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Counseling in couples with genetic abnormalities

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INTRODUCTION

For the past several decades, women have been having their babies later in life. As a result, many are developing diseases that are not as common in younger women. Unfortunately, these diseases often affect the outcome of pregnancy. At the same time, other women have diseases which were previously incompatible with long-term survival and now, after therapy, these women wish to have their own families. These two previously unknown circumstances, plus an increasing awareness of genetic disorders, are leading more and more potential parents to seek specialist genetic advice on pregnancy planning, investigations and management prior to conception. Such information is available in all regions of the UK as well as in other developed and in some developing nations. In the case of the UK, the addresses from which to obtain local services can be found on the British Society for Human Genetics website[1] and the American Society of Human Genetics[2].

The family history is, and for the foreseeable future will remain, the basis of genetic counseling. Medical personnel involved with patients during antenatal care should be able to take and document a simple pedigree, and know when referral for specialist advice is required (Figure 1).

A number of pregnancies can be recognized to be at increased risk of fetal abnormalities and/or a genetic syndrome prior to the pregnancy. As such, they are suitable for preconceptional counseling and special attention and management.

Factors indicating that preconceptional counseling should be considered and discussed in this chapter include:

- Advanced maternal age
- Advanced paternal age
- Risk of fetal exposure to teratogens
- Consanguinity
- Known genetic syndrome within the family
- Unexplained physical or mental handicap within the family
- Genetic causes of infertility
- Maternal disease.

An increase in maternal age is the internationally recognized factor for Down's syndrome and is often understood by the patient; however, this knowledge is commonly thought to be limited to Down's syndrome and other risk factors are less well recognized and may need to be proactively asked about by the health professional. Families have frequently believed that birth injury had been the cause of abnormalities, and it is always necessary to untangle fact from fiction in family stories. The above risk factors are discussed in more detail below.
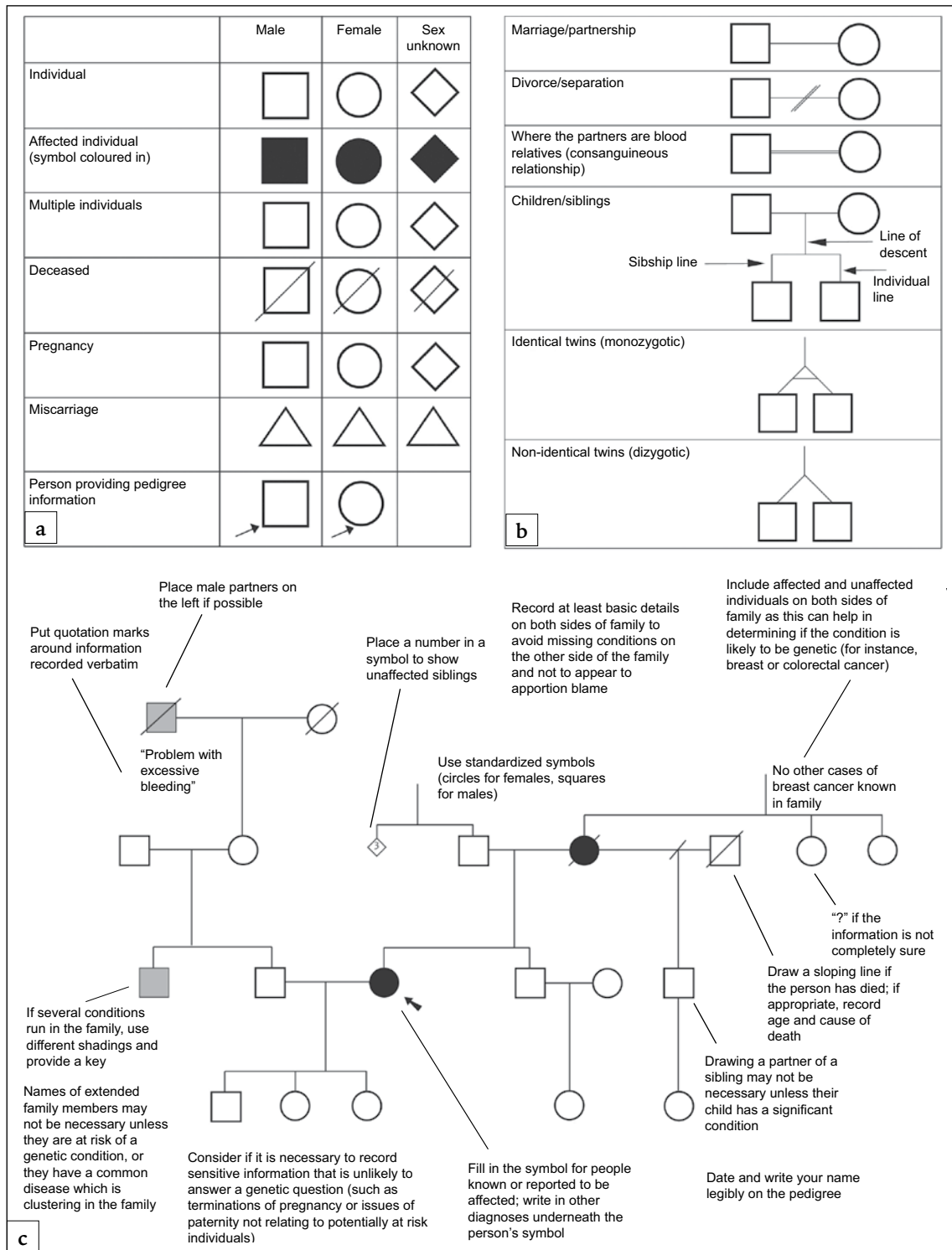
Figure 1 Pedigree. (a) Examples of most commonly used pedigree symbols. (b) Examples of relationship lines. (c) Example of a pedigree. Reproduced from National Genetics Education and Development Centre (www.geneticseducation.nhs.uk)[3], with permission

ADVANCED MATERNAL AGE

Advanced maternal age leads to an increased risk of pregnancies with a trisomic karyotype. Down's (trisomy 21), Edward's (trisomy 18) and Patau's (trisomy 13) syndromes are all well recognized, and screening programs are available for early-stage identification in pregnancy. Other chromosomal trisomies also may occur and lead to early miscarriage or occasionally trisomic rescue. In trisomic rescue, the fetus has 47 chromosomes at conception but loses a chromosome early on in gestation, so that the remaining number is 46. The chromosome lost during this process may be from the parent who passed on only a single copy, so that the baby will have inherited two copies from the other parent. If trisomic rescue affects an imprinted chromosome (6, 7, 11, 14, 15 and possibly 20), this process may lead to major fetal abnormality. (Imprinting is the phenomenon whereby a small subset of all the genes in the genome is expressed according to their parent of origin.) Screening programs do not pick up all cases of the major trisomies, and it is important that couples are aware of the difference between screening and diagnostic tests. Moreover, screening programs vary across the world, and only in a few countries is there a coordinated transparent approach to screening. Technological advances, especially with the arrival of free fetal DNA technology, may change this over the next few years.

