Reproductive decisions after fetal genetic counselling

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A broad range of testing modalities for fetal genetic disease has been established. These include carrier screening for single-gene mutations, first-trimester and second-trimester screening for chromosome abnormalities and open neural-tube defects, prenatal diagnosis by means of chorionic villus sampling and amniocentesis, and preimplantation genetic diagnosis. Reproductive decisions before and after fetal genetic counselling represent the culmination of a dynamic interaction between prospective parents, obstetrician and genetic counsellor. The decision to undergo genetic testing before and after genetic counselling is influenced by a host of interrelated factors, including patient–partner and family relationships, patient–physician communication, societal mores, religious beliefs, and the media. Because of the complexity of personal and societal factors involved, it is not surprising that genetic counselling concerning reproductive decision-making must be individualised. A limited number of principles, guidelines and standards apply when counselling about testing for fetal genetic disease. These principles are that genetic counselling should be non-directive and unbiased and that parental decisions should be supported regardless of the reproductive choice. A critical responsibility of the obstetrician and genetic counsellor is to provide accurate and objective information about the implications, advantages, disadvantages and consequences of any genetic testing applied to prospective parents and their fetuses. These principles and responsibilities will be tested as newer technologies, such as array comparative genome hybridisation, non-invasive prenatal diagnosis and sequencing of the entire genome are introduced into the field of reproductive genetics and become routine practice.

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Introduction

During the past half-century, the number of genetic testing modalities presented to prospective parents has significantly increased. Before the 1970s, reproductive risk assessments were primarily based on family history, patterns of inheritance of known Mendelian diseases, and the prevalence of genetic, developmental disorders, or both, in newborn populations. With the introduction of prenatal genetic diagnoses, first by mid-trimester amniocentesis in the 1970s followed by first-trimester chorionic villus sampling in the 1980s, women were segregated into high-risk and low-risk pregnancies, primarily by preconceived ‘cost’ versus ‘benefit’ comparisons.

The high-risk category included advanced maternal age because of aneuploidy, a previous chromosomally abnormal conception, and known carriers either of a single gene mutation or of a chromosome rearrangement. Population screening for open neural-tube defects, first- and second-trimester screenings for aneuploidy, carrier screening for cystic fibrosis, and spinal muscle atrophy exemplify the use of categorisation of pregnancies by reproductive risks. These categorisations reflected established worldwide standards by healthcare providers concerning the application of genetic screening, genetic diagnostic testing, or both, as well as through legislation or health policies issued by states and countries essentially regulating prenatal testing programmes, pregnancy termination, or both.

Reproductive decisions after fetal genetic counselling, however, are essentially premised on the ‘rational-choice model,’ which views prospective parents as autonomous, sensible and individualistic decision-makers when it comes to prenatal testing. A central principle of genetic counselling that is universally accepted by the health profession is that genetic counselling of reproductive decisions should be non-directive and unbiased in support of parents’ ‘rational choices.’ A considerable disconnect, however, occurs between this fundamental principle of genetic counselling and the actual practice of obstetrics in the care of pregnant women and their partners. Although reproductive decisions after fetal genetic counselling are presumed to be primarily a personal choice, these decisions are directly and indirectly affected by a myriad of personal and social factors. These factors include individual beliefs and experiences, interpersonal and family relationships, clinician–patient relationships, cultural, societal mores, or both, and, possibly, even evolutionary-influenced decision-making. In this chapter, we aim to provide an objective critique of reproductive decisions after genetic counselling, and emphasise factors contributing to the understanding by prospective parents of the potential implications of screening and diagnostic test results.

Decision-making, primary and secondary influences

Genetic testing, preconceptually and prenatally, is ever evolving. Reproductive decisions after genetic counselling must be viewed within the cultural context of the second decade of the 21st century. The dynamics of individualism and society are rapidly changing, with an increase in personal choice, access to information and external influences. The individual can now access media, the internet, social media and unlimited sources of information. Within society, fewer marriages are taking place, we have an increase in the number of older couples, and a greater acceptance of disability. Criticisms of decision-making after genetic counselling, however, have not abated; namely, that prospective parents are not autonomous decision-makers, are not necessarily fully informed by their healthcare providers concerning reproductive choices and options, and are misinformed about the lives of individuals born with developmental disabilities (e.g. Down’s syndrome).

It has been generally accepted that decision-making by prospective parents is based on rational assessment of risk, benefit and choices, specifically: (1) the risk of a fetal abnormality compared with the loss of a normal pregnancy after invasive testing; (2) the benefit of gaining reassurance of a healthy fetus; and, (3) the options available if the fetus is identified as affected by a genetic, developmental disorder, or both. Although the birth of a healthy child is a goal shared by healthcare providers and society, their influence significantly alters, and possibly limits, patient autonomy. In general, either through guidelines established by national committees appointed by legislatures, professional societies dedicated to the treatment of pregnant women, or both, healthcare providers are held to a standard that carries professional and legal consequences. Under these guidelines or national programmes,
obstetricians, midwives and related healthcare providers are obligated to make available all of the current genetic testing modalities appropriate to individual prospective parents.

