], ie belonging to an ethnic minority, but educated within the majority society, so that they can be a bridge for communication. Second, ethnic minorities cannot be targeted through the schools and mass-media. They must be contacted through their own community groups and information resources, and this is difficult for those outside the community. Third, the delicate matter of ethnically-determined susceptibility to disease does not cause problems when counselling is done 'within' the group. Finally, the fact that members of ethnic minorities hold responsible posts in the medical team sets at rest any anxiety about racist overtones.

4.14 Special ethnic counselling is needed for other genetic and congenital disorders besides the haemoglobin disorders, and certainly it will prove more cost-effective to provide it than not to do so.

Tay-Sachs disease

4.15 Tay-Sachs disease was the first recessively-inherited disorder to be prevented at the community level by carrier screening and the offer of prenatal diagnosis [38]. Between 3 and 5% of Ashkenazi Jewish populations and about 0.5% of non-Jewish populations carry the gene. Carriers can be detected reliably by screening, and prenatal diagnosis is accurate. Programmes for population-screening for Tay-Sachs disease have been established in North America, and there is evidence of a more than 70% fall in affected births in the United States between 1970 and 1980, though the contribution of out-breeding is uncertain [39]. There has been little provision for screening for Tay-Sachs disease in the UK, ostensibly because the disease is so uncommon.* However, this view overlooks the relatively large size of the population at risk, the high proportion of carriers in some groups, and the value to individuals and their descendants of knowing their carrier status.

* Screening for Tay-Sachs carrier status is available at the South-East Thames Regional Genetics Centre, Guy's Hospital, London SE1 9RT

Consanguinity

4.16 British Pakistanis are in particular need of a genetics service because of their strong tradition of consanguineous marriage. The rate of first-cousin marriage among young British Pakistanis is 55%, compared with about 32% in Pakistan [40]. It would be inappropriate to try to interfere with this marriage custom, which is socially beneficial for women in the cultures where it is practised [41]. It does, however, have social and service implications.

4.17 Consanguinity increases the chance that two carriers of the same recessively-inherited condition will mate, and so it increases the birth-rate of children with recessively-inherited diseases, but it has no effect on dominant or X-linked disorders. There is probably a small increased risk of many multifactorial abnormalities, but even very common consanguineous marriage has a relatively small effect on the incidence of serious congenital disorders. Untrained health workers can inflict suffering by incorrectly telling parents that their consanguinity is the cause of their child's illness.

4.18 On the other hand, traditional consanguineous marriage increases the possibilities for offering genetic counselling, because most large, highly consanguineous families actually transmitting a lethal recessive gene ultimately identify themselves by the birth of a homozygote. This child in turn then acts as a marker for an extended family cluster at very high risk. The appropriate strategy is to investigate and counsel the extended families of patients with serious recessively-inherited disorders, and to encourage young related couples to attend for genetic counselling before starting their family. However, the problems of communication must first be solved.

4.19 For effective counselling, the woman must understand what is said, and must be able to ask questions. At present this means that British Pakistanis should be counselled by a female (ideally a Muslim) in the appropriate language, and at home if necessary. When these conditions are fulfilled, inheritance of disease can be understood, and first-trimester prenatal diagnosis is often requested [46]. A serious effort should be made to develop an appropriate approach to genetic counselling for all ethnic minorities.

Genetic risks related to maternal age in ethnic minorities

4.20 Some ethnic groups still have large families where women continue childbearing almost to the end of their fertile life. At present, many such older mothers are not being appropriately counselled because it is assumed that they will not want karyotyping and because adequate provision is not made to overcome language difficulties.

Summary

S4.1 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. However, because there is still no national policy, and screening and counselling are not regularly provided, the fall in the birth-rate of affected children has been less than in Southern European countries.

S4.2 The requirements for an adequate screening progamme 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.

S4.3 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.

S4.4 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.

CHAPTER 5 Genetic counselling and education

5.1 Couples at risk for bearing an abnormal child, and pregnant women who discover they are carrying an abnormal fetus, have to choose among the options in Table 10 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 [43].

5.2 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.

5.3 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.

Specialist genetic counselling

5.4 Most couples at recognised high risk are in fact counselled by a clinical geneticist or a similar, highly-qualified specialist [44]. The main requirements for genetic counselling are summarised in Table 11.

5.5 One counselling session is not enough to transmit all the necessary information; back-up information is required in the form of leaflets and booklets as well as the opportunity of contacting a support association where an appropriate one exists (see Appendix 2). A couple's decision on whether to proceed with prenatal diagnosis, or indeed whether to embark on a pregnancy at all, may depend on how the information is transmitted.

Table 10. Possibilities open to carriers of an inherited disease to avoid having affected children

Time at which risk is first discovered	Possible action
Before marriage (uncommon)	1. Remain single (uncommon). 2. Avoid selecting another carrier as partner (very uncommon). 3. Select a partner in the usual way (the commonest choice).
After marriage (more common)	4. Remain childless (common only for severe disease when prenatal diagnosis is impossible). 5. 'Take the chance' (common for less severe diseases and when prenatal diagnosis is impossible). 6. Use prenatal diagnosis (very common). 7. Use AID[a] or other form of 'assisted reproduction' (very uncommon). 8. Separate and find another partner (extremely uncommon).
After birth of an affected child (most common)	*Options 4–8 above for further reproduction, plus:* 9. Accept infant and treatment (usual). 10. Accept infant, but reject treatment (occasional). 11. Reject infant (may happen).

[a] AID = Artificial insemination by donor.

Table 11. Main requirements for genetic counselling

1. **A correct diagnosis of the propositus** (the family member presenting with the disorder, if there is one).

2. **Estimation of genetic risk**. This requires preparation of a family tree and laboratory and other investigations, often of other family members.

3. **Communication of genetic risks and the options for avoiding them**.
   a The nature and prognosis of the disorder involved, and treatment available.
   b The chances of an affected infant in each pregnancy and the reasons for the risk given.
   c Possible ways to avoid the birth of an affected child: techniques, problems, risk of error or complications. Methods for termination of pregnancy.

4. **Assisting the person or couple** to assimilate and evaluate this information and reach a decision appropriate for themselves.

5. **Accessibility for long-term contact**: women or couples at risk need counselling and support during and after every pregnancy.

5.6 The genetic counsellor must be a good communicator, prepared to share professional knowledge fully and on an equal footing, and able to simplify complex and unfamiliar concepts in the presence of serious anxiety and sometimes even of disagreement between partners. Time and a calm atmosphere are essential for people to consider and to ask all the questions they want to, in order to reach a satisfactory decision. Time costs money, but in view of the profound consequences for the family and the expensive technology involved in prenatal diagnosis, it is illogical, and may do more harm than good, to embark on testing unless adequate time can be set aside for satisfactory genetic counselling.

5.7 Clinical geneticists and specialists in particular areas such as the haemoglobin disorders already work with associated counsellors. These counsellors, some with a nursing and others with a non-medical training, are selected for their suitability in assisting with the less specialised area of counselling. There is an urgent need to decide on the definition of associated genetic counsellors, and to develop a recognised training and career structure. In North America, 'genetics associates' already have a qualifying examination, job-description and career structure. In the UK, an Association of Genetics Nurses and Social Workers has recently been founded, with the objective of addressing some of these issues.

Genetic counselling and reproductive behaviour

5.8 No study reported to date has shown that genetic counselling alters marriage patterns. In Cyprus, where premarital screening for thalassaemia is mandatory, 98% of prospective couples who find they are both carriers still proceed to marry.

5.9 However, there is plenty of evidence that genetic counselling affects reproductive behaviour. For instance, among couples counselled when prenatal diagnosis is not available, more than half those at high (more than 10%) risk of producing a child with a serious abnormality and up to one-third of those at lower risk (2–10%) stop reproducing [43, 46]. Before prenatal diagnosis was available, couples at risk for thalassaemia behaved in the same way, but now 98% of at-risk couples who are offered prenatal diagnosis use it to achieve a healthy family [33].

5.10 Prenatal diagnosis is the approach chosen by most informed couples at risk for severe genetic disease. Divorce is not a common solution, and artificial insemination by donor is not popular.

Timing of genetic counselling

5.11 Whenever possible, genetic risks should be known, and counselling and the necessary investigations carried out before a pregnancy occurs so that testing can be offered as a planned procedure. When genetic counselling for prenatal diagnosis is undertaken during pregnancy, it should be carried out as early as possible and should be accompanied by full information.

5.12 Counselling should be given immediately before the diagnostic procedure to act as a 'safety net' for those who book late or whose obstetricians do not recognise the need for early genetic counselling. It also gives an opportunity for those already counselled to ask further questions.

5.13 There are numerous disadvantages in waiting until a woman reaches the antenatal clinic to start the process of testing and counselling:

i the option of whether or not to undertake a pregnancy at all is no longer open;

ii the natural emotional involvement makes choice unnecessarily difficult and painful;

iii some women present too late in pregnancy for prenatal diagnosis to be possible;

iv many carrier tests are more difficult to interpret during pregnancy;

v there is no time to correct clinical or laboratory errors;

vi at-risk couples are usually identified too late for first-trimester prenatal diagnosis;

vii the inevitable existence of a deadline for prenatal tests, particularly tight for CVS, often results in a hurried decision that might have been different had more careful reflection been possible;

viii the level of awareness of the obstetrician is not always what it might be, and rapid turnover of antenatal clinic staff makes it difficult to sustain a consistent policy.

5.14 Screening and counselling for inherited disorders need to be offered at the preconception stage, ie these services should become part of family planning. This is starting to happen, but far more awareness and education will be needed before it becomes routine.

5.15 In order that couples do not remain childless needlessly, it is essential for counsellors to keep in touch with them and inform them of new developments. Many couples at high risk who had decided against having children, have since undertaken a pregnancy because they were informed about chorionic villus sampling and the increased possibility of specific diagnosis using DNA testing.

Support during and after termination of pregnancy

5.16 Abortion for fetal abnormality should be carried out in a unit with specially-trained staff. Most prenatal diagnosis is still done at 16 to 20 weeks' gestation, and the decision to terminate a pregnancy because of fetal abnormality is usually made at about 20 weeks' gestation. Mid-trimester abortion of a wanted pregnancy is psychologically painful and distressing both for the mother and for the attendant staff. Termination of pregnancy after CVS, providing the diagnosis is reached before 13 weeks' gestation, can be done quickly and painlessly under general anaesthesia by the standard suction method, often before others realise that the woman was pregnant. Abortion may now also be induced by medical means in the first trimester [47]. Though earlier abortion is an important advance for the parents, abortion of a wanted pregnancy is distressing at any stage.