ADVANCED PATERNAL AGE

Increasing paternal age results in primary spermatogonia originating from germ cells which have undergone an increasing number of mitoses, which in turn give rise to an increased chance of gene mutations. As a result, single gene disorders arising as new mutations are commoner in progeny of older men. Examples of this process include achondroplasia and Apert's syndrome. Point mutations in

the dystrophin gene more commonly arise in spermatogenesis than in oogenesis, whereas partial gene deletions more commonly arise in oogenesis. Under these circumstances it is possible to see that if there is a single case of Duchenne muscular dystrophy within the family, the type of mutation may dictate the likely origin of the mutation.

EXPOSURE OF THE FETUS TO TERATOGENS

Recreational and therapeutic drugs, and intrinsic maternal metabolites can cause teratogenic effects in the fetus.

Recreational drugs

Alcohol in the first trimester of pregnancy can lead to a number of morphological abnormalities in the fetus such as partial agenesis of the corpus callosum and subtle facial dysmorphic features. Prolonged exposure leads to intrauterine growth retardation and poor brain growth, which may result in learning difficulties and attention deficit hyperactivity disorder. The disorder is commonly characterized as the fetal alcohol syndrome and has been described in detail for the last several decades.

Cocaine abuse is a far more recent phenomenon. It causes major brain abnormalities with septo-optic dysplasia and schizencephaly among those implicated. Cerebral infarction in the newborn has also been reported. Other vasoactive drugs such as amphetamines may cause similar effects. These effects are in contrast to *in utero* exposure to opiates which causes withdrawal symptoms in the neonate but no structural abnormalities.

Smoking, which is not always thought of as recreational drug, causes intrauterine growth retardation and an increased risk of premature delivery and miscarriage.

Therapeutic drugs

Most drugs are contraindicated in pregnancy, as it is generally not possible to carry out clinical trials in pregnant women (only drugs for pregnancy associated diseases such as pre-eclampsia are actively studied in pregnancy). Despite this, many drugs have been used widely in pregnancy and appear to be safe. Certain drugs, however, are required for use in pregnancy for the treatment of maternal disease. Below are some with known associated syndromes; however, it is beyond the scope of this chapter to discuss fetal teratogens in depth, and all drug treatment in pregnancy should be carefully evaluated. It has become increasingly clear that there is an interaction between the fetal and maternal metabolism that determines the variable effects of therapeutic drugs on the fetus.

Anticonvulsants

Anticonvulsants are the most frequent and most well characterized teratogens to cause fetal abnormality in the developed world. Sodium valproate can cause spina bifida, congenital heart disease, dysmorphic features and learning difficulties[4,5]. If possible young women should be changed to a more suitable anticonvulsant prior to pregnancy. Lamotrigine and carbamazepine are the drugs of choice, although no anticonvulsants are completely safe and fetal abnormalities with carbamazepine have been recognized. Lamotrigine is a newer drug, and all the potential effects may not yet have been recognized. Any woman taking anticonvulsants should take 5 mg folic acid daily periconceptionally to try to reduce the effects of the fetal anticonvulsant syndrome. Once a woman has had one child with the fetal anticonvulsant syndrome, the chance of a further future child being affected is approximately 50%, whereas the overall risk for a first pregnancy is approximately 5%. The dose of folic acid for such women is also 5 mg daily.

Retinoic acid analogues

Retinoic acid analogues are well known teratogens used in the treatment of acne and psoriasis. Advice on the avoidance of pregnancy during treatment must always be provided, and the pharmaceutical community is well aware of this hazard and assists in cautioning women in the childbearing years.

Carbimazole

Carbimazole[6,7] is a common treatment for hyperthyroidism and is now recognized as causing a specific malformation syndrome.

Angiotensin converting enzyme inhibitors

Angiotensin converting enzyme (ACE) inhibitors[8] are used in the management of hypertension and cardiac failure. Diabetics are often treated for hypertension at a lower blood pressure than other patients owing to their increased risk of microvascular disease, and these patients are already determined to be at high obstetric risk.

Warfarin

Warfarin embryopathy results from its effect on vitamin K metabolism[9,10]. Patients with prosthetic heart valves and those with previous deep vein thrombosis or pulmonary embolus are those most likely to be taking warfarin. As the effects are mild, it would seem reasonable to change patients to heparin as soon as a pregnancy is confirmed for the remainder of the first trimester rather than preconceptionally in view of the inconvenience of heparin

therapy and prolonged use potentially causing osteoporosis.

Most drugs are contraindicated in pregnancy in view of the potentially catastrophic effects that can be caused. A prime example is thalidomide, developed in the 1950s as a sedative and antiemetic, which caused major limb and other abnormalities. Since that time companies have been extremely reticent to market drugs approved for pregnant women. Many drugs appear to be safe, however, such as the serotonin uptake antagonists, beta-blockers after the first trimester unless they are being used for treatment of hypertension, beta-agonists, steroids and antibiotics. Regardless, tetracyclines should be avoided as they cause discoloration of the developing teeth. (For intrinsic maternal metabolites see section below on Maternal disease.)

