diagnosis and therapy, or even a specific gene therapy, 20 years from now.

Even at the present stage, mutation carriers have the opportunity to reduce the risk of developing cancer by adjusting their diet (e.g. by limiting their fat, and alcohol consumption and increasing their phyto-oestrogen consumption), monitoring their body weight, exercising regularly, and refraining from smoking.

**Conclusion**

The question of whether so-called ‘late onset diseases’ should be subject to prenatal molecular genetic diagnosis has, to date, been given comparatively little consideration (Sachs et al., 1993; Lancaster et al., 1996). While Lancaster et al. (1996) regard prenatal testing for BRCA1 mutations as an ethically controversial issue, they nevertheless accept it as part of an irreversible future trend. Although the availability of gene therapy in humans lags behind our ability to detect genetic disorders, the benefits offered by molecular genetic diagnosis promise to revolutionize medicine in a positive way. However, this can only come true if genetic information is not misused as a tool for injustice, discrimination, or genetic selection (Beardsley, 1996; Parens, 1996).

The original, and inherently positive, intention of protecting people from the fate of an early, painful death or severe disability might easily be perverted. Genetic dispositions conditioning the development of a disease several decades later, if at all, may come to decide the ‘desirability’ of a particular life. It is this decision which holds the danger of potential misuse that might lead to genetic selection with a consequent decrease of genetic diversity, or even to selection on the basis of specific phenotypic features. Not only have the experiences of our century made it abundantly clear how rapidly and cruelly such misuse can affect even our everyday lives, but it is also highly debatable if mankind would currently be able to resist the temptation such a possible misapplication represents. The beginning of commercialization of genetic testing provides little cause for optimism in this regard.

Employed in a professionally as well as ethically competent manner, molecular genetic medicine offers an opportunity for innovative and ground-breaking development. To safeguard its progress against an ethically controversial application and the dangers of careless misuse, its use in prenatal diagnosis should not be extended to include diseases such as hereditary breast cancer. In light of the circumstances outlined above, specific guidelines developed by those branches of medicine most closely involved with this dilemma – specifically the obstetric/gynaecological community, prenatal medicine and gynaecological oncologists – become a matter of prime importance.

**Acknowledgements**

This work was supported by grants of the the ‘Medizinischer Fond des Bürgermeisters der Stadt Wien’, the ‘Kommission Onkologie’, Medical Faculty, University of Vienna and the Ludwig-Boltzmann Institut für Klinisch-Experimentelle Onkologie. We are indebted to Professor A. Smith, M. Hastik and C. Guth for their support.

**References**


**A rational approach to prenatal screening and intervention**

S.Yagel1 and E.Anteby

Department of Obstetrics and Gynecology, Hadassah Mt Scopus, PO Box 24035, Jerusalem, Israel

1To whom correspondence should be addressed

Strides made in the last three decades in the fields of anatomical, chromosomal, molecular, and embryonal diagnosis have made possible the prenatal detection of a daunting range of congenital defects. With improved ultrasound equipment and more experienced examiners, it is theoretically possible to identify even the most subtle anatomical findings: cardiac defects, facial and limb anomalies, abnormal development of brain structures, etc. Since the 1960s, amniocentesis has provided relatively safe and accurate diagnosis of chromosomal anomalies, and newer modalities such as chorionic villus sampling, cordocentesis, and pre-embryonic diagnosis offer earlier diagnostic options for high-risk cases (Brock and Rodeck, 1992; D’Alton and DeCherney, 1993). Recently, advances in molecular biology have allowed for prenatal diagnosis of diseases carried by the fetus, but not always associated with an abnormal karyotype or anatomic anomalies (Maddalena et al., 1992). Molecular diagnosis of such diseases as cystic fibrosis, β thalassaemia, and progressive muscular dystrophy is now possible. It has also become feasible to diagnose congenital anomalies in the embryonic, pre-implantation stage in in-vitro fertilization (IVF) patients, an emerging technique that has already sparked an ethical debate (Testart and Sele, 1995; Fiddler and Pergament, 1996; Handyside, 1996; Schulman and Edwards, 1996). It seems that every week another syndrome is shown to be amenable to prenatal detection. Many of these syndromes are lethal or carry with them severe handicaps and extreme suffering for the child, with little or no chance for a cure. Clearly such cases justify the use of diagnostic interventions which are otherwise unnecessary. The rapid progress in these diagnostic
fields has planted in the minds of the public (and to a certain extent clinicians) the idea that it is possible, and also desirable, to exclude any and all identifiable abnormalities in the developing fetus, if enough tests are performed. Clearly such an approach entails a significant increase in fetal risk as a result of applying these diagnostic tests, and it involves the dilemma of parental counselling. It is therefore necessary to try to establish rational criteria to guide clinicians counselling parents on prenatal testing: what is possible, what is feasible, and what is genuinely desirable.