5.17 Until recently, the psychological implications of abortion for fetal abnormality were sadly neglected by comparison with the technical aspects of prenatal diagnosis. Mothers undergoing this procedure at any stage of pregnancy require constant expert and sensitive physical care, and psychological support and bereavement counselling should be readily available to them. Mid-trimester genetic abortion should be carried out in a labour ward under the care of trained midwives, rather than in a general gynaecology ward. The parents often benefit from seeing and handling the fetus, which to them is already their child, and many are glad to have a photograph. Lactation should be medically suppressed. The parents should also be seen sometime later for a follow-up discussion, and to be told when they can start another pregnancy, while information on the recurrence risk needs to be reinforced. They may also benefit from being put in touch with a support association.*

5.18 When first-trimester prenatal diagnosis was possible but the couple were seen too late to benefit from it, they should be informed that in the event of a future pregnancy, CVS may be possible. Family studies should be initiated, and some placental material from the affected abortus should be stored because it often provides the key to successful family studies. The couple should be given the telephone number of the diagnostic centre and in order to avoid a second mid-trimester abortion, told whom to contact immediately a new pregnancy is suspected.

Information and genetic counselling at the community level

5.19 Despite their relative simplicity, the community-based mass-screening services listed in Fig 4 have the same implications and require the same ethical and clinical standards of information and counselling as the more specialised services. Every pregnant woman is already involved in screening for fetal abnormalities, and the need for community information and genetic counselling is therefore already large, and will increase further when screening for cystic fibrosis becomes available. Education about reproductive risk should begin in schools, and be reinforced in primary health care prior to conception, particularly in family planning clinics.

Genetic counselling and primary health care

5.20 There is a need to integrate community genetic counselling into primary health care, but many practising doctors have received little if any training in genetics. A recent survey showed that two British medical schools appear to have no separate pre-clinical teaching of genetics, and 13 had no separate teaching of clinical genetics [48]. Counselling skills are included in the training of social workers and psychologists but not of doctors. This means that general practitioners, who may be best suited to counselling because of their contact with families, are hampered by lack of training as well as of time.

5.21 Medical genetics should now be included in the core curriculum of doctors and nurses, basic genetic counselling techniques should be systematically taught to family practitioners, midwives, nurses, health visitors and family planning doctors, and they should be provided with time-saving educational aids. Maternal and child health workers such as health visitors, midwives and nurses need to be recruited into community genetic counselling.

Screening in general practice

5.22 Information and screening that can be provided before pregnancy (carrier testing) or as soon as a pregnancy is notified (maternal age) should be initiated at the level of primary health care, particularly in the family-planning clinic. Probably the persons responsible for ensuring that these matters are raised with women should be health visitors, midwives and nurses working with general practitioners. With the increasing range of diagnosable conditions, it is important for the GP to

* For example, SATFA (Support After Termination for Fetal Abnormality) provides literature and the opportunity for contact with other women who have had the same experience. See (Appendix 2) for contact address.

keep in touch with the local clinical genetics service to know what is available for the practice patients.

Antenatal clinic screening

5.23 The integration of prenatal screening into general obstetric care works well where an obstetrician and his or her staff are interested and well informed, and have adequate time for counselling. But there are many problems. For instance, women are quickly informed of an abnormal test result whereas there are often long delays in communicating normal test results, thus generating unnecessary anxiety. In a mistaken attempt to justify the obstetric risk and expense involved in prenatal testing, women are often asked for an undertaking to terminate the pregnancy should the fetus prove to be affected. Insensitive handling during termination of pregnancy is common. If pregnancy is to be terminated, the need for support and for subsequent contact is the same as that required for high-risk conditions. It is perhaps not surprising that there is some public anxiety about the medical application of genetic knowledge.

5.24 In order to raise the general level of community genetics services to the standards set by clinical geneticists, genetic screening and counselling should be identified as a distinct part of antenatal care, and specific staff should be trained to deliver the service. In every obstetric unit there should be at least one midwife trained in the principles of genetic counselling, the clinical features of the disorders that are screened for, and the support of women with an abnormal pregnancy, including care during and after miscarriage or abortion. These recommendations do not necessarily mean that a new member of staff should be appointed, but these tasks should be made a priority for a specific trained member of staff.

5.25 In every specialist centre providing tertiary ultrasound scanning or fetal sampling procedures, there should be a specially trained nurse-counsellor, working with the clinical geneticist and obstetrician. The trained counsellors working with clinical geneticists need to develop a supporting relationship with nurse- or midwife-counsellors in obstetric units and in primary health care, and so build up a community genetic counselling network.

Dissemination of information

5.26 Despite the importance of information on screening and prenatal diagnosis, the amount that is generally available is pathetically small. Present forms of population screening such as routine obstetric ultrasound, testing for infectious diseases, maternal serum AFP screening, screening for haemoglobin disorders, or testing the neonate for phenylketonuria are usually not explained or are explained inadequately to the mother who often remains ignorant of the implications of these tests. Apart from the Health Education Authority's excellent *Pregnancy Book* [49], such information as exists for pregnant women has been developed on a district basis, hospital by hospital. As a result its extent, quality and comprehensibility are uneven, and the duplication of effort involved is wasteful. Most existing information leaflets about specific disorders have been produced by voluntary support associations. However, the resources of these associations are usually very limited and their primary concern is with the well-being of affected families. They cannot reasonably be expected to provide large quantities of free educational materials to the standard required to meet the national need.

5.27 Written information should be freely available both for the public and for health workers, and would also provide a source of correct information for schools and the rest of the community. A wide range of written educational aids about genetic screening and prenatal diagnosis is necessary, and specific messages should be directed to different sections of the community. In addition to some general information about reproductive risks, specific material is needed for many individual disorders.

5.28 The writing of educational material is a specialised and time-consuming task that requires co-operation between geneticists, experts in health education and representative of the support associations. A national information resource is needed to produce, stock and issue genetic educational materials. The relatively small investment would be exceptionally cost-effective because material generated by a single group can be used nationally and even internationally. At least one specialist in health education is required, working from a national genetic information centre at which educational materials can be collected and reproduced, and from which they can be easily obtained.

Summary

S5.1 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.

S5.2 Most individuals and couples who are known to be at high risk are counselled by specialists according to recognised ethical and professional principles. Information and counselling according to the same principles should be part of the community-based population-screening services for sporadic and recessively-inherited disorders, but at present these requirements are rarely fulfilled. To improve the quality and accessibility of genetic counselling and education, we make the following recommendations.

1. Medical genetics should be part of the core educational curriculum of doctors and nurses.
2. In every obstetric unit there should be at least one midwife/counsellor specially trained to support women through screening and prenatal diagnosis, and during and after termination of pregnancy, should that option be chosen.
3. In every specialist centre there should be at least one genetic counsellor, specially trained to counsel couples for prenatal diagnosis. It is important to define a career structure for such non-medical genetic counsellors.
4. Maternal and child health workers such as health visitors, midwives and nurses need to be recruited into community genetic counselling.
5. Basic genetic counselling techniques should be taught routinely to family practitioners, midwives, nurses, health visitors and family planning practitioners.
6. Simple and appropriate genetic information should be incorporated into the school curriculum at a point when it can reach every child.
7. Written information should be freely available both for the public and for health-workers.
8. A national genetic information centre is needed, with at least one suitably-supported specialist in health education, to develop, produce, collect and supply community educational materials.

CHAPTER 6 Evaluation of prenatal diagnosis

Audit

6.1 Regular audit and cost-benefit analysis are basic tools for evaluating medical services.

6.2 The aim of audit is to define a programme and its objectives and to monitor the approach of the programme towards the target. Both the effectiveness and the costs (tangible and intangible) of the programme need to be monitored. The regular reports of the outcome of neonatal screening for phenylketonuria and congenital hypothyroidism [50, 51] are good examples of how a genetic screening service can be monitored.

6.3 Table 12 summarises the information required for monitoring prenatal diagnosis and its present availability. Much of the necessary information exists but is not brought together on a regional or national basis. Terminations of pregnancy for fetal abnormality, and infants born with 'birth defects' are officially notifiable, but there is reason to suspect considerable under-reporting. The level of diagnosis of birth-defects varies considerably from place to place [52], and many congenital malformations and inherited diseases present weeks or months after birth. There are some systematic regional registers of specific inherited diseases. Otherwise, epidemiological information is collected only sporadically by interested doctors. Existing information on the impact of prenatal diagnostic services is given below; its inadequacy shows that national organisation is required to carry out this important work.

Table 12. Availability of information required for monitoring prenatal diagnosis programmes

Type of information required	Information available				
	Rubella	Malformations		Chromosomal karyotyping	Inherited diseases
		msAFP[c]	Ultrasound		
Epidemiology of condition	+	+	+	+	+
Patient register	+	–	–	–	Some
Number of:					
Prenatal diagnoses per year	–	–	–	+[a]	+[a]
Affected fetuses diagnosed	–	–	–	+[a]	+[a]
Terminations of pregnancy[b]	OPCS	OPCS	OPCS	OPCS	OPCS
False +ve and −ve diagnoses	–	–	–	+[a]	+[a]
Replacement pregnancies	–	–	–	–	–
Affected infants born	+	–	–	–	Some

[a] Not used for monitoring on a national basis.
[b] The number of and reasons for abortions are in theory reported to the DHSS and the information is available through the Office of Population Censuses and Surveys (OPCS), but there is reason to doubt the completeness of reporting of abortions for fetal abnormality.
[c] msAFP–maternal serum alphafetoprotein.