CONSANGUINITY

Although marrying within the family is common in certain parts of the world, consanguinity occurs outside these communities as well. In the absence of any known abnormalities in the family, first cousin marriages have a 2–3% higher than background risk of having a child with an autosomal recessive disorder secondary to a rare recessive gene. If there is a known genetic disease within the family, this risk can increase dramatically. If the disorder has been characterized, however, it may be possible to test the carrier status of the at risk couple. In such instances, full diagnostic details must be identified in the affected patient, and referral to a geneticist is strongly recommended. It is mandatory to take a full family history including the common ancestor(s) of the couple. This is easier said than done, unfortunately, as the disease within the family may be extremely rare and the diagnosis may not have been confirmed among many of the affected relatives who may live abroad[11].

KNOWN GENETIC SYNDROME IN THE FAMILY

If a couple present with a known genetic syndrome within the family, it is important to obtain documentary evidence. A full family history should be taken including the dates of birth, addresses and hospitals where affected individuals were treated. Consent for release of information regarding the affected person may need to be obtained before further details can be accessed. Referral to a genetic center is recommended, as these centers are used to collecting relevant information. It is then necessary to ascertain whether a couple is at risk of having an affected baby and what they would wish to do if the baby were to be affected. If molecular or karotypic evidence is available, then the at risk member of the couple can be tested if necessary[3] (Figure 2). A number of considerations influence deciding whether a couple is at risk. The first of these is to determine the mode of inheritance of the disorder.

Autosomal dominant inheritance

Autosomal dominant inheritance is direct inheritance from one generation to the next. Even when present, it is important to recognize that the disease may vary between generations and affected children. If the disease does not present until later in life after the couple have reproduced, there will be no selection against the disease. Some diseases may show anticipation; this is the process by which a mutation changes as it passes from one generation to the next, and thus the disease may become more severe in successive generations. The severity may vary according to the sex of the carrier parent; examples include myotonic dystrophy and Huntington's chorea. If the mother is affected, then her health may be adversely affected for a pregnancy.

If inheritance is autosomal dominant, the following questions should be considered:
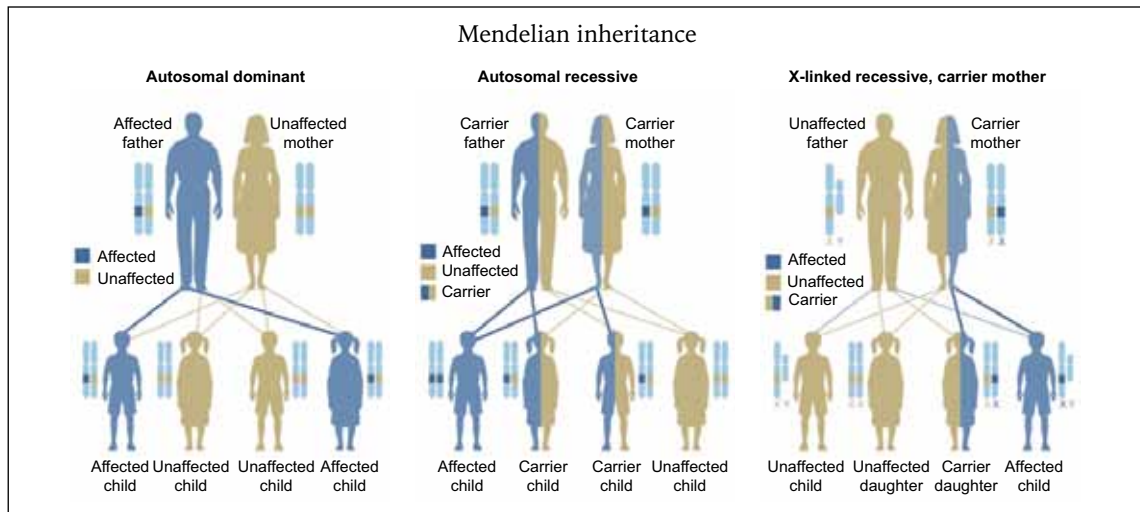
Figure 2 Inheritance patterns. Reproduced from US National Library of Medicine. (http://ghr.nlm.nih.gov/handbook/inheritance/inheritancepatterns), with permission

- Could the patient be mildly affected?

- Is the patient affected?

- Could the patient be an unaffected carrier?

Autosomal recessive inheritance

In autosomal recessive inheritance, both parents are carriers of a mutation, but the disease only manifests itself if a child inherits both copies of the abnormal gene. Hence, if the parents are well but carriers, every child has a 1:4 chance of being affected. The incidence of the disease depends on the carrier frequency within the population, and this often varies between ethnic groups. For example, the carrier frequency for sickle cell anemia is 1:8 in West Africans and 1:24 for cystic fibrosis in northern Europeans, whereas cystic fibrosis is almost unheard of in the Chinese.

Consanguineous couples show a higher incidence of autosomal recessive diseases in their offspring because they are more likely to share the same rare deleterious mutations, and they may have children with very rare and previously unrecognized diseases. If a parent is affected with an autosomal recessive disease

it may be possible to test her/his partner to determine whether he/she is a carrier and whether future children would be at risk.

If inheritance is autosomal recessive, the following questions should be considered:

- Can the patient be tested for carrier status?

- Is the disease common enough so that the partner could also be a carrier?

- Is it possible to test a partner? In many diseases, a few common mutations cause the disease and these can be tested for, whereas in others there are no common mutations, and it is impractical to test an unrelated spouse for carrier status.

- Are the couple consanguineous and therefore could they share rare deleterious genes?

- Do the couple already have an affected child?

X linked

Women have two X chromosomes and men have only one. There are a few similar genes

on the Y chromosome in the pseudoautosomal region where the X and Y chromosome can pair at meiosis. As men are monosomic for most genes on the X chromosome, if there is a mutation on a gene located on the X chromosome, in nearly all cases males will be much more seriously affected. Duchenne muscular dystrophy is the commonest recognized X-linked disease with an incidence in boys of 1 : 3000.

In females partial expression may occur in some X-linked diseases, and this is frequently dependent on X-inactivation patterns; for example, Coffin-Lowry syndrome and fragile X syndrome. (X inactivation occurs in all people with more than one whole X chromosome. Only one X chromosome remains active, and the X chromsosome is inactivated as a random event. Therefore, in a women with two X chromosomes there should be an approximate 50 : 50 ratio for inactivation. If the inactivation is unequal and a high proportion of the X chromosome with the mutated gene remains active, a woman may be partially affected.) Some deleterious mutations may be lethal in early pregnancy in the hemizygous male, and only females are seen with the disease. Examples of the latter process include incontinentia pigmenti and Rett syndrome.

