European Journal of Human Genetics (2006) 14, 509–511

www.nature.com/ejhg

POLICY

The need for interaction between assisted reproduction technology and genetics

Recommendations of the European Societies of Human Genetics and Human Reproduction and Embryology

European Journal of Human Genetics (2006) **14,** 509–511. doi:10.1038/sj.ejhg.5201600

Recommendations in context

Infertility and reproductive genetic risk are both increasing in our societies due to lifestyle changes and possibly environmental factors. Owing to the magnitude of the problem, it has not only implications at the individual and family level but also at the community level.

This leads to an increasing demand for access to ART and genetic services, especially as the cause of infertility may be genetic in origin. The increasing application of genetics in reproductive medicine and *vice versa* requires closer collaboration between the two disciplines.

ART and genetics are rapidly evolving fields where new technologies are currently introduced without sufficient knowledge of their potential long-term effects. As for any medical procedures, there are possible unexpected effects which need to be envisaged to make sure that the balance between benefits and risks are clearly on the benefit side.

The development of ART and genetics as scientific activities are creating an opportunity to understand the early stages of human development, which is leading to new and challenging findings/knowledge. However, there are opinions against investigating the early stages of development in humans that deserve respect and attention.

For all these reasons, these two societies, ESHG and ESHRE, have joined efforts to explore the issues at stake and to set up recommendations in order to maximise the benefit for the couples at need and for the community. See for full discussion the background document in the back of this issue.[1]

Recommendations

Importance of reproductive confidence

(1) Infertility and increased genetic risk for disease are serious health threats which deserve appropriate attention and action. The goal of ART and genetics services is to restore reproductive confidence for couples facing these types of difficulties.

(2) Reproductive health is a value for the community. Prevention of infertility should be a prior goal of health care, in addition to social measures to counter parental age, abuse of drugs, sexually transmitted diseases, obesity, environmental factors, etc. Earlier parenthood should be made easier by societal changes to improve the possibility of combining children and career, and encouraged by informing young adults of the impact of ageing on reproductive performance. Adoption should be promoted.

Standard practices

(3) In couples with documented infertility, it is standard practice to explore the aetiology of their infertility for the information of the couple, particularly since it may have implications for treatment and genetic risks to the offspring. Based on the medical, family and reproductive history, appropriate counselling should be offered and genetic testing should be implemented when indicated. If a genetic cause is suspected, the couple should be referred to a geneticist.

(4) Couples should obtain evidence-based information on the techniques and their implications as well as birth rates in that clinic in a standardized way. It is recommended that the performance of that infertility clinic through clinical pregnancy rate per oocyte retrieval and through delivery rate per oocyte retrieval and the percentage of singletons should be presented.

(5) Although the autonomy of couples has to be respected, professionals have a duty to convey a wider perspective preserving the child's interest.

Selection of donors

(6) Family and reproductive histories of female and male donors should be obtained and genetic tests should be performed according only to the family history or the standard testing practices in the population or ethnic group from which the donor or the recipient originate.

(7) Any selection of donors should be evidence based. Donors should not be excluded because of heterozygosity for an autosomal recessive disease because they can be matched with suitable recipients. Counter selected donors need to be offered genetic counselling.

PGD

(8) In families with inheritable disorders, for which PND is offered, PGD should be available as an alternative.
(9) Appropriate genetic work-up is needed in PGD to ensure that a correct diagnosis has been established. All couples at high genetic risk due to structural chromosome abnormalities or monogenic diseases and seeking PGD should see first a clinical geneticist or genetic counsellor who will discuss with them the use of PGD for their particular disorder; then, a clinical fertility specialist who will evaluate the couple as for routine IVF and discuss with them the different options and explain the burden, invasiveness, limited success rate, cost and unknown risks for those involved. PGD has to be considered in the context of all other possible options and pros and cons have to be appropriately balanced.
(10) Both pre-PGD counselling and post-test counselling should be performed in a proper genetic counselling setting. Referral to a psychologist should be made when needed in the pre-test period as well as in the post-test period.
(11) PGD should be performed only if couples agree to know the results and accept all the implications of the test.
(12) PGD could be used to solve other medical problems in the family, including HLA-typing for tissue donorship, although this practice remains controversial.
(13) If social sexing is to be considered, it should be limited to family balancing. Equal respect for both genders should be guaranteed.

PGS

(14) There is evidence that PGS may have the potential to increase the pregnancy rate and to reduce the abortion rate by the detection of numerical chromosomal anomalies. However, more randomised controlled trials are needed to establish the usefulness of this approach and to define the potential indications.
(15) If PGS is proposed, counselling should include the information on the uncertainties of the indications and benefits of the procedure. Counselling should be given by appropriately trained fertility professionals.