The goal of those providing care to pregnant women and their partners is to deliver a normal, healthy child, and healthcare providers have increasingly used preconceptual and prenatal genetic testing as a means of providing prospective parents as much reassurance as possible during the course of managing a pregnancy. The relationship between a pregnant woman and her obstetrician or allied healthcare provider cannot be over-emphasised as a factor that influences the decision-making process and the initial choices made concerning genetic testing. Reproductive decisions made after counselling in the case of a fetal genetic disorder has been the subject of a large body of research, emphasising the multi-faceted factors involved in assessment and choice.2–10 Prospective parents must first address their views concerning their real and perceived risks of the possible birth and care of a child with a genetic disability compared with the benefit of information of fetal wellbeing through genetic testing and the prospect of selective termination, if affected.11 Resolution of these questions depends on how individuals make decisions in the face of competing or inconsistent value systems.

The numerous factors that initially influence reproductive decisions before and after genetic counselling, and some of their interactions, are shown Fig. 1. The importance and effect of each of these factors can only be presumed to vary considerably among different decision makers. Quantifying or assigning value to each factor is understood to be extremely difficult. Research does not present a clear picture of the interaction of factors influencing reproductive decisions made before undertaking preconceptual or prenatal genetic testing. No sufficiently comprehensive model or explanation has categorised the factors influencing reproductive decisions.3

In a systematic review of 32 publications of the perceptions of women, their partners and health professionals of Down’s syndrome prenatal testing,3 the most frequently reported sources of difficulty for decision-making in women were pressure from others, emotions and lack of information; in partners, emotion was the most frequently reported source of difficulty; and in health professionals, it was lack of information, length of consultation, and personal values.3 The most important sources of reassurance were, in women, personal values, understanding and confidence in the medical system; in partners, personal values, information from external sources, and income; and, in health professionals, peer support and scientific meetings.3 In most Western cultures, be it in the USA where healthcare is provided on a private, non-governmental basis, or in Canada and many European countries where medical care is provided as a government service, most prospective parents expect and empower their
own healthcare provider to provide guidance and direction in making reproductive decisions. As such, they become the dominant, compelling influence in the means and forms of genetic testing.

A decision to terminate a pregnancy after identifying a fetal anomaly illustrates the complexity of the process. Issues thought to affect decision making were related to timing of the diagnosis, the nature of the anomaly, type and severity, level of certainty about the diagnosis and prognosis, and religious and moral convictions of the parents. The effects of diagnosis, demographic factors and gestational age have been evaluated after identifying a perinatal lethal condition. Pregnancies with a central nervous system defect or severe urinary tract defect were more likely to be terminated, whereas pregnancies with unexplained oligohydramnios or a twin pregnancy, in which one twin was affected, were more often continued to term. Demographic factors, gestational age at the time of diagnosis, and referral indications did not influence decision-making in pregnancies diagnosed with a lethal condition. Whether timing of diagnosis (first trimester compared with second trimester) influenced decision-making, however, is controversial.

The rationale in support of parents favouring first-trimester termination included obstetrical safety, less emotional damage and privacy issues (i.e. the pregnancy is not yet physically evident). Yet, after diagnoses of fetal aneuploidy or structural anomalies, reproductive decisions were not affected by gestational age, as long as legal limits for termination were met.

Several studies have shown that the specific chromosome abnormality and its prognosis are major determinants of the parental decision to continue or to terminate a pregnancy. Parental decisions to terminate a pregnancy varied by type of chromosome abnormality, by the presence of fetal ultrasound anomalies, and by the number of previous children. For example, in one Turkish study, 85% of parents terminated the pregnancy if autosomal aneuploidy was present, whereas 60% continued their pregnancy when a sex chromosome abnormality was identified. In a similar study of Swiss parents, pregnancy termination rates were as follows: Turner syndrome 100%; Klinefelter syndrome 50%; 47,XXX females 70%; 47,XY 50% and mosaic cases 43%.

Prospective parents have three options for assessing reproductive genetic risk: screening, diagnostic testing or rejection of genetic testing, either completely or selectively. A minimum of nine major testing modalities are available relative to reproductive decisions after genetic counselling; their timing, advantages, risk to fetus and limitations are presented in Table 1.