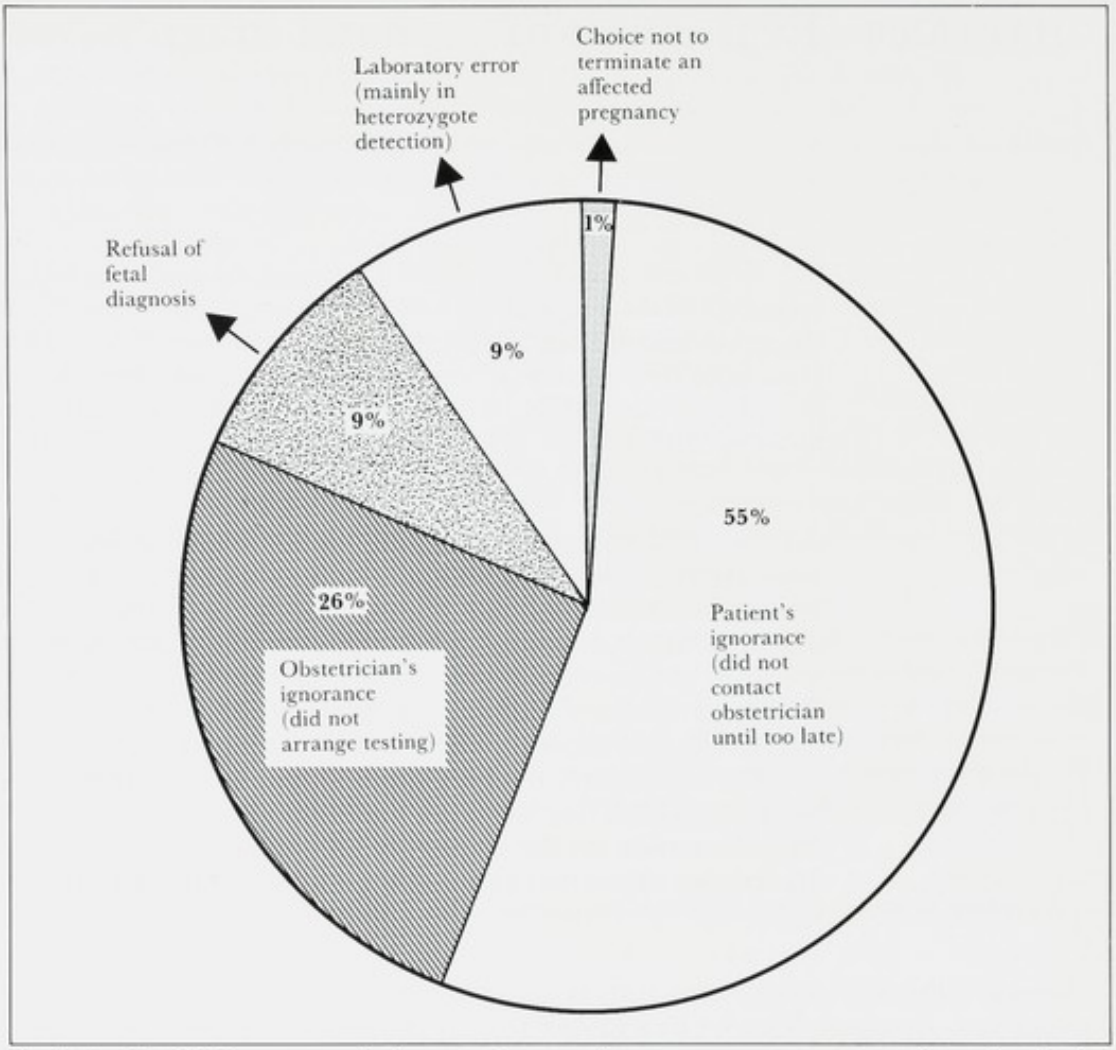


Fig 8. In the Mediterranean thalassaemia control programmes, one aspect of monitoring is to follow up residual births of affected children, to identify the cause. The pooled results from three programmes, including follow-up of 193 thalassaemic infants [32], show that the main reason for residual births of infants with this severe condition is lack of information.

Pregnancy screening for Rhesus blood group and rubella infection

6.4 The annual number of stillbirths and neonatal deaths due to rhesus haemolytic disease of the new-born has fallen by over 95% since 1950 [53]. The national figures are monitored regularly, using figures from the OPCS.

6.5 Before termination of pregnancy and rubella immunisation were available, at least 250 babies with congenital rubella syndromes were born annually, and when an epidemic occurred there were many more. Since 1970, the annual number of affected infants born has fallen from 89 to 19, and is expected to fall further with the introduction of the measles, mumps and rubella immunisation programme. The national rubella surveillance programme monitors births of affected infants in order to evaluate the effectiveness of prevention strategies [54].

Congenital malformations

6.6 There is extremely little information on the present effect of routine ultrasound scanning on the birth-incidence of malformed infants, but a research study is presently under way. The value of ultrasound screening in late pregnancy for improved treatment of congenital malformations in newborns has not yet been assessed.

6.7 It is thought that about 70% of all pregnant women undergo maternal serum AFP screening, ranging from none in some areas to nearly 100% in many others.

Evaluation of the result of this screening is difficult because of a simultaneous pronounced fall in the background incidence of neural tube defects. In areas where screening is routine, the birth incidence of infants with neural tube defects has fallen by 60 to 70%. Over half of this fall is considered to be due to prenatal diagnosis and selective termination of pregnancy [55].

Prevention of chromosomal disorders

6.8 The total number of births of children with Down's syndrome are not being monitored, even though the statistics could be compiled relatively easily from the records of the clinical cytogeneticists. Information on the number and outcome of prenatal cytogenetic diagnoses is collected regularly by the Association of Clinical Cytogeneticists [56].

6.9 Studies from the UK and other European countries agree in showing that 60–85% of informed women at risk request amniocentesis [57, 58]. This figure sets the target for prenatal tests, but in 1984 only 27% of 35–39-year-old mothers and only 44% of those over 40 actually had a prenatal diagnosis. The proportion differed considerably between regions, reflecting differences in the adequacy of the cytogenetics and counselling services [56]. It can be calculated that karyotyping in pregnancy has probably reduced the birth incidence of Down's syndrome by less than 15%. The number of amniocenteses is rising quite rapidly, and diagnosis by CVS must now be added, but the total number of those tested still falls far short of the target of around 70%. In view of the new possibilities for screening for chromosomal abnormality, the establishment of an improved monitoring system is urgently required.

Prevention of inherited disorders

6.10 Data collected at centres dealing with specific genetic diseases are not aggregated on a national or systematic basis. The results of monitoring some of the Mediterranean thalassaemia control programmes, illustrated in Fig 7 (p. 18) and Fig 8 shows what can be achieved. As the possibilities for prevention are increasing particularly rapidly in this area, information on such avoidable inherited diseases should be collected nationally.

Cost-benefit analysis

6.11 The aim of cost-benefit analysis is to find ways to describe the financial and non-financial costs and benefits of a service, to develop ways of evaluating services, and to determine the most efficient ways to deliver them.

6.12 There are few published analyses even of financial costs to the NHS of treating specific congenital or hereditary disorders, and in most cases the real cost far exceeds the cost to the NHS. Figure 9, which summarises lifetime costs for 100 Down's syndrome patients by comparison with average normal individuals [59], indicates the heavy burden of caring for chronic mental disability that usually falls on the family. When treatment is effective, relatively more costs fall to the health service, and these are easier to calculate. Table 13 illustrates the approximate NHS treatment costs of some inherited diseases. Costs to the family and the cost to society of premature death are not included.

6.13 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 13 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.

6.14 The literature contains few useful economic appraisals of prenatal diagnosis services [59, 60]. A full cost-benefit analysis can be difficult and time-consuming

[61], so usually, as a short-cut, only financial costs and benefits have been considered. This type of analysis applied to prenatal diagnosis, as shown in Fig 10, generally indicates that it actually saves money, in the sense that it averts cost increases which would otherwise be inevitable. However, this limited approach leads to serious misunderstandings by treating patient management and prenatal diagnosis as alternatives, when in fact they are complementary approaches to the control of genetic disease. It is therefore appropriate to make some recommendations about the nature of the costs and benefits that should be taken into account in future studies of prenatal diagnosis.

Costs and benefits of prenatal diagnosis

6.15 The medical and social costs and benefits of a comprehensive screening and prenatal diagnosis programme for an inherited disease, when prospective carrier detection is possible, are shown in Fig 11. There are many measurable non-financial (intangible) costs and benefits which reflect the true objective of the service. Outstanding benefits are an informed population, informed choice for couples at risk, the birth of healthy infants or of accepted affected ones, and the replacement of aborted affected fetuses with healthy infants. The financial cost of each of these items of service to the NHS in the UK in 1987 for the populations at risk for thalassaemia is included in the Figure as an illustration. The most important conclusions are:

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.

Summary

S6.1 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.

S6.2 Some data is 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.

S6.3 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. More realistic studies are needed.

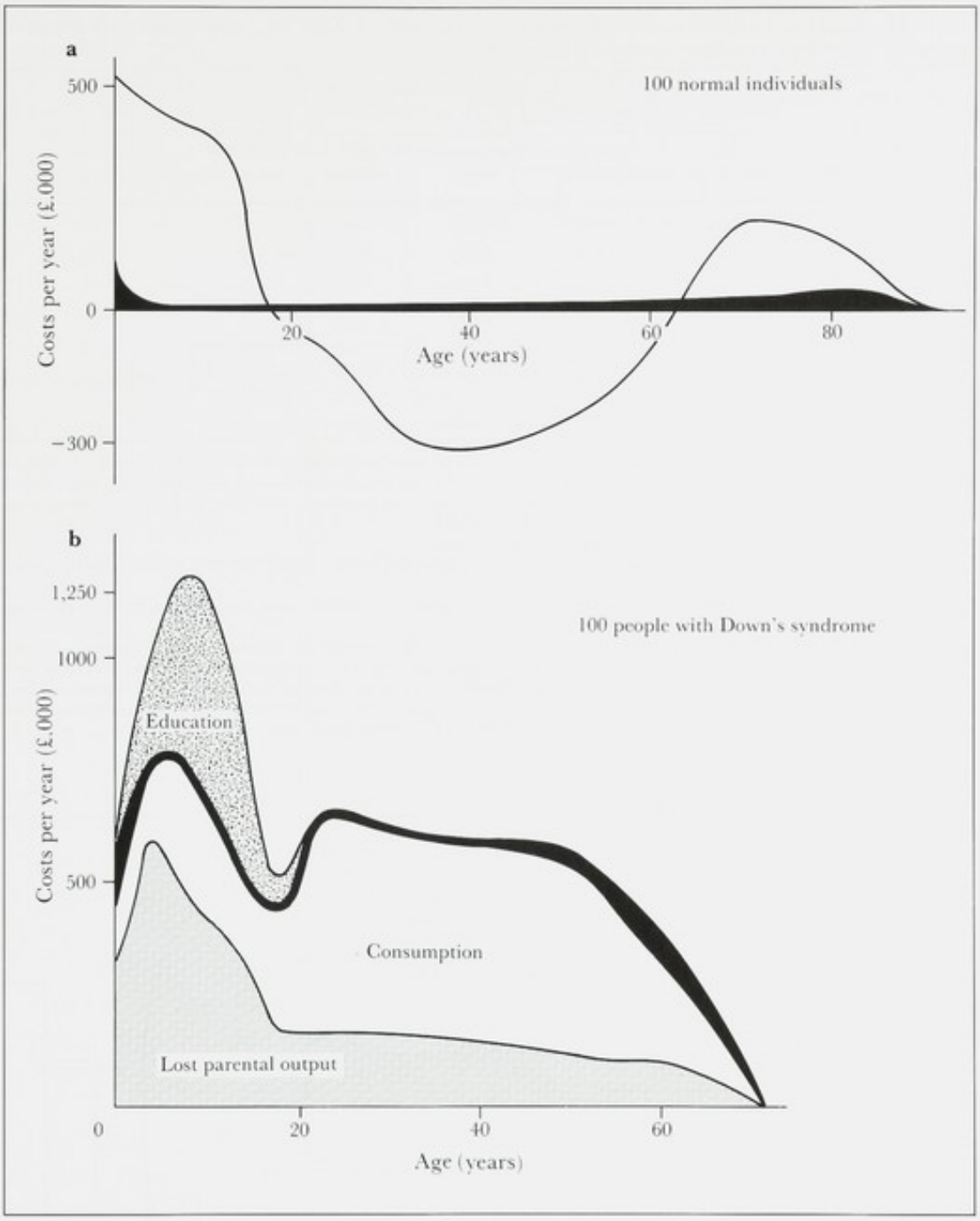


Fig 9. *Summary of an attempted comprehensive analysis of the financial costs for people with Down's syndrome by comparison with normals* [59]. The costs are approximately broken down into those that fall on society in different ways, and on the family. Financial costs to the Health Service, including costs of adoption and fostering, are shown in black.

a Summary of average life-time costs and contribution to society of 100 individuals without Down's syndrome. Costs both to society and to the health service, shown above the line are greatest during childhood and the educational period, and after retirement. However, they are more than offset by net input during adult life, shown in the lower part of the diagram as negative costs.

b Summary of average life-time costs to society of 100 individuals with Down's syndrome. Costs in childhood exceed those of non-Down's children, and costs to the family, society and the NHS continue throughout the relatively shortened life. They are not offset by input. Costs to the NHS, though considerably higher than for non-Down's individuals, represent a very small proportion of the total burden of care. The Figure shows that it is unrealistic to evaluate costs and benefits of prenatal diagnosis services only in terms of financial costs to the health and social services, and underlines the extent of the service that prenatal diagnosis provides to the family and to society as a whole.