If inheritance is X-linked recessive, the following questions should be considered:

- Is molecular diagnosis possible?

- If molecular diagnosis is not possible as the affected patient died prior to molecular testing, can the carrier status be inferred using other family samples?

Non-Mendelian inheritance

Mitochondrial inheritance

Mitochondria have their own genome. All mitochondria are inherited from the mother. Therefore, if there is a mutation in the mother's mitochondrial genome all her offspring are at risk, but as each cell contains multiple copies of the mitochondrial genome, only some of which might contain the deleterious mutation, the number of abnormal copies inherited determines how severely/mildly the baby will be affected. This is known as heteroplasmy.

Epigenetic factors

Because epigenetic change in gene expression is not related to an underlying change in DNA sequence, it is therefore not passed on to future generations. An example is the imprinting defects causing Beckwith-Weidemann syndrome, although the genetics of Beckwith-Weidemann are complicated, and expert advice should be sought for recurrence risks in future pregnancies. Diseases with a parent of origin effect occur normally due to epigenetic changes such as methylation.

Free fetal DNA

Free fetal DNA (ffDNA) testing has only recently been introduced into clinical practice, and many patients will be unaware of its availability. If the patient is a carrier of an X-linked recessive disorder, preconceptional counseling should discuss fetal sexing using ffDNA. Blood for ffDNA testing can be taken from 8 weeks' gestation onwards[12]. Invasive testing will then only be required for male pregnancies. Congenital adrenal hyperplasia is an autosomal recessive disorder most commonly owing to a mutation in the 21 hydroxylase gene. An affected female fetus is at a 75% risk of developing moderate to severe clitoromegaly. Maternal dexamethasone treatment from approximately 7 weeks of gestation can be used for prevention. Only 1 : 8 at risk pregnancies will require this treatment and, by offering sexing by ffDNA, only women carrying female fetuses will need to continue the

steroids until chorionic villus sampling (CVS) can be performed at 11 weeks to determine whether the baby is affected. The applications for ffDNA are likely to expand widely over the next few years.

UNEXPLAINED PHYSICAL OR MENTAL HANDICAP WITHIN THE FAMILY

Many families have a family member with unexplained mental or physical handicap. A careful family history may suggest an X-linked disorder. Female carriers may be asymptomatic or may have mild disease manifestations. An X-linked history is suggested if there are two or more boys affected in two successive generations connected through unaffected or mildly affected females. To date, 60 genes have been identified to cause X-linked mental handicap resulting in syndromic (associated with other features than just mental handicap) and non-syndromic mental handicap[13]. Identification of X-linked inheritance is often difficult if only a single male or two male siblings are affected. In the latter case it is more likely to be as a result of an autosomal recessive gene rather than an X-linked gene. Another cause of unexplained physical or mental handicap, that could cause recurrence in a healthy couple without an affected child in the absence of consanguinity, is a syndrome with autosomal dominant inheritance with variable penetrance and chromosome translocations. In the past many parents believed that a baby was damaged at birth and, without good evidence of prematurity or cerebral palsy, this diagnosis should be viewed with caution. Chromosome analysis of the parent with the family history is a straight forward investigation which will exclude chromosome translocations except for cryptic translocations. A cryptic translocation cannot be identified by conventional cytogenetics; to date, this can only be diagnosed using fluorescent *in situ* hybridization.

Chromosome translocations

A chromosome translocation is the process by which two non-homologous chromosomes exchange chromosomal material between them and therefore do not have an identical pair to undergo crossing over at meiosis. There are two major forms of chromosome translocations.

Robertsonian translocation

Acrocentric chromosomes (13, 14, 15, 21 and 22) do not have short arms (p arms) that contain essential genes, and therefore two acrocentric chromosomes can join together with no deleterious effect on the carrier. The carrier will only have 45 chromosomes rather than the normal 46. This can lead to unbalanced chromosome rearrangements in the offspring of the carriers. The risk depends on the chromosome involved and the parent of origin of the translocation. The commonest Robertsonian translocation is 13:14 with an overall incidence of $1:1300$[14,15]. Only trisomy 13 and 21 are viable; very rarely a trisomy 22 fetus can survive pregnancy.

Survival for trisomy 14 and 15 is only possible if the embryo undergoes trisomic rescue but, as both these chromosomes are imprinted, major fetal abnormalities will be present depending on the parent of origin of the chromosome (Figure 3).

Reciprocal translocation

Reciprocal translocation is an exchange of chromosomal material between two non-homologous chromosomes resulting in the same total number of chromosomes. These translocations are individually very rare, and it is often difficult to predict the likelihood of a fetus having an unbalanced karyotype as the result. The larger the translocated segment the
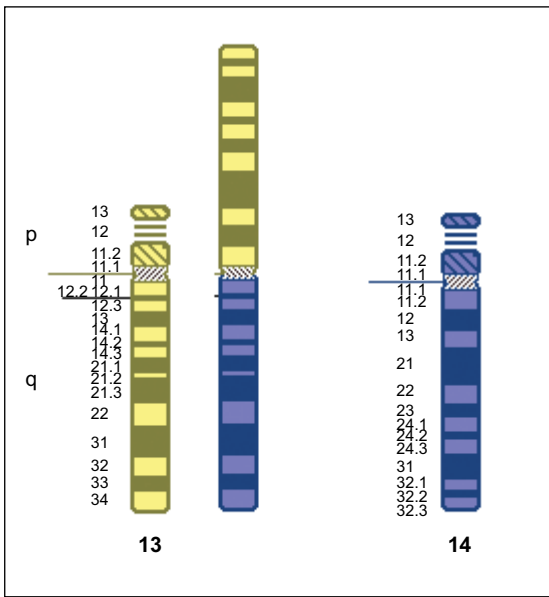
Figure 3 Robertsonian translocation

smaller the risk that the fetus will be viable if the karyotype is unbalanced[16].

Multiple miscarriages may occur in translocation carriers. Following three miscarriages it is recommended that a couple undergo chromosomal analysis to investigate the presence of a chromosomal abnormality (Figure 4).