Recently there have been reports of prenatal testing to diagnose mutations in the breast cancer gene (BRCA1) (Wagner and Ahner, 1997) and other late-onset diseases. In an increasingly demanding consumerist environment, where some parents expect only a ‘perfect’ child, it is tempting to apply all available modalities to appease them. But what are the limits of such an approach? In the case of the breast cancer gene, the affected individual may or may not develop a disease, which even today is highly treatable, and generally does not affect the patient before the age of 30 years. Who can foresee what medical advances will be achieved in those intervening years? Who can predict the quality of life for that individual in three decades or more of healthy life? Because testing provides information which will allow an individual to make responsible choices concerning her own health, in this case prior knowledge of an increased risk of breast cancer and subsequent closer attention to screening for early diagnosis, denying the patient that information would be inexcusable. Yet the question arises whether this information should be provided to the parents or the patient herself when she reaches an appropriate age. By providing expectant parents with information that may lead to termination of the pregnancy, or that one may act upon only when the child reaches adulthood, we may be doing more harm than good. How will a healthy young girl react to a medical ‘sword of Damocles’ hanging over her head, and how will this contribute to her quality of life? Is the use of sophisticated prenatal diagnosis justified in such a case?

A categorical approach to prenatal screening and intervention

Because congenital abnormalities are an heterogeneous group of defects which are rather a continuum than categorical, it is difficult to draw a distinct line between them. However, for practical reasons it is important to attempt to categorize fetal anomalies. Our approach is to classify congenital abnormalities according to their severity, age of onset, and type: structural–functional versus mental. Severity can range from mortality to any degree of morbidity or handicap, physical or intellectual. Aberrations can appear early or late in fetal life, some following a developmental course in utero, or be characterized by early or late onset post-partum (Yagel et al., 1995, 1997). Lethal malformations include anencephaly among those diagnosed anatomically; trisomy 18 among chromosomal diagnoses, and Tay–Sachs among the molecular diagnoses. Severe handicap includes such malformations as tanatophoric dwarfism or absent pulmonary valve; or molecular diagnosis of progressive muscular dystrophy (PMD) or Hunter’s disease. A classification of moderate handicap would include transposition of the great vessels, trisomy 21, and cystic fibrosis. Mild handicap includes such anomalies as cleft lip or clubfoot, triple-X, and albinism. Mental handicap is classified separately, because those syndromes which are typically accompanied by mental retardation are by many considered more catastrophic than those associated with physical handicap or outwardly noticeable defects, but normal intelligence. This is culturally variable, but often based on considerations as to a child’s potential quality of life and future independence. These syndromes would include, among others, unbalanced translocation in chromosomal diagnosis, and fragile X under molecular diagnosis (the above is obviously only a partial listing of all diagnosable syndromes and defects.)

This classification system may be arbitrary, however, it is the most defensible: it highlights those anomalies of all types which are: (i) clearly lethal; (ii) which lead to moderate or severe handicap with little or no prospect of improvement or cure; (iii) are characterized by early onset of the disease; and/ or (iv) carry with them obvious mental retardation.

The case of trisomy 21: a paradigm for prenatal screening programmes

The case of trisomy 21 is particularly germane to the present debate. With an incidence in the general population of 1:660, Down syndrome is the most common pattern of malformation in humans. Trisomy 21 is characterized by significant degrees of mental retardation, associated physical defects with varying degrees of handicap, hypogonadism, no anticipated cure or improved prognosis, and early onset (Jones, 1988). Clear criteria exist for the early identification of Down fetuses: triple test programmes, nuchal translucency examinations, amniocentesis for older mothers and targeted organ screening. These extant systems of progressive screening, which attempt to identify high-risk cases and offer them progressively more invasive procedures, (e.g. a mother aged <35 years old with an increased risk for Down syndrome according to her triple-test score, will be offered amniocentesis; likewise if an anatomical marker for Down appears in targeted organ screening, etc). Trisomy 21 has been singled out for such attention by such bodies as the World Health Organization, not only because of its prevalence, but because it carries with it the overwhelming threat of mental deficiency.

Surely there are those who feel these guidelines and the implication that all Down syndrome fetuses be aborted is unconscionable; there is certainly no reason to extend them further to include other, perhaps much less devastating, syndromes. Our approach, based on the extent recommendations for trisomy 21 diagnosis, is an attempt to classify those anomalies for which termination can reasonably be offered to parents: they are lethal or carry with them moderate to severe (or progressive) handicap, early onset, mental deficiency, and little or no chance of improvement or cure. Further, they offer clinicians in many fields involved with the counselling of expectant parents a concise and rational basis for discussing the options presently available in prenatal
testing, while preventing many of the potential abuses of these emerging modalities.

References