<table>
<thead>
<tr>
<th>Testing modality</th>
<th>Timing and advantages</th>
<th>Risk to fetus</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parental carrier screening</td>
<td>Preferably preconceptually</td>
<td>None.</td>
<td>Not all mutations in genes analysed. False-positive rate; false-negative rate.</td>
</tr>
<tr>
<td>First-trimester screening for aneuploidy</td>
<td>10–13 wks; high detection rate.</td>
<td>None.</td>
<td>High false-positive rate; later in pregnancy.</td>
</tr>
<tr>
<td>Chorionic villus sampling</td>
<td>10–13.6 weeks; early diagnosis.</td>
<td>Depends on operator skill.</td>
<td>Results available late in gestation.</td>
</tr>
<tr>
<td>Amniocentesis</td>
<td>From 15 weeks onward; detects open neural-tube defects.</td>
<td>Depends on operator skill.</td>
<td>Pregnancy rates less than 30%; accuracy of genetic analyses not established.</td>
</tr>
<tr>
<td>Preimplantation genetic diagnosis</td>
<td>Transfer of only unaffected embryos.</td>
<td>None.</td>
<td>May identify copy-number variations of unknown clinical significance.</td>
</tr>
<tr>
<td>Array comparative genome hybridisation</td>
<td>Anytime; higher detection rate of copy-number variations.</td>
<td>None.</td>
<td>Skill of ultrasonographer; anxiety caused by presence of 'soft' signs.</td>
</tr>
<tr>
<td>Ultrasound fetal anatomic survey</td>
<td>18–22 weeks; minimal risk.</td>
<td>None.</td>
<td>Limited to aneuploidy; false negative rate; false positive rate.</td>
</tr>
<tr>
<td>Non-invasive prenatal diagnosis</td>
<td>10 weeks onwards.</td>
<td>None.</td>
<td></td>
</tr>
</tbody>
</table>
Population carrier screening and risk

Screening connotes a non-invasive approach to evaluating a pregnancy either by means of testing the prospective parents for their carrier status for single-gene mutations or by the use of ultrasound and maternal serum markers for determining the risk of aneuploidy, open neural-tube defects, and other structural anomalies associated with developmental and genetic syndromes. Screening provides a quantitative assessment of risk for a genetic disorder, compared with a diagnostic test, which leads to a ‘yes’ or ‘no’ result (i.e. affected or unaffected). Population-wide carrier screening for single-gene disorders (e.g. cystic fibrosis) identifies specific mutations within a gene, and leads to a reduction in the risk of being a carrier.

A common misconception by patients, and many times reflected in the language used by health professionals, is that carrier screening is definitive in determining carrier status for single genes. It is common for pregnant women to report that they are not a carrier for cystic fibrosis or spinal muscle atrophy after genetic testing. A negative carrier screening result signifies a reduction in risk, the magnitude of which is dependent on a number of factors, such as the composition of mutations comprising the testing panel, their frequency in the population undergoing screening, and family history. Even the application of DNA sequencing, which identifies sequence changes in the coding regions of a gene known as exons while significantly reducing the risk of being a carrier, does not eliminate that possibility. Indeed, after population-carrier screening for cystic fibrosis or open neural tube defects, it is not unusual for women, and many times supported by health professionals, to categorise a negative result in absolute terms (e.g. I am not a carrier, or ‘the maternal serum alpha-fetoprotein was normal’).

The challenge to those counselling is formidable, as numerical assessments run counter to pregnant women’s desires to confirm and reinforce that their pregnancy is normal, healthy and not at risk. This desire for confirmation is understandable and likely correct, given that most pregnancies are normal and healthy. This categorisation of negative results in absolute terms fails to help pregnant couples grasp the idea of ‘probability’. This approach fails to properly inform pregnant couples who, despite a negative carrier screening result, may deliver a newborn with that specific genetic disability. The latter also has the obvious potential of significantly compromising relationships with healthcare providers.

What constitutes an appropriate panel for population screening has not been established; examples include the number of mutations in the cystic fibrosis gene, whether to test for spinal muscle atrophy and fragile X, and what genes and mutations are medically indicated for the Ashkenazim Jews. These issues will be further complicated in the near future by the introduction of technologies capable of sequencing the entire genome (‘next generation sequencing’).

Both the American College of Obstetrics and Gynecology and the American College of Medical Genetics recommend screening of the general population for 32 of the most common mutations in the cystic fibrosis gene, a selection biased toward their frequencies among white people with the apparent mistaken belief that cystic fibrosis is uncommon among other races. Commercial companies in the USA make available panels that encompass nearly 100 gene mutations, offering a broader spectrum of cystic-fibrosis mutations present in other racial groups (e.g. Hispanic people). On the other hand, the American College of Medical Genetics also recommends population-wide screening for spinal muscle atrophy. With the carrier frequency of the fragile X ranging from 1 in 60 to 1 in 80, screening for this mental retardation syndrome is becoming widespread especially in the USA and Israel.