Other chromosome abnormalities

Chromosome inversions

A segment of a chromosome may invert involving both the long and the short arms of the chromosome and this is known as a pericentric inversion. Depending on the position of the breaks on the chromosome this can have a reproductive risk for a pregnancy. If the breaks
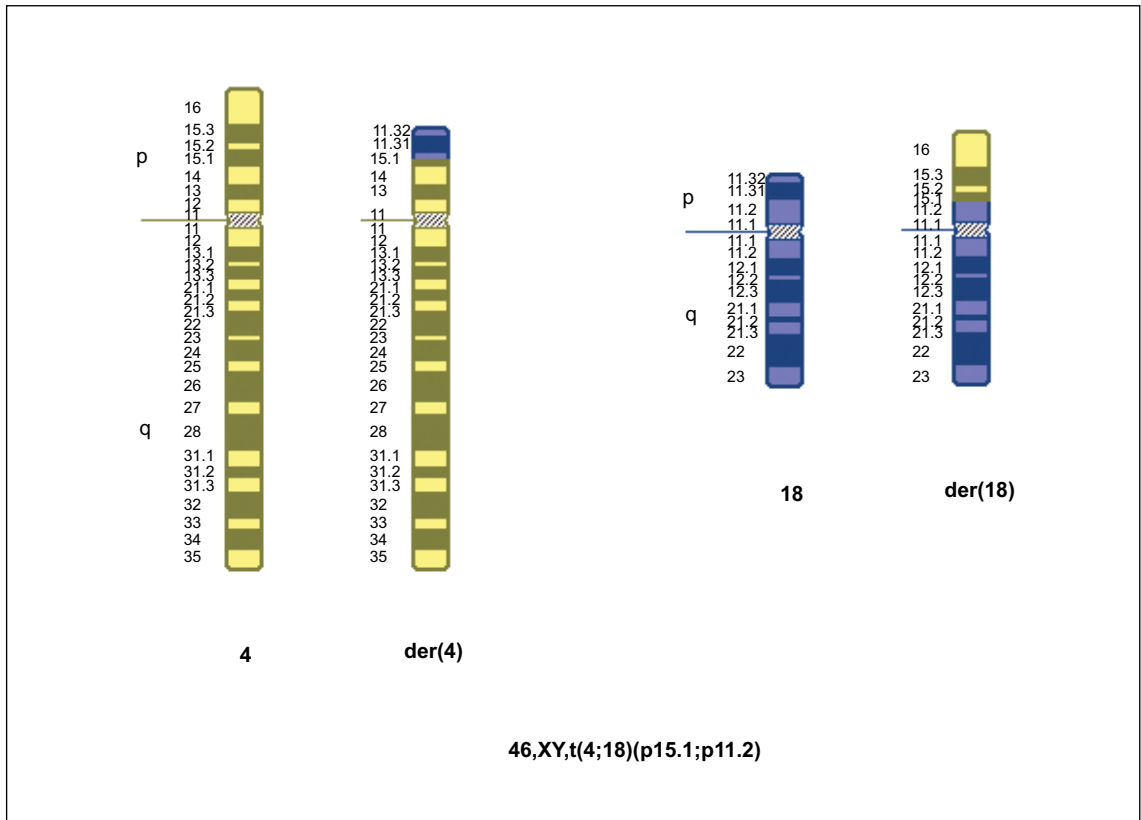

Figure 4 Balanced reciprocal translocation

are on the same side of the centromere, known as a paracentric inversion, the reproductive risks are very low (Figure 5).

Chromosome markers

Marker chromosomes are small extra parts of chromosomes that can cause major congenital abnormalities depending on the chromosomal origin. If a parent carries a marker and is unaffected, it is unlikely to cause problems in a baby. Chromosome markers can potentially reduce fertility and lead to imprinting defects. Marker chromosomes are frequently identified only in a proportion of cells (chromosome mosaicism, i.e. different groups of cells within an individual have a different chromosome makeup), as they are innately more unstable during mitoses and have a tendency to get lost during cell reproduction. If, however, the parent is a mosaic and the baby has the abnormality in every cell, there is a potential that there could be a phenotypic effect.

If a chromosome abnormality is suspected, the karyotype can be examined on blood chromosomes. If the abnormality is very small, it may only be recognized using fluorescence *in situ* hybridization (FISH); this would not be routinely undertaken. Molecular analysis does not identify balanced carriers and, therefore, is not a useful adjunct to cytogenetics. Small translocations cannot be identified by standard cytogenetics as they are beyond the resolution of the microscopes used. Methods of preparing chromosomes for analysis have improved over the past 15 years; therefore, a karyotype may need to be repeated if it was performed many years ago.

Preconceptional counseling considerations

It is necessary to assess the following points when considering a future pregnancy:

1. Is the couple at risk?
    a. What is the risk?
    b. What is the burden of the disease?
    c. Is preventative intervention possible?

2. What are the parents' expectations for a future pregnancy?
    a. Do they wish to avoid the birth of an affected baby by conventional prenatal diagnosis (CVS, amniocentesis, ultrasound)?
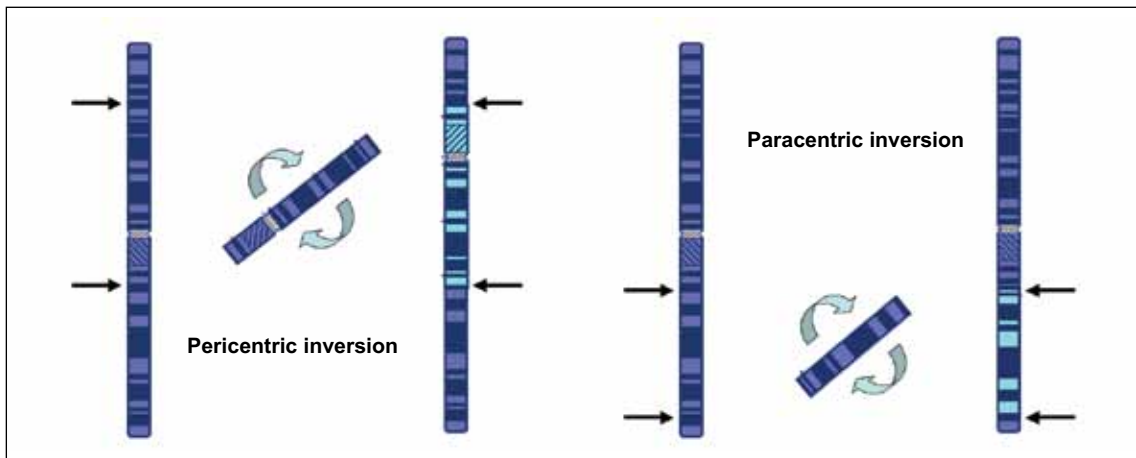   b. Do they wish to investigate the possibility of preimplantation genetic diagnosis (PGD)?