Table 13. 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		Approximate cost per year to NHS		Effectiveness score for treatment[a]	Minimum expected survival with treatment (year)	Expected final number of patients on treatment[h]	Multiples of present number
	Born per year	Now on treatment	Per patient (££s)	All (£ millions)				
Cystic fibrosis[b]	360	6,000	4–6,000	36	3	25	12,000	×2
Sickle cell disease[c]	>100	4,000	2,500	10.0	2	?60	6,000	×1.5
Phenylketonuria[d]	75	1,280	2,080	2.7	1	70	5,250	×4
Haemophilia[e]	>70	>4,300	7,800	33.5	1	70	>4,900	×1.5
Thalassaemia[f]	60	360	5,500	2.0	3	35	1,800	×3
Huntington's chorea[g]	50	800	1,560	1.3	5	16 from diagnosis	800	
TOTAL	815	16,740	5,100	≈86	—	—	30,850	×1.9

[a] '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.
[b] Figures from Office of Health Economics, 1986; *Cystic Fibrosis* [68].
[c] Figures courtesy of Dr B. Wonke. Refer to complete costs of treatment.
[d] Figures courtesy of Dr I. Smith. Only the cost of diet per year for first ten years is included. No costs are included for outpatient visits or for resumption of diet by pregnant adults.
[e] Figures courtesy of Dr R. Mibashan. Costs of outpatient visits not included. Account has not been taken of the major short and long-term implications of the infection of so many patients with HIV virus.
[f] Figures courtesy of Dr B. Wonke. Refer to hospital treatment only. There are also considerable costs for treatment in the community.
[g] Figures courtesy of Professor P. Harper. Refer to costs of hospital care only. Community and voluntary services costs are not included.
[h] In conditions where improved management has increased survival, the number of births of affected patients at present exceeds the number of deaths. Total patient numbers are therefore increasing. The increase will stop when all patients achieve maximum survival and the number of deaths balances the number of births. The time at which this equilibrium will be reached differs in different conditions.

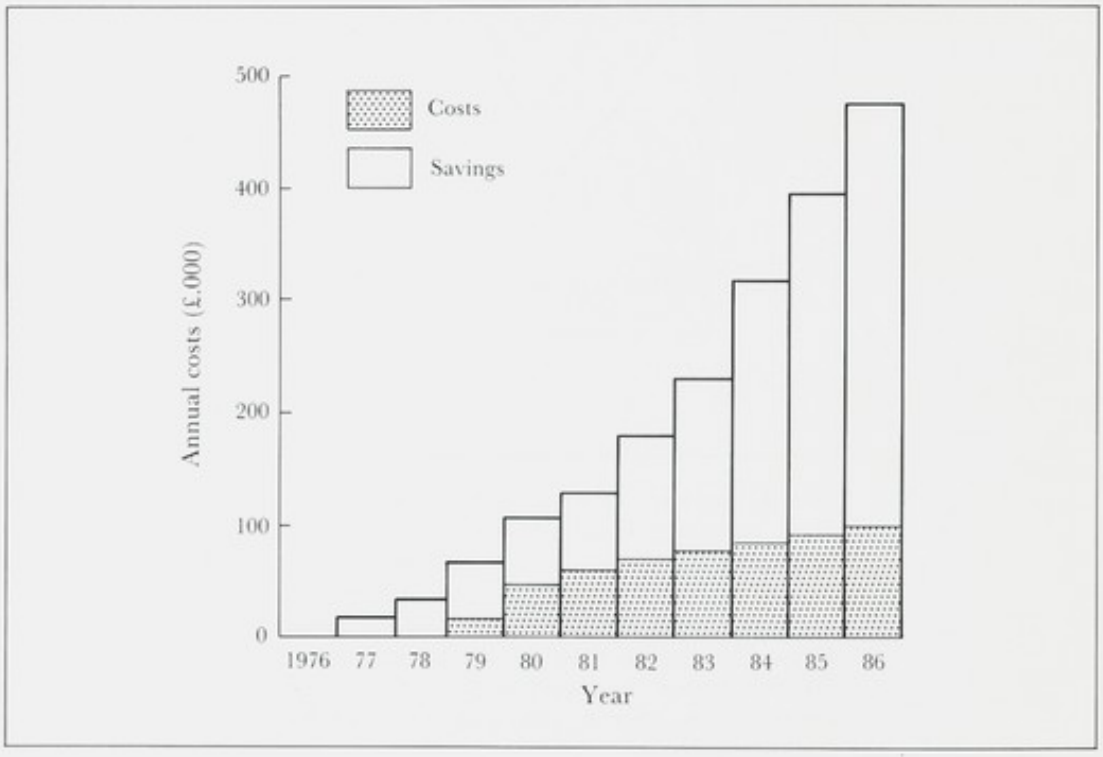


Fig 10. Actual financial costs and savings resulting from a prenatal diagnosis service for thalassaemia in the UK [65]. The columns show the cost of treatment saved each year by avoiding the birth of thalassaemic children. The shaded area shows the cost to the NHS of running the service; this was covered from research funds up to 1978. The annual savings rise steadily with the cumulative number of births avoided. The cost of the service also rises, to allow for development of improved methods such as DNA technology and chorionic villus sampling for first-trimester prenatal diagnosis, but the latter rise is negligible compared to the 'savings'.

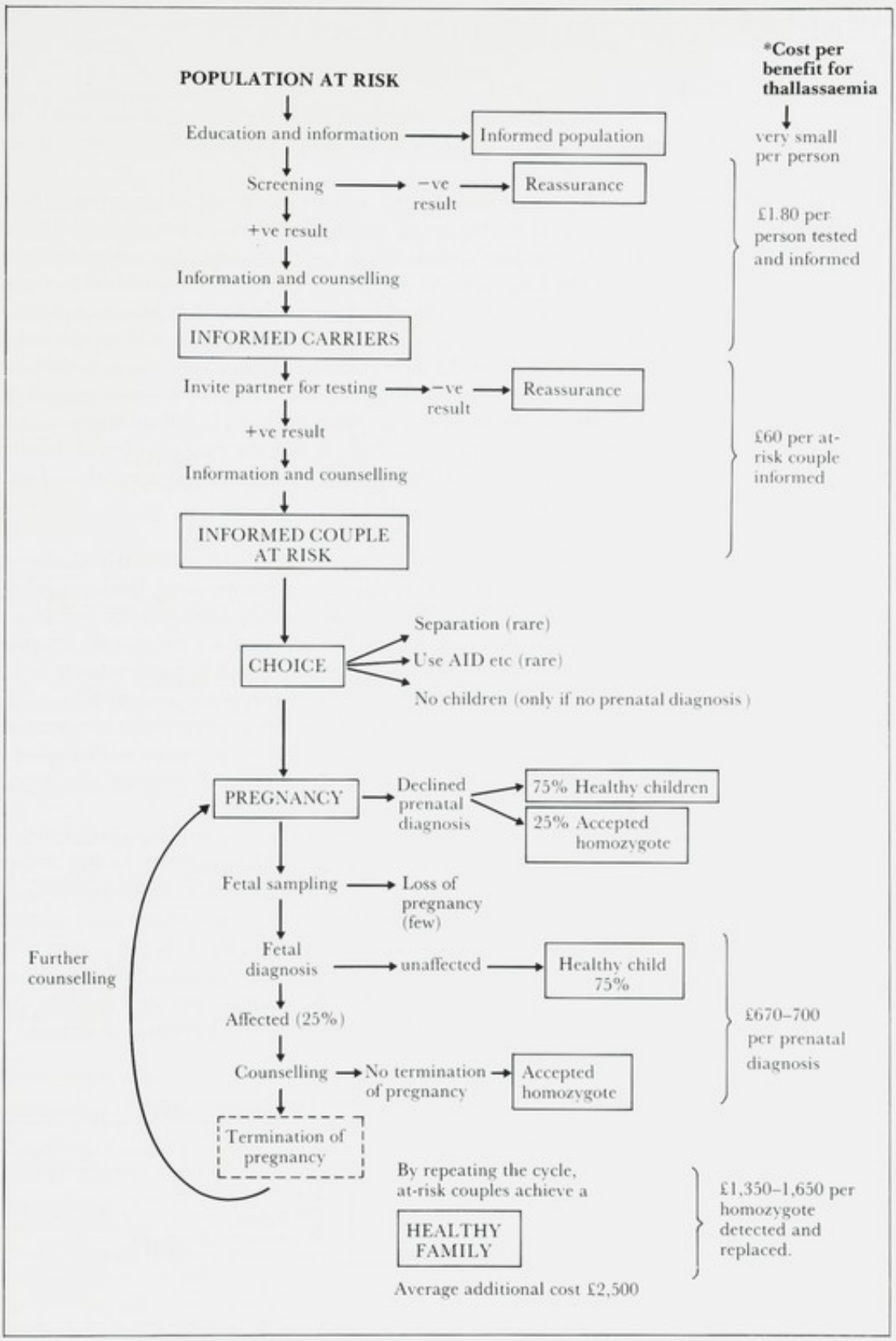


Fig 11. Flow-chart summarising some of the real costs and benefits of screening for prenatal diagnosis. Benefits are framed. It should be noted that the birth of an accepted affected child to informed parents is counted as a benefit. The main cost, termination of pregnancy, is in a dashed frame. For the sake of clarity some costs, such as the consequences of false positive and false negative results in screening tests, have been omitted. *The average financial cost per person for each step is indicated in the right-hand column.

CHAPTER 7 Organisation of services

7.1 The principles of diagnosis and counselling, developed by the clinical geneticists and described in Chapter 5, should be extended to genetics services in the community.