Carrier screening among Askenazim Jews began in the 1960s with Tay Sachs disease. The original recommendation of the American College of Obstetrics and Gynecology and the American College of Medical Genetics was to screen for mutations in four genes: Tay Sachs; cystic fibrosis; Canavan; and Familial Dystonomia. Five other genes were subsequently added: Fanconi anaemia group C; Niemann-Pick type A; Bloom syndrome; Mucolipidosis IV; and Gaucher disease Type 1. Most commercial companies offer carrier screening for as many as 16 genes, with the rationale that the carrier rate is greater than 1 in 100 for each gene. With whole-genome sequencing, there is a push for rewarding any technology that would sequence the entire human genome for $1000 or less. Consequently, in the near future, it is anticipated that carrier screening in the general population will generate significant problems to prospective parents and to their healthcare providers because of the
total amount of information made available and the uncertainty associated with DNA sequences whose clinical effects are either unknown or range from ‘normal’ to ‘affected’.

What is acceptable as ‘normal’ to prospective parents and their healthcare providers needs to be redefined. This is exemplified by a study of decision-making related to Gaucher disease. After carrier screening for the N370S gene mutation, five parents elected pregnancy termination, whereas none of the 21 children homozygous for this gene mutation presented with severe disease after 15 years.

Carrier screening for the N370S mutation causing Gaucher disease resulted in termination of asymptomatic fetuses, emphasising the need to determine guidelines for what gene mutations should and should not be reported in accordance with their frequencies in different populations. A wide spectrum of clinical effects are associated with the 1720 mutations in the gene for cystic fibrosis, from non-classical to classical. In a direct sense, selecting certain cystic fibrosis gene mutations primarily present in white people also lowers the detection rates when applied to other races.

The compositions of different mutation panels needs to be re-evaluated on a regular basis, particularly as technology for identifying carriers is constantly improving. A consequence of professional organisations or government authorities determining the composition of carrier-screening panels for any gene is the erosion of patient autonomy in reproductive decision-making. Sequencing of the entire genome is becoming more widely available. It is expected that healthcare providers will face even greater difficulties when counselling in the future because of the availability of genetic information whose clinical effects are unknown. In response, genetic counselling is likely to become less individualised and more formal and fixed in content. The entire genome of a fetus has already been sequenced non-invasively by analysis of cell-free fetal DNA present in the maternal circulation (Lo YM, personal communication).

First-trimester and second-trimester screening and risk

First-trimester screening using measurement of nuchal translucency and maternal serum proteins, free beta human chorionic gonadotropin, and pregnancy associated plasma protein A, has become a critical means to assess the genetic health of a pregnancy. Increased nuchal translucency (greater than 99th centile) is associated with increased risk for a broad spectrum of genetic and developmental disorders, including single-gene mutations, especially Noonan syndrome, chromosome abnormalities, cardiac malformations and pregnancy loss. Levels of placental-derived maternal serum proteins below the 1–2% centile have been associated with an increased risk for a series of pregnancy complications, including prematurity, intrauterine growth retardation and eclampsia. A fetal nuchal translucency greater than the 95th centile is associated with an increased risk of a multiplicity of adverse pregnancy and postnatal outcomes. As a consequence, counselling of women about their testing options and range of pregnancy outcomes becomes increasingly difficult and complicated.

An increased nuchal translucency requires continuous counselling. Staging the diagnostic evaluation of the pregnancy is needed first for chromosome abnormalities by chorionic villus sampling, followed by molecular analysis for single-gene mutations, particularly Noonan syndrome. Echocardiography is needed to rule out a cardiac malformation, and ultrasonography is needed at 18–20 weeks’ gestation to identify any structural anomalies associated with skeletal dysplasias. In most fetuses, however, nuchal translucency measurements are less than the 95th centile at 11–13.6 weeks’ gestation. Women can be counselled that 97% of such pregnancies come to term and have a healthy outcome. Therefore, after first-trimester measurement of nuchal translucency and maternal serum proteins, genetic counselling can be reassuring to at least 95% of pregnant women.