Figure 5 Chromosome inversions

c. If no prenatal diagnosis is available, is the risk to future pregnancies known?

d. If they would not consider having a pregnancy that might be affected and could not consider (a) or (b), then the available options are:
   i. Avoid further pregnancy;
   ii. Adoption;
   iii. Artificial insemination donor (AID)/ovum donation.

Preconceptional counseling is more preferable than counseling once a patient is pregnant, as information gathering and molecular testing may take a prolonged length of time resulting in:

1. Undue anxiety in pregnancies that may not be at risk;

2. Prenatal diagnosis not being available as test results are not obtainable;

3. Prenatal diagnosis being undertaken late;

4. Couples not having enough time to consider their options carefully.

Certain common disorders may be amenable to mass preconceptional screening such as sickle cell disease, thalassemia and cystic fibrosis. They are common genetic diseases with a high carrier frequency in specific populations. Screening for hemoglobinopathies is possible on a full blood count and screening for four mutations in the cystic fibrosis gene would pick up 75% of all carriers in the northern European population. Accessing the target population remains a challenge as on average 60% of pregnancies are unplanned, and uptake of this type of service is likely to be low. There are no preconceptional screening programs in the UK. Vaccination for rubella in the mumps, measles and rubella (MMR) vaccine is the only preventative measure undertaken in this group and this is at the age of 12 months!

Folic acid

It currently is recommended that all women take folic acid prior to as well as after conception. Spina bifida incidence has reduced since the recommendation of periconceptional folic acid and through the fortification of all wheat products in some countries such as the US, although the incidence of anomalies had already been falling especially in previously high risk areas. In couples who have already had a baby with spina bifida it is recommended that 5 mg daily is taken rather than the normal recommended daily dose of 0.4 mg. Folic acid is also said to reduce the recurrence risk of cleft lip and palate, and women with a previously affected pregnancy are also recommended to take 5 mg daily of folic acid.

GENETIC CAUSES OF INFERTILITY

A few couples presenting at infertility clinics have identifiable genetic causes for their infertility. Azoospermic men with congenital absence of the vas deferens should be tested for cystic fibrosis mutations which account for more than 50% of this group[17–19]. Azoospermic men should also have their karyotype examined, as Klinefelter syndrome, 47,XXY, is present in 1:500 men and is increasing in incidence for undetermined reasons. Y chromosome microdeletions can also cause azoospermia, and molecular or FISH analysis is likely required to identify these individuals. Intracytoplasmic sperm injection (ICSI) can be used in a proportion of men with azoospermia, but the cause of the infertility may then be passed on. In women, Turner's syndrome, 45,X/46,XX, may cause infertility. If these women succeed in conceiving, they have a higher incidence of chromosomally imbalanced offspring. Women with polycystic ovary syndrome may have a mild form of congenital adrenal hyperplasia which is amenable to treatment.

As chromosomal translocations may cause multiple miscarriages and infertility, karyotyping may be recommended. Clementini and colleagues[20] identified 3.95% of couples as carrying a chromosomal translocation in a study of patients referred for assisted reproduction. Many other disorders can also interfere with fertility, but it is beyond the scope of this chapter to consider them further.

MATERNAL HEALTH AND GENETIC DISEASE

With the improved prognosis of many childhood-onset diseases, many women who in the past would have either died or whose health would not have permitted a pregnancy now are able to consider a pregnancy. A number of issues need to be considered:

1. The fetus may be at risk of the same disease, as an autosomal dominant disease has a 1:2 chance of being passed to the fetus.

2. The disease process may affect the developing fetus.

3. Maternal health might be severely compromised by the pregnancy. Some diseases improve during the pregnancy only to deteriorate postnatally.

4. Maternal age for first pregnancy is increasing, and women may now have an illness in pregnancy that is rare in younger women, such as coronary artery disease.

Autosomal dominant diseases that may be inherited by the fetus and present *in utero*

All autosomal dominant diseases that affect one parent have a 50:50 chance of being passed on to the fetus. The disease may be of extremely variable severity, and the baby may be much more severely affected than the mother.

Myotonic dystrophy

Myotonic dystrophy affects approximately 1:5000 individuals. It can be asymptomatic for all of a patient's life, i.e. it is possible to be an asymptomatic carrier, or it can prove fatal in the neonatal period as a result of pulmonary hypoplasia and severe arythrogryposis. The congenital form is almost exclusively inherited from the mother. This disease exhibits anticipation. Classical myotonic dystrophy presents in early adult life with myotonia which is worse in the cold, facial diplegia, progressive muscular weakness, cataracts and extreme fatigue. Arrhythmias are common later on in the disease. It is slowly progressive, and the majority of patients show mental slowing with time. Both men and women have lower fertility with hypogonadotropic hypogonadism developing in men. Women who succeed in becoming pregnant have a higher risk of miscarriage and labor poorly with discordant uterine contractions resulting in a high rate of cesarean sections and postpartum hemorrhage. Anesthetics may cause malignant hyperthermia, and patients can have a prolonged recovery from anesthetic. All women affected with myotonic dystrophy should be carefully counseled regarding their own health and the risk to their fetus. Referral to specialized genetic counseling is strongly recommended[21].