Specialist clinical genetics

7.2 The interdisciplinary nature of medical genetics, the need for integrated services, and the training requirements for clinical geneticists are well recognised [62]. There is now a national network of clinical geneticists, with one or more units in most NHS Regions (Appendix 1). Services for particular disorders (for example of the eyes, ears, gut or blood) are usually located at corresponding specialist centres. In essence, the services run by clinical geneticists fit within the existing medical framework, and to the extent that patients are referred, they work well because the essential components summarised in Table 14 are recognised, taught, and delivered to a high standard. Many families are seen by clinical geneticists through referral by one of the routes shown in Fig 12, but the rate of referral does not match the service need, indicated in Table 1 (p. 2). Self-referral is a valid and quite common mode of access to the clinical geneticst.

7.3 Almost all clinical genetics units are medically under-staffed [62], and the number of trained staff available for counselling, liaison and outreach is extremely small. Although some centres with integrated genetic services exist, they are in the minority, and in many cases the services are extremely fragmented. Many centres are separated from diagnostic facilities and in particular may have limited access to DNA analysis. Although the need for close association of obstetric and genetic expertise has been shown clearly in this report, there is not at present a single centre in the UK that combines expert clinical genetics with expert fetal medicine. This contrasts with the situation in many other European countries.

Genetics services in the community

7.4 The necessary components of the community prenatal diagnosis services based on population-screening have been summarised in Fig 4 (p. 8). Although these services now touch everyone at some time in their lives, the way to deliver them has not been properly defined. Table 15 summarises the general requirements for a screening service [63], and shows that in the UK the community prenatal diagnosis services are falling far short of the recommendations. There is a conspicuous inadequacy of information for the community and health workers of educational aids, and of counselling for screening and prenatal diagnosis. The services are not

Table 14. Components of a specialist clinical genetics service

Clinical geneticist(s) with:
Genetics centre and staff
Adequate laboratory resources for: Karyotyping; DNA diagnosis; Biochemical diagnosis
Counselling, and associated counsellors
Educational aids
Awareness of whom to refer, among doctors in the community and other medical specialists
Treatment (in collaboration with clinicians, social services etc)
Collaboration with experts in fetal medicine for prenatal diagnosis and post-pregnancy support
Collaboration with neonatologists
Fetal pathology
Monitoring of services

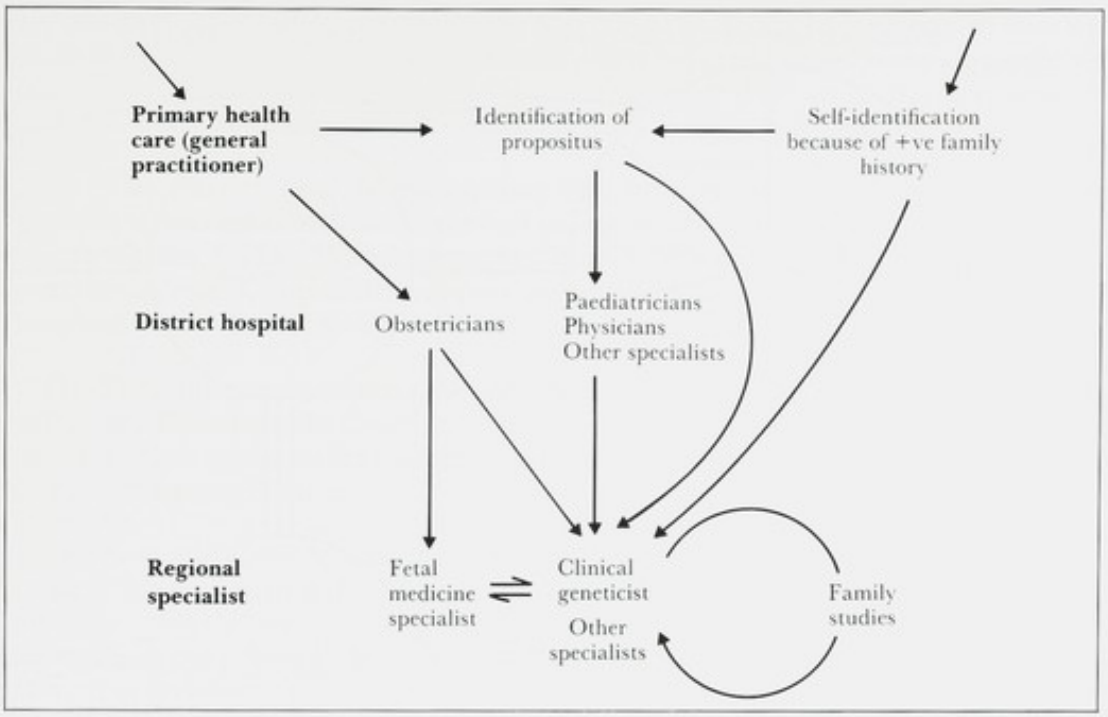


Fig 12. Routes by which people can reach specialists in clinical genetics and fetal medicine.

Table 15. Requirements for a screening programme and their general availability for genetic screening services in the UK

Requirement	Availability for:			
	msAFP	Ultrasound	Maternal age	Haemoglobin disorders or Tay-Sachs
Community information	Poor	Poor	Poor	Variable
Adequate screening resources	Yes	No	Variable	Yes
When result is positive, a mechanism for repeat testing and definitive diagnosis	Yes	Yes	Yes	Yes
Counselling (once or repeatedly)	Limited	Very limited	Limited	Very limited
Educational aids[a]	Local	No	Local	Local
Availability of prenatal diagnosis	Yes	Yes	Yes	Yes
Support and counselling for termination of pregnancy	Limited	Very limited	Very limited	Limited
Monitoring	No	No	Limited	No

[a] Apart from the Health Education Authority's 'Pregnancy Book' [49].

delivered equitably, and monitoring of the impact of prenatal diagnosis is almost nonexistent.

7.5 Though many shortcomings are due to underfunding, some are due to poor spatial arrangements and lack of organisation. This has arisen partly because these services have not been recognised as an entity and thus no designated person has been responsible for making sure that they are delivered and monitored. Furthermore, no defined body of basic clinical genetic knowledge has been introduced into the medical or nursing curriculum.

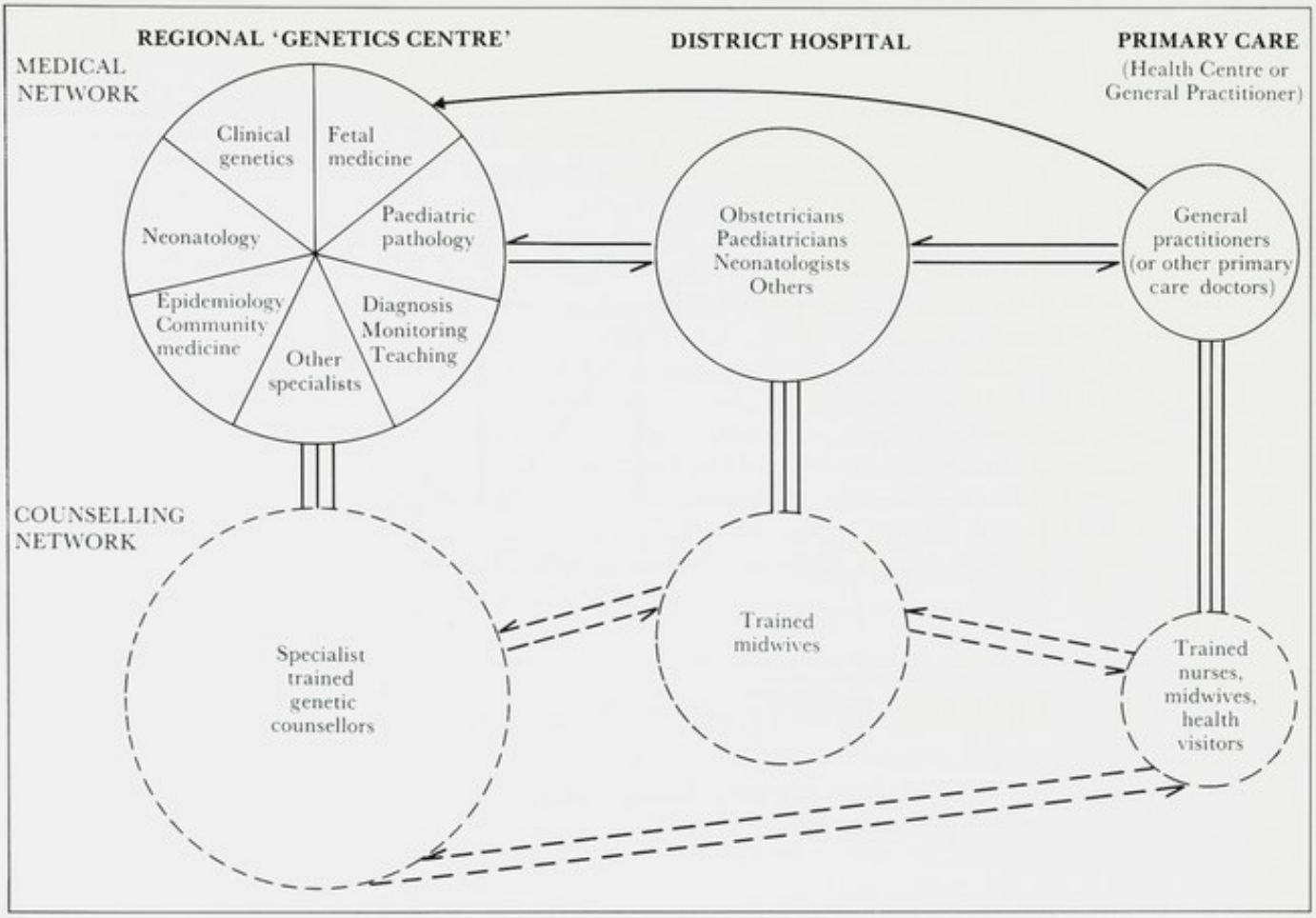


Fig 13. Proposed organisation of community prenatal diagnosis services. Solid lines represent the medical referral system; the dotted lines indicate the importance of specialist counsellors and of trained midwives and health visitors, in delivering the service.

7.6 The effective delivery of prenatal diagnosis in the community requires an organisation, as summarised in Fig 13. A designated named co-ordinator should be responsible for bringing the relevant people (indicated in Fig 4, p. 8) together on a district and a regional basis. The identity of this co-ordinator will depend on local circumstances, but in many cases the most appropriate person will be a clinical geneticist.

7.7 A prenatal diagnosis service would appropriately be organised as follows.

The national level

7.8 The national level is appropriate for formulating national policies, supporting the development and distribution of educational material, and organising the monitoring of the service.

The regional level

7.9 The regional level is appropriate for the organisation of clinical genetics and fetal medicine, prenatal diagnostic laboratories, and most screening laboratories for reasons of efficiency, economy, experience, and monitoring. Because of their close relationship and need for continual interaction, all these services should ideally be located together in regional genetics centres which should be capable of planning, providing a comprehensive service, training, and education.