The factors contributing to the decision to undergo or not undergo prenatal screening for aneuploidy have not been adequately defined. Studies in several Western countries have documented ethnic differences, with women from minority groups and of non-Western ethnic origin less likely to participate. It has not yet been determined to what extent pregnant women are offered prenatal screening, whether they are interested in the information generated, and to what extent they actually understand and use counselling information to make an informed decision about whether to participate in prenatal screening or not. It has not yet been determined how factors such as ethnic background, religious beliefs, language barriers, educational level and health literacy contribute to informed decision-making concerning participation in prenatal aneuploid screening.
Many prospective parents have limited experience with risk assessments after first- and second-trimester screening for aneuploidy or after second-trimester screening for open neural-tube defects. Ultrasound evaluation at 18–20 weeks’ gestation is known to produce substantial and long-term parental anxiety when a ‘soft sign’ for Down’s syndrome is identified or when an anatomical measurement is below the 5th centile or above the 95th centile. Prospective parents have an overwhelming desire to receive assurances that ‘everything is fine with their pregnancy’. Counselling about the implications and consequences of screening for aneuploidy or an open neural-tube defect represent a considerable challenge to all healthcare providers (e.g. a realistic assessment of the meaning of a false–positive result or a false–negative result in the light of the parental anxiety that accompanies pregnancy).

A new ‘pyramid of care’ has been proposed, using a series of first-trimester ultrasound and maternal serum markers capable of identifying risks for a large number of adverse pregnancy outcomes. This pyramid of care encompasses risk assessments for preterm delivery, pre-eclampsia, gestational diabetes, small for gestational age, and fetal macrosomia. These added measures have the potential of early recognition and treatment of a number of serious pregnancy complications, thereby enhancing a more positive outcome. The new pyramid of care also has the potential of dramatically increasing the anxiety of all prospective parents, and this will require judicious counselling during the performance and subsequent interpretation of first-trimester screening measurements.

This counselling will have to acknowledge each patient’s level of anxiety and understanding while undergoing first-trimester screening. If prospective parents are to make reproductive decisions that are rational and reflect their individual interests, it is necessary that genetic counselling becomes an essential component of first-trimester screening and separate from conventional, routine obstetrical care. The potential fall-out of the new pyramid of care requires that professionals recognise and acknowledge adverse side-effects and develop the counselling skills necessary to guide parents in understanding and coping with the uncertainty associated with first-trimester screening.

Prenatal diagnosis

Since its inception, the standard of care for prenatal genetic diagnosis has been to provide genetic counselling before the procedure to inform women how the invasive procedure will be carried out, the obstetrical risks and benefits of testing, and, most importantly, the limited options if genetic testing shows that the pregnancy was affected. If this standard is fulfilled, women undergoing invasive testing provide informed consent, as they have been specifically informed that they may have to consider pregnancy termination. Although ensuring patient autonomy based on personal beliefs and experiences should be the focus of reproductive decisions concerning prenatal diagnostic testing, patient choices and actions are significantly influenced by numerous other factors and interactions, including partner support, obstetrician support and direction, medical standards, country of origin, and religious and social influences.

The two major external forces influencing patient decisions to undergo invasive prenatal diagnosis are health providers providing or even encouraging chorionic villus sampling and amniocentesis, and the policies and standards of individual states and countries defining the application of these genetic testing modalities.

Several reports have been published on reproductive decisions after the detection of a fetal anomaly. Significant factors contributing to this decision vary, and include the nature of the anomaly, the gestational age at diagnosis, obstetric history, socioeconomic status, educational level and religious background.

Understanding the role and importance of various influences on the original decision to undergo or forgo invasive genetic testing has been primarily limited to proposing theoretical models of reproductive decision-making. What is clear is that most women want to know as much as possible about the health of their fetus and, when found to be at risk, these women become anxious and more likely to undergo invasive diagnostic testing even when counselled about the low but real obstetrical risks of chorionic villus sampling and amniocentesis.

Patients’ risk perceptions, like those of health providers and policy makers, may be different from objective reality. These misperceptions are a consequence of complex psychological phenomena and often resistant to genetic counselling and education.
Currently, in several European countries, an assessment is ongoing to establish whether rapid detection of aneuploidy by quantitative fluorescence polymerase chain reaction or multiplex ligation-dependent probe amplification are appropriate replacements for conventional chromosome analysis after prenatal diagnosis. Proponents of the former methods argue that substitution of conventional chromosome analysis will shorten the stressful waiting time for parents, resulting in more straightforward prenatal and genetic counselling, offer substantial cost savings, and provide assessments that have only a small chance of failing to identify chromosome abnormality with serious clinical, long-term consequences.

Those opposed to replacing conventional chromosome analysis by rapid aneuploid detection argue that the latter approach will lead to an unacceptable increase in live births presenting with conditions that result in severe developmental disabilities because of undetected chromosome abnormalities. This choice was presented to pregnant women undergoing amniocentesis for advanced maternal age (36 years or older) or increased risk for Down’s syndrome after first-trimester screening (risk greater than 1 in 200 at time of testing). Offering a choice between conventional chromosome analysis and ‘stand alone’ rapid aneuploid detection by quantitative fluorescent polymerase chain reaction (QFPCR) did not have any influence on levels of anxiety, stress, personal perceived control, or generic health.