Research and development

(16) Prior to the introduction of new procedures, every attempt should be made to test the methods preclinically on *in vitro* models and animals.
(17) It is recommended that new technologies and new practices be introduced as clinical research projects. This implies that protocols are in place, that they have received ethics approval, that the data are collected in a way which will allow for rapid conclusion on the safety and efficacy of the new technology or protocol, and that couples are informed that they are offered a technology/protocol not yet fully validated.
(18) Research on safety and efficacy can only progress if large sets of data are collected in a standardised way. Large prospective collaborative multicentric efforts as well as cohort studies are strongly recommended to assess the long-term effects and the possible transgenerational effects.
(19) There is a conflict between, on one hand, the need for research on safety aspects and, on the other hand, the need to minimise research on embryos. Attempts to resolve this conflict should be encouraged.
(20) Ethical, legal, social and psychological research in the field is needed.

Organisation of services

(21) Availability and accessibility of ART services should be equal in Europe, which is not currently the case. Couples in need of this treatment are increasingly choosing to cross national borders, which may not provide the appropriate condition for treatment due to quality, language and economical issues. Shared protocols and comparable counselling and laboratory protocols should be introduced to guarantee the quality of the treatment in such cases.
(22) Licensing and quality assurance of services should be put in place in order to meet the expectations of the consumers for reliable services. Quality standards have to be defined on European and/or national level, including both laboratory procedures and other elements of care including counselling.
(23) Any person involved in reproductive or genetic counselling has to have appropriate training.
(24) Although ART is considered to be of low priority in many countries, there are situations that should have high priority, like genetic infertility of young couples, and the medical need of PGD. Appropriate funding is needed to treat such cases.
(25) Networking of PGD centres should be encouraged, especially in cases of very rare diseases.
(26) In order to improve free informed choice, it is strongly recommended that evidence-based information leaflets be developed in a style understandable for the vast majority, and to make them widely available on any appropriate support.
(27) Nonmedical use of ART, although desired by some groups, has a much lower priority. Implications have to be clearly evaluated before being accepted and should respect Human Dignity.
(28) Multidisciplinary teams are needed to manage the multifacetes of this field.

Definitions of technical terms used

ART – Assisted Reproductive Technology. Procedures used to help establish a pregnancy. This includes *in vitro* fertilisation (IVF), gamete intrafallopian transfer (GIFT), zygote intrafallopian transfer (ZIFT), gamete and embryo cryopreservation, oocyte and embryo donation and gestational surrogacy. ART does not include assisted/artificial insemination (AI) using sperm from either a woman's partner or a sperm donor (WHO 2002 Glossary).

IVF – In vitro fertilisation. Method used to assist fertilisation and help a couple achieve a pregnancy. The woman is superovulated to produce multiple oocytes which are collected and mixed with sperm. After fertilisation, the oocytes are kept in culture and usually 1–2 resulting embryos are transferred to the uterus between days 2 and 5 of development. Indications include blocked fallopian tubes, infertility of unknown cause, etc.

ICSI – Intracytoplasmic sperm injection. Method to assist fertilisation, variant of IVF. A single spermatozoon is injected through the zona pellucida into the ooplasm of the oocyte. ICSI is indicated in cases of severe male-factor infertility, in which male patients have either malformed sperm or an abnormally low sperm count, and in cases of previous failed fertilisation with conventional IVF. ICSI is also used in PGD to prevent contamination errors after PCR.

PGS – Preimplantation genetic screening for aneuploidy. Method that can be used in addition to morphological screening to identify the embryos best suited for transfer in an IVF/ICSI cycle. Usually, between 5 and 9 chromosomes are examined.

PGD – Preimplantation genetic diagnosis. Method used to determine a specific abnormality in embryos generated by parents carrying that abnormality. Indications include patients carrying X-linked disease, monogenic disorders and structural chromosomal abnormalities such as translocations, etc.

Reproductive counselling – Consultation with a fertility professional during which patients are given information on different forms of fertility treatment, the advantages and disadvantages and any diagnostic tests which need to be conducted, as well as possible health implication for the prospective offspring.

Genetic counselling – A communication process which deals with the occurrence, or risk of occurrence, of a genetic disorder in the family. The process involves an attempt by appropriately trained person(s) to help the individual or the family to (1) understand the medical facts of the disorder; (2) appreciate how heredity contributes to the disorder and the risk of recurrence in specified relatives; (3) understand the options of dealing with the disorder; (4) choose the course of action which seems appropriate to them in the view of their risk and their family goals and act in accordance with that decision and (5) make the best possible adjustment to the disorder in an affected family member and/or to the risk of recurrence of that disorder.

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Reference

1 Soini S, Ibarreta D, Anastasiadou *et al*: The interface between assisted reproductive technologies and genetics: technical, social, ethical and legal issues. *Eur J Hum Genet* 2006; **14**: 588–645.