7.10 Every region will almost certainly have to support a DNA laboratory capable of carrier testing for cystic fibrosis and other common diseases. Experience so far suggests that diagnosis, especially prenatal diagnosis, is best performed by experts in specific disorders such as haemoglobin disorders, Duchenne muscular dystrophy,

Huntington's disease, haemophilia etc. Experts at each centre are likely to develop skills in diagnosis of specific disorders, and their expertise could be made available nationally by developing a network for consultation and referring samples between regional DNA laboratories on a consensus basis.

The district level

7.11 The district level is appropriate for the organisation of the community genetics services, which involve general practitioners, obstetricians, paediatricians, health visitors, midwives and nurses working in close conjunction with the regional genetics service. Community support associations should also, when possible, be involved at the district level.

Planning

7.12 Prenatal diagnosis services must be incorporated into regional and district planning. Their place in the wider context of health care planning and administration therefore needs to be clarified. A useful way to do this is to start from the consumer's point of view.

7.13 A couple about to start on their reproductive life should be considered in the context of the district health authority (DHA) and the local authority (LA) administering the area where they live. Between them, these bodies are responsible for many of the practical decisions that will inform the young couple about services related to pregnancy and child-bearing, and for the organisation and delivery of the service. The two authorities liaise by means of a Joint Consultative Committee which has a budget and expresses a view on matters of mutual concern (though it has little real power). Specific tasks are handled one tier below by joint teams of officers who are likely to include members of or representatives from the DHA, LA, and relevant local authority departments such as housing, education, environmental health and social services.

Sheffield 2000

7.14 In Sheffield for example, the joint teams of officers considered prenatal diagnosis in the context of the district planning strategy 'Sheffield 2000' (see Fig 5, p. 9), which has been established and modestly funded in response to the WHO initiative 'Health for All by the year 2000'. 'Sheffield 2000' has identified prenatal diagnosis as one of more than 30 objectives for positive health planning. Its selection as an objective promotes the concept of prenatal diagnosis and stimulates the professionals concerned to take it into consideration in developing their own initiatives. In addition, the DHA and the LA are involved in all the channels that can be used to make the service available to the community.

7.15 Several local authority departments are involved in the issues of genetic counselling and prenatal diagnosis. Ideally, the young will have been educated about the issues implicit in prenatal diagnosis before they leave school, and this information will be reinforced by the local media at the behest of joint local authority and health service initiatives. There is also the much more personal interaction between client and social workers (supported by the local Family and Community Services Department): in many cases social workers are best placed to reach those members of the community most in need of help and least capable of asking for it.

7.16 The contribution from the DHA can be conveniently divided into that provided by the community unit, the primary care services, and the hospitals. The community unit delivers information as propaganda via the District Health Education Department, and in a more individual way via the family planning services and the community child health services. Many young couples will encounter the last two services for other reasons, and thus there will be the opportunity to inform them about genetic risk and prenatal diagnosis. They may also encounter information when they seek primary care from a GP, nurse or health visitor, or later, in pregnancy from an obstetrician or midwife, or from a paediatrician when they already have a child.

7.17 It follows that a prenatal diagnosis service will only be developed as the professionals are educated and motivated. It is therefore the responsibility of those with special knowledge and expertise in prenatal diagnosis to convince the decision-makers within the local community of the importance of this service and to provide specific advice on ways and means of delivering it and on educational aids. In particular, it is necessary to plan for the imminent need for community screening for cystic fibrosis.

Summary

S7.1 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.

S7.2 Policy formulation, development and distribution of education materials, and service monitoring should be organised at a national level.

S7.3 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.

S7.4 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.

CHAPTER 8 Ethical aspects of prenatal diagnosis

8.1 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.

8.2 Codes of medical ethics are generally made up of statements of principle which would command fairly general assent such as: 'It is wrong for a doctor to kill'; 'A doctor should prevent suffering'; 'Increase in medical knowledge is a worthy objective'; and 'A patient's autonomy must be respected'. Practical difficulties arise when such principles come into conflict as happens in many areas of medicine. The particular ethical dilemmas of prenatal diagnosis revolve around the central position of the fetus, which clearly is not autonomous, cannot be consulted, and whose legal status is indefinite. This places a particular burden of responsibility on parents and their advisers.

8.3 Unless prenatal diagnosis is to be devoid of practical application when it reveals a major defect in the fetus, a responsible doctor must discuss with the parents the option of terminating that pregnancy and must in some circumstances provide information that may deter them from further reproduction. We have thus already departed from one extreme position, that termination of pregnancy and even contraception should be forbidden. The opposite extreme, use of prenatal diagnosis for a directed eugenic programme at the population level, is equally unacceptable. Rejection of two extremes leaves a substantial middle ground with an increasing number of options (see Table 10).

8.4 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, both in terms of its scientific quality and of the manner in which it is given.

8.5 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.

8.6 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.

8.7 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.

8.8 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.

8.9 The facts must be communicated to the parents not necessarily by a member of any particular discipline, but by someone with the required knowledge, sympathy, experience and time. The principles of genetic counselling have been covered in Chapter 4. Here, it is appropriate to emphasise the importance of providing training in genetic counselling. All those clinically involved with prenatal diagnosis should learn counselling skills from an experienced practitioner.

8.10 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.

8.11 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 the family may have to carry. Some parents are able to accept a degree of handicap in a child, and may find fulfilment in looking after a dependent, but their decision should also take account of the long-term implications, for example the situation that may arise after their own deaths. Research is ethically indicated that leads to more definitive diagnosis, and to better understanding of the natural history of disorders diagnosed *in utero,* in order to assist the parents in their decisions. The mother should be encouraged to come to a decision jointly with her husband although, in the event of differing views, the mother's decision should normally prevail.

8.12 The ethical case has already been made for carrying out genetic counselling prior to marriage or pregnancy, when possible. For moral reasons, every effort should be made to develop and evaluate earlier methods for prenatal diagnosis.

8.13 New problems with an ethical dimension always arise as new knowledge and techniques become available. For instance, since the introduction of CVS it is possible to determine fetal sex very early in pregnancy. Of course fetal sex is relevant to prenatal diagnosis of sex-linked disorders. However, prenatal diagnosis services are concerned with the diagnosis of disease and should not be used *primarily* for the determination of fetal sex.

CHAPTER 9 Conclusions and recommendations

9.1 Half the world's women will at some stage conceive an abnormal embryo, and although most abort spontaneously, about 2.0% of full term births carry congenital or genetic abnormalities. Although everyone is at risk for having offspring with a congenital or genetically-determined disorder, almost all couples also have the potential to bear healthy children. The objective of prenatal diagnosis is to provide reassurance when the fetus is unaffected, and information, prognosis and choice, when a severe abnormality is present. All available evidence shows that prenatal diagnosis is wanted by the majority of couples, provides major benefits for the family and often spares substantial resources.

9.2 Political as well as professional will is needed to ensure the delivery of these services, but to date the necessary decisions have not been made. Consequently, there is a lack of accepted policy guidelines for service planning and delivery, professional responsibility, resource allocation, education and training, monitoring, cost/benefit evaluation and ethical principles [1]. The services presently available are imperfectly delivered, and many couples are avoidably deprived of information and choice. This is a loss not only to them but to society as a whole.

9.3 The development of powerful new laboratory and obstetric technologies, which is rapidly expanding the scope of genetic screening and prenatal diagnosis makes it urgent to address these shortcomings.

RECOMMENDATIONS

Equity in health care

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.

Policy advisory structure

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

Code of practice

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.

Resources

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.

Professional training

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.

Information and counselling

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.

Specialist genetic counsellors

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 prenatal diagnosis. It is urgent to define a career structure for such specialist counsellors, who may have differing professional backgrounds, and carry out a wide range of activities.

National organisation

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.

Regional organisation

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.

District organisation

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.

District and regional co-ordinators

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.

National audit

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.

Genetic health education

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.

Implementation

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

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APPENDIX 1

Clinical Genetics Centres (1988)

Regional Health Authorities—England and Wales

NORTHERN Regional Genetic Centre	Prof DF Roberts: Consult CG*: Dr J Burn	Regional Genetics Advisory Service, University Department of Human Genetics, 19 Claremont Place, Newcastle upon Tyne NE2 4AA
YORKSHIRE Regional Genetic Centre	Prof RW Smithells: Consult CG: Dr R Mueller	Genetic Clinic, Clarendon Wing, Leeds General Infirmary, Belmont Grove, Leeds LS2 9NS
TRENT Regional Genetic Centres	Consult CG: Dr E Blank	Centre for Human Genetics, (Sub-Department of Medical Genetics), Langhill, 117 Manchester Road, Sheffield S10 5ND
	Consult CG: Dr J F Fitzsimmons	City Hospital, Hucknall Road, Nottingham NG5 1PD
	Consult CG: Dr I Young	Genetic Clinic, Leicester Royal Infirmary, Leicester LE1 5WW
EAST ANGLIA Regional Genetic Centre	Prof MA Ferguson-Smith Consult CGs: Dr Clare Davison (P/T), Dr J Yates	Regional Genetic Advisory Service, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ
NORTH WEST THAMES Regional Genetic Centre	Consult CGs: Dr M d'A Crawford, Dr RM Winter, Dr E Thompson	The Kennedy Galton Centre, Northwick Park Hospital, Watford Road, Harrow, Middlesex HA1 3UJ
Specialist Clinics		
Dysmorphology	Dr R Winter	Kennedy Galton Centre, Harperbury Hospital, Harper Lane, Radlett, Herts WD7 9HQ
Prenatal diagnosis	Dr R Stephens	Queen Charlotte's Maternity Hospital, Goldhawk Road, London W6 0XG
Neuromuscular disorders	Prof V Dubowitz	Department of Paediatrics, Hammersmith Hospital, Ducane Road, London WI2 0HS
Sickle cell disease	E Anionwu	The Sickle Cell Centre, Willesden Hospital, Harlesden Lane, London NW10 3RY
NORTH EAST THAMES Regional Genetic Centres	Consult CGs: Dr M Baraitser, Dr M Pembrey	Genetic Clinic, Institute of Child Health, The Hospital for Sick Children, Great Ormond Street, London WC1N 3JH
	Consult CG: Dr J Slack	Royal Free Hospital, Pond Street, London NW3 2QG
	Consult Clin Cytogeneticist: Dr M Lucas	University College Hospital, Gower Street, London WC1E 6AU
Specialist Clinics		
Hereditary bleeding disorders	Dr PBA Kernoff, Dr EG Tuddenham	Royal Free Hospital, Pond Street, London NW3 2QG
Neurological disorders	Dr M Baraitser	The National Hospital for Nervous Diseases, Queens Square, London WC1N 3BG
Ophthalmic disorders	Dr B Jay	Moorfields Eye Hospital, City Road, London EC1V 2PD