If individualised choice in prenatal diagnostic testing is appropriate, and to be the standard of care, this demands the development and implementation of sound strategies to counsel objectively about the advantages and disadvantages of each technology. Despite the uncertainty surrounding the application of QFPCR, certain countries, such as the UK through policies developed by the National Health Service, are instituting QFPCR as a first-line test for women undergoing invasive prenatal diagnostic testing. Conventional chromosome analyses, or a more sophisticated genetic analysis by array comparative genome hybridisation, will be carried out only in the presence of a structural malformation and in the absence of aneuploidy for the five chromosomes, 13, 18, 21, X and Y.

A major argument justifying prenatal genetic diagnosis by chorionic villus sampling or amniocentesis is that these technologies provide concrete means for obtaining information that a genetic abnormality is not present. It has been repeatedly claimed by reproductive obstetricians and geneticists that the availability of these diagnostic modalities has increased the overall birth rate by encouraging high-risk couples to undertake a pregnancy. The detection of a genetic disorder after chorionic villus sampling or amniocentesis, however, presents couples with the ethical dilemma of pregnancy termination, and this, in turn, raises legal considerations about fetal viability based on legal concepts not medical realities. This situation results in conflict between individual rights and governmental regulations concerning personal choice and autonomy in health and family planning decision-making.

Policies to regulate pregnancy termination vary among the different states in the USA as well as among countries in the European Union. In the USA, at the federal level, a woman is allowed pregnancy termination for social as well as medical reasons but not beyond the limit of viability. A increasing number of state-based efforts are in existence to influence a woman’s exercise of her rights by requiring healthcare providers to adhere to schedules of ultrasounds and information disclosures intended to discourage pregnancy termination. In European countries, policies regulating pregnancy termination range from complete prohibition to authorisation under specific conditions. These conditions include indications for diagnostic genetic testing, gestational age, the process and regulation of decision-making, and the clinical severity of the genetic disorder under consideration. What has been the choice of women when a genetic disorder has been identified?

In France, pregnancy termination is available at the mother’s request, regardless of gestational age, if at least two clinicians, who are members of the Multidisciplinary Centre for Prenatal Diagnosis authorised by the Ministry of Health certify that there is a high probability that a fetus is affected by a severe, incurable disease.

In a study of pregnancy termination after prenatal diagnosis, 94% of the decisions to terminate were made by women and professionals in response to anomalies that are considered clearly lethal or resulting in substantial physical, mental disabilities, or both. These anomalies included chromosome abnormalities, single- or multiple-organ system malformations, Mendelian disorders, fetal infections or exposure to teratogenic agents, as well as obstetrical complications (e.g. premature rupture of membranes).
In Greece, most pregnant women would terminate for a lethal fetal anomaly (86%) as well as for an anomaly causing mental or physical handicap (66–78%), even late in pregnancy (65%). In the USA, several studies have shown that specific karyotype abnormalities and resulting prognoses were the major reasons for parental decision to continue or terminate a pregnancy: for autosomal aneuploidy, unbalanced translocations and monosomy X, elective termination rates ranged from 82–99%, whereas for sex chromosome aberrations, the rates of termination ranged from 42–88%. In contrast, in chromosomally normal pregnancies, genetic counselling about the prognostic severity of the ultrasound diagnosis was a major determining factor in arriving at a reproductive decision: after classifying ultrasound abnormalities in euploid pregnancies as ‘mild’, ‘uncertain,’ and ‘severe,’ termination rates were 0, 12 and 66%.

The magnitude of the genetic risk was found to be of relative importance in reproductive planning. When the disorder was perceived as severe, and the risk was interpreted as high (greater than 15%), 72% chose to have children. The availability of prenatal diagnosis became important only in combination with a high genetic risk. Forty-seven per cent of the couples with a high genetic risk refrained from having children when prenatal diagnosis was not available. In the absence of prenatal diagnosis, couples who had an affected child were more cautious about trying again than those who did not: 50% compared with 14% decided to avoid future pregnancies.

Preimplantation genetic diagnosis

Reproductive decisions after genetic counselling for preimplantation genetic diagnosis (PGD) has long been a subject of discussion, starting before its actual implementation as a clinical test. Preimplantation genetic diagnosis (PGD) may have altered traditional prenatal diagnosis by completing genetic testing before embryo implantation; however, after more than 20 years, knowledge is still limited about the decision-making process that couples of high reproductive risk undergo in deciding whether to use PGD. The decision-making process is viewed as dynamic and consists of four interrelated phases: (1) the identity phase, becoming aware of high reproductive risk; (2) the contemplative phase, exploring reproductive options; (3) the resolution phase, formulating plans for implementing the decision to use PGD; and, (4) the action phase, initiating PGD scheduling.