Autosomal dominant polycystic kidney disease

Autosomal dominant polycystic kidney disease (ADPKD) is a common cause of end-stage renal failure. It has an incidence of 1:400–1:1000[22] individuals. There may be no previous family history of the disease. Two genes have been discovered that cause the disease, PKD1 and PKD2, with 85% of cases being due to mutations in PKD1 and a milder phenotype in PKD2. Cysts do not normally occur until early

adult/late teenage years; however, presentation may occur *in utero*[23]. This may be the first presentation in the family and, in any fetus that is identified as having cystic kidney disease, both parents should have a renal ultrasound. The most common form of fetal severe renal cystic disease is autosomal recessive polycystic disease (ARPKD), which invariably leads to renal failure in childhood and is normally lethal at birth owing to oligohydramnios and pulmonary hypoplasia. If the diagnosis is ADPKD, the outcome for the baby is good with normal renal function in childhood to be expected. Careful management of the child's blood pressure and treatment of urinary tract infections prolongs renal function. Pregnant women with ADPKD are at increased risk of developing hypertension during pregnancy, and renal function needs to be monitored. If a couple have had one child with prenatal presentation of ADPKD and one of the parents is affected, then the recurrence risk for the *in utero* presentation is 1:4.

Marfan's syndrome

Marfan's syndrome has a prevalence of 1–5:10,000, the major physical features being tall stature with arrachynodactyly with an arm span 10% more than the height, high arched palate, scoliosis and stretch marks. The major complications are lens dislocation and dissecting thoracic aortic aneurysm. The latter is of concern during pregnancy, and it is necessary for affected women to have an echocardiogram prior to pregnancy to look for any aortic root dilatation that may dissect during pregnancy. Marfan's syndrome may be identified in the fetus on ultrasound but normally this is the neonatal form of the disease which, although due also to mutations in fibrillin 1, is normally a result of specific mutations which are lethal in childhood. Most cases of Marfan's

syndrome would only be identified *in utero* by DNA analysis at CVS[24].

Ehlers-Danlos syndrome

Ehlers-Danlos syndrome (EDS) encompasses a large number of different genetic diseases with widely differing severity[25]. Ehlers syndrome type I which is associated with joint hypermobility, tall stature, hyperextensibility of the skin, easy bruising and cigarette paper scars can result in premature rupture of the membranes if the fetus is also affected due to weakness of the amniotic membranes. Repair of any tears/incisions after delivery should only be undertaken by an experienced surgeon as tissues are extremely friable.

Tuberous sclerosis

Tuberous sclerosis is a highly variable disorder due to mutations in two genes, TSC1 and TSC2. In its most severe form, it is associated with severe mental retardation and intractable fits; however, in its mildest form it may have only mild skin manifestations. The majority of affected patients have mild learning difficulties, well controlled epilepsy, some skin manifestations and possibly leiomyomata of the kidney. The patient may wish to undergo invasive prenatal diagnosis in view of the approximately 10% of cases that have the severe form of the disease, a mutation needs to have been identified within the gene in the family prior to the pregnancy for this to be feasible. A fetus may develop cardiac rhabdomyoma *in utero*. These rarely cause fetal/neonatal compromise and disappear over the first year of life but are an indication that the fetus is affected. An affected woman may be on antiepileptic drugs which may need to be changed prior to the onset of pregnancy.

MATERNAL GENETIC DISEASE THAT MAY BE AFFECTED BY PREGNANCY

Cardiac disease

Many women with successfully repaired congenital heart disease are now becoming pregnant. Most of these defects are unlikely to reoccur in the fetus, but careful assessment of the heart will be required both preconceptionally and during the pregnancy, as cardiac decompensation is not uncommon. Detailed cardiac examination of the fetus is often offered. Although the offspring risk is only of the order of 3.2%, the risk is higher if the mother rather than the father is affected[26].

Di George syndrome (velocardiofacial syndrome)

Di George syndrome is the commonest microdeletion syndrome. It is caused by a microdeletion on chromosome 22q11.2. Conotruncal cardiac defects are the commonest type of congenital heart disease. All couples where one parent is affected should be offered either prenatal diagnosis by CVS or detailed cardiac scanning. Other abnormalities include cleft palate, renal abnormalities, immune deficiency, short stature, mild to moderate mental retardation and hypocalcemia. Hypocalcemia needs to be screened for during or prior to every pregnancy as it can be asymptomatic, and the fetus, even in the absence of the deletion, may become hypocalcemia if the mother is hypocalcemia.

Cardiomyopathy

Hypertrophic cardiomyopathy Hypertrophic cardiomyopathy (HCM) is the commonest form of inherited cardiomyopathy with an incidence of 1:500[27]. Most adult-onset cases of HCM are inherited as autosomal dominant diseases with very variable penetrance. HCM is surprisingly well tolerated during pregnancy, with few patients with previous stable cardiac function deteriorating during pregnancy[28,29]; however, many women may be taking beta-blockers and a few will have implantable cardioverter defibrillators (ICDs). Children may be affected with HCM, but it is extremely unusual for a child to become symptomatic before the age of 8, even in the presence of hypertrophy that has been already identified.

Dilated cardiomyopathy The incidence of dilated cardiomyopathy has only been formally assessed by Codd and associates[29] in 1989. This study found the prevalence to be 1:2700; however, this was a gross underestimate. Dilated cardiomyopathy is thought to have a genetic basis in a less than 50% of cases; other causes include viral agents, drugs, radiation, coronary artery disease and hypertension. Decompensation is commoner in pregnancy than in HCM, and careful assessment needs to be undertaken prior to pregnancy. Labor needs to be particularly carefully monitored, and anticoagulation may be required. Patients with impaired cardiac function at the beginning of pregnancy are at the highest risk.

Arrhythmogenic right ventricular dysplasia The overall incidence of arrhythmogenic right ventricular dysplasia (ARVC) is about 1:5000. ARVC was only recognized in the 1990s, and it is a difficult diagnosis to confirm in the early stages as it requires cardiac magnetic resonance imaging and other specialist cardiac investigations[30]. Referral to a cardiologist specializing in inherited cardiac disease is advisable if the diagnosis is uncertain. Successful pregnancies have taken place in ARVC with the highest risk patients being those who have evidence of cardiac failure prior to the onset of the pregnancy.