* Consultant CG = Consultant clinical geneticist

sickle cell disease		London WC1E 6AU
Inherited metabolic disorders	Dr R Stephens, Dr J Leonard	The Hospital for Sick Children, Great Ormond Street, London WC1N 3JH
	Dr D P Brenton	University College Hospital, Gower Street, London WC1E 6AU
SOUTH EAST THAMES Regional Genetic Centre	Consult CGs: Prof M Bobrow, Dr C Berry	Paediatric Research Unit, The Prince Philip Research Laboratories, Guy's Hospital Medical School, Guy's Tower, London Bridge, SE1 9RT
Specialist Clinic		
Inherited red cell and coagulation disorders	Prof AJ Bellingham	Department of Haematological Medicine, King's College School of Medicine and Dentistry of King's College London, Bessemer Road, London SE5 9PJ
SOUTH WEST THAMES (DHSS 1981)	Consult CG: Dr M Palton	St George's Hospital, Blackshaw Road, London SW17 0QT
WESSEX Regional Genetic Centre	Consult CG: Dr N Dennis	Genetic Clinic, Southampton General Hospital, Tremona Road, Shirley, Southampton SO9 4XY
OXFORD Regional Genetic Centre	Consult CGs: Prof JH Edwards (P/T), Dr R Lindenbaum	Department of Medical Genetics, Old Road, Headington, Oxford OX3 7LE
SOUTH WESTERN (DHSS 1981)	Consult CG: Dr C Garrett	Scott Hospital, Beacon Park Road, Plymouth, Devon PL2 2PQ
WEST MIDLANDS Regional Genetic Centre	Consult CGs: Dr P Farndon, Dr J Insley	Infant Development Unit, Birmingham Maternity Hospital, Edgbaston, Birmingham B15 2TG
	Consult Clin Cytogeneticists: Dr M Hulten, Dr C McKeom	East Birmingham Hospital, Birmingham B9 5ST
MERSEY	(No Consult CG) Dr DW Fielding	Genetic Advisory Clinic, Maternity Wing, Countess of Chester Hospital, Liverpool Road, Chester CH1 2BA
NORTH WESTERN	Consult CGs: Prof R Harris, Dr D Donnai, Dr H Kingston	University Department of Medical Genetics, St Mary's Hospital, Hathersage Road, Manchester M13 0JH
Regional Genetic Centres	Consult CG: Dr M Super	Department of Clinical Genetics, Royal Manchester Children's Hospital, Pendlebury, Manchester M27 1HA
Specialist Clinics	Dr I Sardharwalla	Willinck Biochemical Genetics Laboratory, Royal Manchester Children's Hospital, Pendlebury, Manchester M27 1HA
WALES Regional Genetic Centres	Consult CGs: Prof P Harper, Prof KM Laurence, Dr H Hughes	Wales Medical Genetics Clinic, Regional Genetic Centre, Welsh National School of Medicine, Heath Park, Cardiff, CF4 4XN
		Child Health Laboratories, Welsh National School of Medicine, Heath Park, Cardiff CF4 4XN

Health Board Areas — Scotland and Northern Ireland

HIGHLAND	(No Consult CG)	Paediatric Unit, Raigmore Hospital, Inverness, IV2 3UJ
GRAMPIAN	(No Consultant CG) Dr AW Johnston (Physician)	Genetics Clinic, Royal Aberdeen Children's Hospital, Cornhill Road, Aberdeen AB9 2ZD
TAYSIDE	(No Consult CG) Consultant Paediatrician	Perth Royal Infirmary, Taymount Terrace, Perth PH1 1NX
LOTHIAN	Consult CG: Dr JA Raeburn	Genetic Clinic, Human Genetics Unit, Department of Medicine, Western General Hospital, Crewe Road, Edinburgh, EH4 2XU
GREATER GLASGOW	Consult CGs: Prof JM Connor, Dr J Tolmie	West of Scotland Regional Genetic Service, Duncan Guthrie Institute of Medical Genetics, Royal Hospital for Sick Children, Yorkhill, Glasgow G3 8SJ
NORTHERN IRELAND	Consult CG: Prof N Nevin	Department of Medical Genetics, Institute of Clinical Science, Grosvenor Road, Belfast BT12 6BJ

APPENDIX 2

Some addresses of support groups for hereditary and congenital disorders

Association for Spina Bifida and Hydrocephalus
22 Upper Woburn Place
London WC1H 0EP

Association to Combat Huntington's Chorea (COMBAT)
34A Station Road
Hinckley
Leicester LE10 1AP

British Retinitis Pigmentosa Society (BRPS)
Greens Norton Court
Greens Norton, Towcester
Northants NW12 8BS

College of Health
2 Marylebone Road
London NW1 4DX

Cystic Fibrosis Research Trust
Alexandra House
Blyth Road
Bromley, Kent BR1 3RS

Down's Syndrome Association
12–13 Clapham Common (South Side)
London SW4 7AA

Edward's Syndrome Society
3 Devon Close
Perivale, Greenford
Middlesex UB6 7DM

MENCAP National Centre
117–123 Golden Lane
London EC1Y 0RT

Muscular Dystrophy Group of Great Britain
Nattrass House
35 Macaulay Road
London SW4 0QP

National Centre for Down's Syndrome
8 Wakeley Street
London EC1V 7QE

National Council for Voluntary Organisations
26 Bedford Square
London WC1 3H4

National Society for Phenylketonuria and Allied Disorders
Worth Cottage
Lower Scholes
Pickles Hill
Keighley, Yorks BD22 0RR

Sickle Cell Society
Green Lodge
Barretts Green Road
London NW10 7AP

Society for Mucopolysaccharide Disease
30 Westwood Drive
Little Chalfont, Bucks HP6 6RJ

Support after Termination for Abnormality (SAFTA)
22 Upper Woburn Place
London WC1

Tay-Sachs and Allied Disease Association
17 Sydney Road
Barkingside, Ilford
Essex IG6 2ED

Tuberous Sclerosis Association of Great Britain
Martel Mount
Holywell Road
Malvern Wells, Worcs WR14 4LF

UK Thalassaemia Society
107 Nightingale Lane
London N8 7QY

APPENDIX 3

WHO-sponsored recommendations for screening for haemoglobin disorders

The basic screen for haemoglobinopathy disorders

1. *Red cell indices* If the MCH is < 25pg, measure the Hb A_2	For the thalassaemias
2. *Haemoglobin electrophoresis*	For abnormal haemoglobins (includes raised Hb F)
3. *Sickle solubility test*	Specific for Hb S

Requirements for a haemoglobin disorder screening programme

The requirements for a screening programme for haemoglobin disorder summarised by a WHO expert group [32] and given below, are generally applicable for community genetics services. The requirements for screening for cystic fibrosis will be almost identical.

i 'Special centres for haemoglobin disorders' should be recognised. They should include specially trained ethnic counsellors.

ii Adequate clinical and laboratory facilities should be available for patient management, carrier and prenatal diagnosis, and neonatal diagnosis when indicated.

iii All people in risk groups should be informed about the haemoglobin disorders, the existence of risk, the desirability of testing and the possibility of avoiding serious consequences.

iv They should be provided with easy access to testing.

v Testing should be reliable, the laboratory involved participating in a quality-control system.

vi Whether the test result is positive or negative, everyone tested should be issued with a card giving the result and the address of the testing centre.[1] The result, whether positive or negative, should be recorded in a conspicuous place in the person's primary health care records.

vii All carriers should have the result and its meaning explained to them. They should be provided with an information booklet,[2] and given the address of a specialist counselling service or support organisation for further help or advice.

viii Information and screening during pregnancy is the absolute minimum that should be provided. Wherever screening is routine, a poster[3] should be conspicuously displayed to inform patients of the existence of risk and the fact that testing will be offered, or is routinely carried out.

ix Carrier identification and counselling (of single heterozygotes) should, as far as possible, be done prior to pregnancy by the primary health care team.

x Information should be provided for primary health care workers such as general practitioners, health visitors, family planning doctors, midwives and nurses, through their training curriculum, meetings and written guidelines.

xi Where consanguineous marriage is common, health-workers need information on its genetic implications in order to avoid giving harmful misinformation to families.

[1] Cards may be obtained from . . . They should be issued only from the laboratory making the test, and answerable for its interpretation and accuracy.

[2] Counselling booklets for people who carry thalassaemia trait are available from the UK Thalassaemia Society, and for carriers of sickle-cell trait, from the Sickle Cell Society.

[3] Posters alerting people in the appropriate ethnic groups to the existence of the haemoglobinopathies, suitable for display in antenatal or other NHS clinics, are available from Bloomsbury Health Education Unit, Elizabeth Garrett Anderson Hospital, 144 Euston Rd, London NW1.

xii Neonatal screening is clinically indicated for sickle cell disease. Carriers of abnormal haemoglobins can be detected as easily as homozygotes, so this could be an efficient approach for carrier screening. However, adequate counselling must be available for the large number of families identified.

xiii Patients and families should be put in touch with each other, and encouraged to form thalassaemia or sickle-cell associations, for mutual information and support. The activities of 'support groups' should be promoted to help to increase the awareness of the population at large.

APPENDIX 4

Sickle cell and thalassaemia counselling centres and voluntary organisations

(This list may not be comprehensive)

Counselling centres

LONDON

Brent
Brent Sickle Cell Centre
Willesden Hospital
Harlesden Road
London NW10 3RY
(01-459 1292 Ext 4235)

Islington
Sickle Cell Centre
Royal Northern Hospital
Holloway Road, London N7
(01-272 7777 Ext 351)

City and Hackney
City and Hackney Sickle Cell Centre
St Leonards Hospital
Nuttal Street
London N1 5LZ
(01-739 8484 Ext 369)

Lambeth
Lambeth Sickle Cell Centre
Swan Mews, 2 Stockwell Road
London SW9 9EN
(01-737 3588)

St Thomas' Sickle Cell Centre
Midwifery Sister for Haemoglobinopathies
Midwifery Unit
St Thomas' Hospital, London SE1 7EH
(01-587 3939)

Haringey
Prince of Wales Hospital
Community Health Clinic
South Tynmouth Road
Tottenham, London N15 4AW
(01-801 0935 Ext 123)

Newham
Sickle Cell Centre
Shrewsbury Road Health Centre
Forest Gate, London E7 8QR
(01-470 1311 Ext 38)

Waltham Forest
Sickle Cell Centre
Leyton Green Clinic
Leyton Green Road, London E10
(01-539 8646)

BIRMINGHAM SICKLE CELL CENTRE
Carnegie Centre for Community Services
Hunters Road, Hockley
Birmingham B19 1DR
(021-554 3899 Ext 236)

CARDIFF
The Sickle Cell and Thalassaemia Counselling Centre
Butetown Health Centre
Loundoun Square Docks
Cardiff
(0222 488026)

LIVERPOOL
Liverpool Sickle Cell Centre
Abercromby Health Centre
Grove Street, Liverpool 8
(051-708 9370)