The original rationale for PGD was to provide a viable response to couples at high reproductive risk for a genetic disorder unwilling to terminate any pregnancy, affected or unaffected. High risk included couples at risk for Mendelian disorders (e.g. cystic fibrosis, Duchenne muscular atrophy, and balanced carriers of structural chromosome rearrangements). Preimplantation diagnosis provides the opportunity to select embryos before transfer by means of conventional in-vitro fertilisation. Genetic information from individual embryos can be derived from three biological sources: polar bodies I and II; blastomeres on days 3–4; and, trophectoderm on days 5–6.

Over the past 2 decades, progressive improvements have taken place in molecular technologies, resulting in improved accuracy of genetic analyses carried out on single cells. For example, fluorescence in-situ hybridisation for the screening of aneuploidy and whether an embryo was chromosomally balanced, has been replaced by microarrays. The latter is capable of detecting a potentially significant problem relatively unique to PGD, namely, allelic ‘drop-out,’ wherein selective amplification of one gene sequence takes place over its homologue.

At a minimum, genetic counselling of high-risk parents considering PGD requires detailed, individualised discussion of the process of in-vitro fertilisation, including pregnancy and ‘take home baby’ rates; the source of tested cells and their processing; and, the type, accuracy and additional cost of genetic analyses. All of these factors vary considerably among programmes and healthcare providers offering PGD.

The European Society of Human Reproduction is completing a clinical trial of the efficacy of microarrays applied to polar bodies. It has now been recognised that fluorescence in-situ hybridisation has serious shortcomings, and has not resulted in substantial improvements in the overall pregnancy outcome when applied as a screening assay for aneuploidy in the case of advanced maternal age, infertility, previous pregnancy loss, male or female factors and previous failed in-vitro fertilisation. No randomised, multicentre trial has been conducted in the USA on the efficacy and
safety of PGD. Couples most likely to benefit from PGD are known carriers of single-gene mutations or are balanced translocation carriers. Their decision to undertake PGD is typically made after the birth of one or more affected offspring. With population-wide carrier screening becoming universally accepted for cystic fibrosis, spinal muscle atrophy, fragile X syndrome and a series of gene mutations more common among Ashkenazim Jews, PGD for primagravida women is now becoming more common.

Preimplantation diagnosis is not without controversy. In certain European countries, such as Italy, PGD is not permitted. In certain European countries, biopsy of the preimplantation embryo is permitted in limited circumstances, only if the parents have a predisposition to a serious genetic illness, such as in Germany. In the USA, no limits have been imposed on the type and nature of medical disorders to which PGD can be applied. Thus, PGD for adult-onset disorders, such as breast cancer in the case of the BRCA genes, or for typing of an embryo as a potential bone marrow donor for Fanconi anaemia, have been reported.44,45

From a pregnancy management perspective, it has been a standard policy of those providing PGD to recommend strongly the need for confirmation of any PGD analysis by invasive diagnostic testing, such as chorionic villus sampling or amniocentesis. This is an anathema to most couples, yet must be part of any genetic counselling provided before undertaking PGD.

Prospective problems

At least two new genetic technologies leading to reproductive decisions after genetic counselling are characterised by uncertainty and debate: (1) non-invasive prenatal diagnosis for Down's syndrome; and (2) the application of microarrays and next-generation sequencing to chorionic villi and amniocytes.

Non-invasive prenatal diagnosis for Down’s syndrome has been introduced into the USA marketplace, and is expected shortly in China and Western Europe. It has, however, already generated vigorous discussion: first, about its appropriate application46 and, second, whether prenatal testing for Down’s syndrome represents coercion and eugenics47 or options and choices.48

The International Society for Prenatal Diagnosis agreed that, with appropriate genetic counselling, non-invasive prenatal diagnosis can be helpful for women determined to be high risk for Down’s syndrome but did not endorse the ad-hoc use for women at lower risk. The International Society emphasised that (1) the non-invasive test currently available is only for fetal Down’s syndrome, which comprises only one-half of the fetal aneuploidy identified through diagnostic testing; (2) that the test does not detect all cases of fetal Down’s syndrome; (3) that there are false-positive results; and, that other genetic disorders, particularly Mendelian and microdeletion syndromes, would still require either first-trimester chorionic villus sampling or midtrimester amniocentesis.46

At the same time, concern was raised over discrimination against families of children with Down’s syndrome who chose not to have prenatal testing or chose to continue a pregnancy after a prenatal diagnosis.47 Examples of governmental rhetoric and policies condoning eugenic and commercial policies meeting criteria established by experts for eugenics were given.47

McCabe and McCabe in their paper47 attempted to sensitise the clinical genetics community to these issues and emphasise the need to provide neutral non-directive prenatal genetic counselling. In response, members of the California Prenatal Screening Program stated that their program provided information to women that allowed them to make informed choices about prenatal screening and prenatal diagnosis, and that women could decline any or all of these and follow-up services, based on established guidelines for non-directive genetic counselling.48 These issues, and the reproductive choices made after genetic counselling about non-invasive prenatal diagnosis, will likely continue to be discussed by national and international professional societies as well as by the popular media.