Primary rhythm disorders

Long QT (LQT) syndromes are the most well recognized of this group with an overall incidence of 1:5000. The majority are inherited as an autosomal dominant trait, and the penetrance is highly variable. Pregnancy is a relatively safe time for patients with LQT syndrome, although severe hyperemesis can cause metabolic decompensation and should be treated more aggressively than in unaffected patients. Rashba and co-workers[31] undertook a retrospective study of cardiac events in LQT syndrome and compared prepregnancy, pregnancy and postpregnancy events of syncope, palpitations and sudden death. Of these patients, 2.8% had a cardiac event prepregnancy, 9% during pregnancy and 23.4% postpartum. Postpartum seems to be the most vulnerable time, especially in carriers of LQT2 mutations[32]. Many drugs (refer to CRY website[33] for up to date list) are contraindicated in LQT syndromes, and it is essential that these are not given to affected women as they may precipitate arrhythymia. Sleep deprivation may make patients more vulnerable to arrhythmias, and sudden waking from a deep sleep is a known risk factor in these disorders. Beta-blockers should be taken regularly during this period. There appears to be a small increase in the risk of sudden infant death syndrome in babies with LQT syndrome which may cause an increased amount of stress on the mother.

Other rhythm disturbances are even rarer and beyond the scope of this chapter, including Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia (CPVT) and isolated ventricular tachycardia.

Hypercholesterolemia

Statins are contraindicated in pregnancy. Although systematic review of the teratogenic effects has not supported the initial reports, it is advisable for these agents to be stopped during pregnancy[34].

Ehlers Danlos syndrome type I

EDS type I is mentioned above regarding premature rupture of the membranes. EDS type IV (EDS IV) is probably the most dangerous genetic disease of all during pregnancy; it is caused by mutations in collagen III. It can be inherited as an autosomal dominant or recessive form, and affected patients can be recognized by their premature aged appearance. They are highly prone to vascular rupture of medium sized arteries, such as the cerebral arteries, resulting in subarachnoid hemorrhage, coronary artery dissection, and mesenteric artery and intestinal rupture. Mortality has been quoted as up to 30% during pregnancy, and therefore pregnancy should be discouraged.

Respiratory disease

Cystic fibrosis

Many women with cystic fibrosis are now of child-bearing age. Whereas men with cystic fibrosis are azoospermic, women are able to conceive naturally. The success of a pregnancy depends on appropriate management of maternal health. The safety of a pregnancy must be discussed with the patient's respiratory physician. It is advisable that the partner is tested for cystic fibrosis. The northern European population carrier frequency is 1:24, but in other parts of the world it is lower. Of the mutations in the northern European population, 90% can be screened.

Metabolic disease

Survival without mental retardation was rare in this group of diseases, but early management

means there are an increasing number of adults of reproductive age who may wish to consider a pregnancy. There are many metabolic diseases, and specialists in metabolic medicine should be consulted for optimum management.

Phenylketonuria

Women affected with phenylketonuria (PKU), but effectively treated in childhood, are now having their own children, although the risk of the child being affected with PKU is low as it is an autosomal recessive disease. A strict low phenylalanine diet needs to be followed preconceptionally to avoid mental handicap and microcephaly in the fetus. Poor maternal control of PKU also results in an increased risk of congenital heart disease.

Ornithine carbamoyltransferase deficiency

Ornithine carbamoyltransferase deficiency (OCT) is an X-linked disorder frequently lethal in early infancy in males if not recognized. It is a urea cycle defect resulting in hyperammonemia and hepatic encephalopathy. Carrier women may have a protein aversion and present with hyperammonemia during intercurrent illness[35]. The presentation in girls may be subtle and missed. Treatment consists of a low protein diet and arginine supplementation. The puerperium is particularly high risk for these women when the body is catabolic. Labor needs to be carefully managed with early fluid replacement. Prenatal diagnosis can be requested.

Skeletal dysplasia

Women with skeletal dysplasia are not at high risk during pregnancy, and no particular management needs to be considered preconceptionally. Very short women may become breathless during advancing pregnancy, and delivery may occasionally have to be expedited. Women with kyphoscoliosis may be at particular risk. Women with osteogenesis imperfecta do not seem to have a high risk of fracture during pregnancy, but associated deafness may deteriorate during pregnancy. Increased osteopenia may occur during the postnatal period. Cesarean section is common and may be advisable due to abnormalities of the pelvic anatomy. Anesthetic review should take place as a number of skeletal dysplasias are associated with atlanto-occipital instability. Spinal anesthesia is unlikely to be contraindicated but may be technically challenging. If both partners have a skeletal dysplasia and the baby inherits both diseases, this can result in a very severe/lethal skeletal dysplasia and prenatal diagnosis may need to be discussed.

NON-GENETIC MATERNAL DISEASE LEADING TO CONGENITAL ABNORMALITIES IN THE FETUS

Systemic lupus erythematosus

Systemic lupus erythematosus is covered in Chapter 7.

Diabetes mellitus (diabetic embryopathy)

Diabetes mellitus is the most common chronic illness in pregnant women. The incidence of both type 1 and 2 diabetes is increasing. Type 2 diabetes is becoming increasingly problematic in pregnancy due to increasing obesity and increasing maternal age – developments that are seen in most developed countries and many parts of the developing world. Preconceptional counseling for diabetic mothers is well recognized and does not need to be reiterated in this chapter (see Chapters 5 and 32). Diabetic embryopathy is closely related to

maternal control of blood sugar. The congenital abnormalities described in infants of diabetic mothers are protean and include neural tube defects, congenital heart disease, renal abnormalities, caudal regression, hemifacial macrosomia and limb abnormalities[36].

Periconceptional counseling in women with learning difficulties

Many women with mild to moderate learning difficulties become pregnant and have children. It is vitally important that they have access to normal antenatal services and equally important that information be explained in simple terms, as often they will not be able to read or write, and this may not be obvious to the doctor or health professional. They also may have specific health needs secondary to the underlying diagnosis which need to be addressed, and the risk of the baby having a similar or more severe learning disability needs to be assessed. Referral to the local genetics service for such assessment may be required. For example, a number of X-linked disorders such as fragile X syndrome may have partial expression in a girl, whereas a boy could be much more severely affected and prenatal diagnosis will need to be discussed.

In more severe cases of learning disability, the patient may not be capable of looking after a baby, and family discussions and involvement of social services are entirely appropriate. It is also useful to have frank discussions with the parents or caregivers in cases of severe disability to attempt to determine whether the sexual activity that led to the pregnancy was consensual or forced and whether the patient has the capacity to protect herself against sexual predators who may meet with her. The partner may also have learning difficulties and details of the cause of his problems may also need to be investigated. It is important to address the care of the child postnatally.

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