MANCHESTER
Sickle Cell Centre
Moss Side Health Centre
Monton Street, Manchester 14
(061-226 8972)

NOTTINGHAM
Sickle Cell Service
Victoria Health Centre
Glasshouse Street
Nottingham NG1 3LW
(0602 480500 Ext 127)

Prenatal diagnosis for haemoglobin disorders

NHS Haemoglobinopathy Reference Centre (DNA),
Nuffield Department of Clinical Medicine,
John Radcliffe Hospital, Oxford OX3 9DU
(0865-64711)

Counselling, obstetric procedures and conventional methods for prenatal diagnosis

Dr B Modell,
Perinatal Centre, University College and Middlesex School of Medicine,
Dept of Obstetrics and Gynaecology,
88–96 Chenies Mews, London WC1E 6HX
(01-387-9300 ext 5230)

Mr E H Nicolaides,
Dept of Obstetrics and Gynaecology,
King's College Hospital, Denmark Hill, London SE5 9RS
(01-274-6222)

Voluntary organisations

The UK Thalassaemia Society,
107 Nightingale Lane, London N8 7QY
(01-348-0437)

The Sickle Cell Society,
Green Lodge, Barretts Green Road, London NW10 7AP
(01-961-7795/8346)

Leaflets

Information leaflets on thalassaemia may be obtained from the above organisations. Leaflets on sickle cell disease may be obtained from local Health Education Units or the Health Educational Authority, 78 New Oxford Street, London WC1H 9TX

Posters

Posters about haemoglobin disorders for display (for example in antenatal clinics) may be obtained from the Bloomsbury Health Authority, 4 St Pancras Way, London NW1 0PE

APPENDIX 5 Glossary

Achondroplasia — A dominantly-inherited form of dwarfism. Disturbed growth of bones leads to marked shortening of the limbs and a characteristic long, slightly flattened appearance of the face.

Alpha-1 (α-1) antitrypsin deficiency — A recessively-inherited disorder with a wide range of severity. It often leads to emphysema, especially if those affected smoke. In some cases it causes juvenile cirrhosis of the liver.

Alpha (α) fetoprotein — A plasma protein characteristic for the fetus. It is found in small quantities in the amniotic fluid and in traces in maternal serum. The level of AFP in maternal blood can be used for screening for neural tube defects and to some extent for Down's syndrome, in the fetus.

Amniocentesis — A procedure, usually carried out at around 17 weeks of pregnancy, in which a few ml of the amniotic fluid surrounding the fetus is withdrawn through a needle inserted through the abdomen and uterine wall. The fluid and the fetal cells it contains may be tested for some genetic diseases in the fetus.

Anencephaly — A severe congenital malformation in which the brain and skull are very poorly developed. Inevitably fatal in the first few days of life, usually within an hour.

Aneuploidy — An abnormal number (either an excess or a deficiency) of chromosomes or chromosome sets.

Carrier — A person who carries a variant gene and is capable of transmitting it to offspring. Carriers may or may not have symptoms, depending on whether the variant gene is dominantly or recessively inherited.

Chorionic villus sampling (CVS) — A procedure by which a small amount of the chorionic villi that make up the placenta, are withdrawn for genetic analysis. CVS can be performed at any stage of pregnancy from about 8 weeks of gestation onwards.

Chromosome — Specific lengths of DNA and associated proteins are tightly coiled to make up the individual chromosomes, which are the microscopically visible components of the hereditary material. In humans, 23 chromosomes make up a single haploid set (1n). Humans and higher animals are diploid (2n) ie they inherit one chromosome set from each parent to give 22 matching (homologous) pairs, and 2 sex chromosomes, XX or XY, a total of 46.

Chromosomal disorder — Any disturbance of the normal number or structure of the chromosomes that is directly visible using a microscope. Many lead to severe disturbances of normal development and function.

Chromosomal rearrangement — Alteration of the usual arrangement of the chromosome set. Includes inversion or deletion of part of a chromosome, and translocation of part of a chromosome or a whole chromosome to another chromosome.

Congenital — Existing at the time of birth.

Consanguineous marriage — Marriage with blood relative. The commonest forms of consanguineous marriage that can have genetic implications are first-cousin marriages and uncle–niece marriages (which are common in some parts of the world eg South India.)

Cystic fibrosis — A recessively-inherited disorder that affects exocrine gland function and leads to pancreatic insufficiency and chronic lung disease. It is the commonest recessively-inherited disease among Caucasians, and is most often seen in children and young adults. Death, which is usually due to progressive destruction of the lung by recurrent infections, may be postponed until after 25 years of age.

Cytogenetics — The study of the chromosomes. Clinical cytogenetics is the study of the relationship between chromosome aberrations and disease.

DNA (deoxyribonucleic acid) The essential part of chromosomes that carries genetic information in the form of the genetic code.

Dominant Everyone inherits two copies of each gene. A dominant disease occurs even if only one copy of the gene is defective.

Down's syndrome A severe disorder caused by the presence of three copies of chromosome 21 (trisomy 21) or by two copies of chromosome 21, plus a third chromosome 21 translocated to a different chromosome (usually chromosome 14). Trisomy 21 causes severe mental retardation and may also lead to congenital heart defects and other congenital malformations. Individuals with Down's syndrome have a shortened life expectancy.

Duchenne muscular dystrophy A severe X-linked disease with onset in early childhood, almost always affecting males. It causes progressive wasting (atrophy) of the muscles, beginning in the arms and progressing to the legs. It is usually fatal in early adult life.

False negative A negative test result in someone who actually has the disease or characteristic being tested for.

False positive A positive test result in someone who does not have the disease or characteristic being tested for.

First degree relatives A person's parents, offspring and siblings.

Gametes Mature male or female reproductive cells—sperm or ova. They contain a single set of chromosomes (1n = 23).

Gene Unit of inheritance. Part of the DNA molecule that directs synthesis of a specific protein or protein sub-unit, or of an RNA component.

Glucose 6-phosphate dehydrogenase deficiency A condition with X-linked inheritance that increases the risk of neonatal jaundice or of developing acute anaemia in reaction to some drugs. It affects hemizygous males more often than homozygous females.

Haemoglobin disorders Recessively-inherited diseases caused by an abnormality of structure or reduced production of the protein sub-units of haemoglobin. Anaemia is a common characteristic of haemoglobin disorders. (See thalassaemia and sickle cell disease.)

Haemophilia An X-linked disease that causes an increased risk of bleeding, due to a defect in the clotting mechanism of the blood.

Hemizygous male Male expressing a trait determined by a gene on his X-chromosome.

Hereditary Passed from parents to children through their DNA.

Heterozygote Person having two different genes for a particular characteristic, in corresponding (homologous) positions on a pair of chromosomes, one inherited from each parent.

Homozygote Person having two identical genes for a particular characteristic in corresponding (homologous) positions on a pair of chromosomes, one inherited from each parent.

Huntington's chorea Severe dominantly-inherited disorder. Onset is usually in the fourth or fifth decade of life. It leads to uncontrolled involuntary movements and progressive physical and mental disability. It is usually fatal within 20 years of onset.

Hypercholesterolaemia The presence of an excessive amount of cholesterol in the blood. Familial hypercholesterolaemia is a recessively-inherited disorder with a raised serum cholesterol. It predisposes to coronary heart disease.

Incidence	The frequency of new occurrences of a disease within a defined time interval. It is usually expressed as the number of new cases in a given number of people in a population, usually over one year. For inherited conditions, incidence is usually expressed in births per 1,000 per year.
In utero	Within the uterus.
In vitro	In a laboratory or test tube.
Karyotyping	Laboratory methods for defining the number, size and shape of chromosomes in a cell.
Linkage	Associated inheritance within families of two or more genes, indicating that they are close together on the same chromosomes.
Mendelian	The pattern of inheritance that follows Mendel's laws. Traits with mendelian inheritance are controlled by a single gene and therefore show a simple pattern of inheritance (dominant, X-linked or recessive).
Mid-trimester	The second three of the nine months of pregnancy.
Multidisciplinary	Involving collaboration between people trained in several different specialties.
Multifactorial	Control of a characteristic by several genes with additive effects and also by environmental factors.
Mutation	A spontaneous change in the structure of DNA. It includes point mutations affecting one or a few base pairs of DNA, and also changes in the structure and number of chromosomes.
OPCS	Office of Population Censuses and Surveys (UK).
Perinatal	Occurring around the time of birth (usually two weeks before to two weeks after birth).
Phenylketonuria	Recessively-inherited disturbance of phenylanine metabolism which causes severe mental retardation. It can be prevented by neonatal diagnosis and careful dietary control.
Polycystic disease of the kidneys	A dominantly-inherited condition in which a progressive deterioration of kidney function is associated with the development of large numbers of cysts in the kidney. It is often compatible with a nearly normal length of life.
Prevalence	The number of cases of a disease present at a particular time, in relation to the size of the population. Usually expressed as cases per 1,000, 10,000, or 100,000.
Propositus	The first person in a family diagnosed as having an inherited disease. Correct diagnosis in the propositus is usually the key to understanding genetic risks for other family members.
Prostaglandins	Hormones used, among other things, for inducing mid-trimester abortion.
Recessive	Everyone inherits two copies of each gene. A recessive disease only occurs if both copies of the gene are defective.
Screening	Mass examination of a population to detect the existence of a particular trait or disease before it has become manifest clinically. Screening should be done only when there is an effective intervention.
Sex chromosomes	The X and Y chromosomes which determine the person's sex. XX = female; XY = male.
Sickle cell disease	A recessively-inherited blood disorder that is common in the tropics and sub-tropics. It occurs particularly among people of African descent. It is characterised by anaemia, excessive susceptibility to infection in early childhood and sudden attacks of severe pain and tissue damage in different organs. It is very variable in severity.

Single gene disorder	A disorder with Mendelian inheritance.
Spina bifida	A defect in the closure of the bones around the spinal cord during fetal development. Spina bifida can be either open—ie the spinal cord is partially exposed, or closed, ie the defect is covered with skin. It usually causes severe disability.
Tay-Sachs disease	A recessively-inherited disease caused by a deficiency of hexosaminidase A, an enzyme that breaks down certain structural materials in nervous tissue. Abnormal accumulations of these materials collect, particularly in the brain leading to developmental retardation paralysis, dementia and blindness. Death usually occurs before the end of the third year of life. There is no treatment.
Translocation	The shifting of a segment of one chromosome into another part of a chromosome.
Thalassaemia	A recessively-inherited severe anaemia that is common in the tropics and sub-tropics. It occurs particularly among people of Asian and Mediterranean origin.
Ultrasound	High frequency sound waves that can be focused and used to picture tissues, organs or structures within the body.
X-linked traits	Determined by genes located on the X-chromosome. Also sometimes called sex linked.
Zygote	A diploid cell produced by the union of ovum and sperm, including the fusion of their haploid (1n) nuclei; this would have 2n nuclei, 46 in normal human zygotes.

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