Array comparative genome hybridisation is anticipated to be a first-tier test in prenatal diagnosis and likely to replace conventional chromosome analysis.49 This technology can be high throughput, with turnaround times as fast as 1 day from DNA extraction, compared with a conventional chromosome analysis requiring 7–10 days for complete karyotyping. Array comparative genome
hybridisation can certainly be more comprehensive and of higher resolution than conventional chromosome analysis, depending on the platform and genomic content. Many submicroscopic chromosome rearrangements that lead to copy number variations have been shown to cause distinctive and recognisable clinical phenotypes. A large number of commercially available array platforms have been applied to the identification of different types of copy number variations, ranging from pathological to benign to unknown clinical significance.

Genetic counselling before and after the application of array comparative genome hybridisation in the case of prenatal diagnosis is anticipated to consume a significant amount of time on the part of the genetic counsellor. To illustrate this anticipated problem, numerous cases have been shown to have sizable microdeletion (e.g. greater than 100 kb) present in the fetal genome and have been associated previously with autism that is also present in a parent reported as ‘normal’. A number of explanations have been forwarded, such as the nature of gene penetrance and expressivity, the role of other genes either enhancing or reducing the clinical phenotype of autism, and whether the parents are indeed ‘normal’. Prospective parents will have to weigh the ‘cost’ of such information, particularly the uncertainty generated, against the ‘benefit’ of gaining considerably more information about fetal wellbeing than currently available by means of conventional chromosome analysis of chorionic villi or amniocytes.

**Conclusion**

A basic conflict exists between prospective parents and their caretaker. During the course of a pregnancy, prospective parents continuously seek the highest level of reassurance that the fetus is developing normally and free of genetic disease. Despite application of the most extensive genetic screening and diagnostic testing available, healthcare providers must continuously evaluate the pregnancy for developmental and genetic disorders.

Genetic testing approaches differ significantly between countries. These include molecular compared with antibody testing for rhesus status, conventional chromosome analysis compared with rapid aneuploidy testing using fluorescent in-situ hybridisation, and quantitative fluorescence polymerase chain reaction or related technology. Decisions made after genetic counselling have limited parameters: parents must consider diagnostic testing after positive screening for a genetic disorder and then either continue the pregnancy or electively terminate, if the pregnancy is affected.

Presently, gene therapy as an option is confined to a small set of inborn errors of metabolism. It is anticipated that molecular testing for assessing the fetal genome will expand enormously within the next 3 years and, as a result, the amount of genetic information will far exceed understanding the clinical implications and consequences of that information. This development will likely prove extremely challenging to healthcare providers and their patients in their decision-making.

**Practice points**

- Reproductive decisions before and after fetal genetic counselling requires mutual understanding and co-operation between the obstetrician and genetic counsellor.
- The decision to undergo genetic testing before and after genetic counselling is influenced by several inter-related factors, including patient–partner and family relationships, patient–physician communication, societal mores, religious beliefs, and the media.
- Because of the complexity of personal and societal factors involved, genetic counselling concerning reproductive decision making must be individualised.
- Genetic counselling must be non-directive and unbiased.
- Parental decisions should be supported regardless of the reproductive choice.
- A critical responsibility of the obstetrician and genetic counsellor is to provide accurate and objective information about the implications, advantages, disadvantages and consequences of any genetic testing applied to prospective parents and their fetuses.
Research agenda

- Evaluate which educational tools best serve to inform the obstetrician about the implications, cost and benefits and consequences of existing and anticipated testing modalities for genetic disease.
- Develop self-inventories of objectivity and biases when counselling prospective parents about genetic testing.
- Evaluate factors influencing prospective patients initial and final reasons for undergoing genetic testing.
- Assess objectively prospective patients experiences after reproductive decision-making.
- Assess influence of health policies and legislation addressing the use of genetic screening and testing on reproductive decision-making after fetal genetic counselling.
- Assess effect of QFPCR and multiplex ligation-dependent probe amplification on reproductive decision-making after fetal genetic counselling.

Conflict of interest

EP is a consultant to the following companies: Perkin Elmer; Aria; and Cellscape.
DP serves on the Board of ‘Child’s Voice’.

References
