

- (2) The prominent function of kisspeptins and GPR54 in the stimulatory control of gonadotropin secretion, mostly through direct actions on GnRH neurons; the ability of sex steroids to inhibit KiSS-1 gene expression at the arcuate nucleus of the hypothalamus being mechanistically relevant for conveying their negative feedback effects on gonadotropin release.
- (3) The involvement of a population of KiSS-1 neurons, located at the antero-ventral periventricular nucleus (AVPV) of the hypothalamus, in the generation of the pre-ovulatory surge of gonadotropins selectively in the female; a phenomenon which is sensitive to the organizing effects of sex steroids during critical periods of sex differentiation.
- (4) The fundamental role of the KiSS-1/GPR54 system in the control of reproductive function by the state of body energy reserves and metabolic cues; leptin playing an essential function in the metabolic regulation of KiSS-1 expression at the hypothalamus.

In sum, the above data, coming from functional studies in different animal species, have unambiguously demonstrated the paramount importance of kisspeptins and GPR54 in the dynamic regulation of essential aspects of reproductive function, from puberty onset to the hormonal control of ovulation.

### O-083 Human molecular genetics of GPR54 and Kisspeptin

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#### INVITED SESSION

## Session 21: Health economics and reproductive medicine

Monday, 2 July 2007

17:00–18:00

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### O-084 Principles of health economics

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Health economic evaluations have been conducted for the last 40 years. In the beginning the studies were rather crude comparisons of the costs and benefits of health care programmes using the human-capital approach in which the value of improved health was measured in terms of increased labour production. With time the methods have become more sophisticated and a number of key methodological principles have been specified together with several guidelines of how to conduct cost evaluations and how to interpret data from such studies.

Two features are said to characterise an economic evaluation. Firstly, that it deals with both costs and consequences of activities. Before deciding to pay for a health service, both the price that have to be paid and what form of beneficial outcome will be the result needs to be known. Secondly, that it concerns itself with choices because resources are scarce and it is not possible to produce all desired outputs and therefore choices of what outputs to prioritise have to be made. These characteristics lead us to define economic evaluation as the comparative analysis of alternative courses of action in terms of both their costs and consequences. The specific techniques that are used to make these appraisals primarily differ in the extent to which the benefits are measured and valued.

In economic literature, cost is often defined as the consumption of a resource that otherwise could have been used for another purpose. The opportunity to use the resource for this other purpose is lost and therefore, the next best use is called the opportunity cost. In the allocation of resources within health care systems, there are almost always several choices to be made and hence, several opportunity costs. One of the goals for health economics is to help identify these opportunity costs and to provide guidance in the best use of the allocated resources.

Depending on the choice of perspective of a study, different types of costs may be included or excluded. The study can have the perspective of the patient, the health provider or have a societal view. The choice of method for the analysis may also influence the costs to be included. Another question might be for how long time period costs should be tracked and included. The agreement amongst analysts is that for therapy-specific costs, the follow-up period should not bias the analysis in favour of one intervention over another. The main objective for all of these choices should be to avoid misleading the user of the analysis.

### O-085 The NHS EED and EURONHEED databases - sources of evidence for researchers and decision-maker

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**Introduction:** The cost-effectiveness of health care technologies and interventions is increasingly required to be demonstrated to national regulatory bodies prior to reimbursement or recommendation for use in clinical practice (the so-called 'fourth hurdle'). Two major databases that provide public and free access to structured and critiqued economic evaluation evidence, in all clinical areas, are the NHS Economic Evaluation database (NHS EED) and the European Network of Health Economic Evaluation Database (EURONHEED). This study provides a summary of the background and accessibility of these resources and then reports the findings of a systematic search of NHS EED and EURONHEED to locate studies in the area of human reproduction and embryology. An example abstract in a topical field of interest will then be presented to demonstrate the potential use of these databases to researchers and decision-makers within the scope of evidence-based clinical practice.

**Materials and Methods:** A comprehensive search strategy was created using key words to identify all relevant human reproduction and embryology studies available from NHS EED and EURONHEED. These were broken down into three categories: infertility treatment - male or female (IT), sterilisation (including reversal) or contraception (ST), diseases or conditions affecting fertility - including surgical techniques and drug treatment (DA). To demonstrate a more focussed and pragmatic approach to find evidence in a particular area of human reproduction and embryology, studies were located in the clinical area of IVF/IUI for male sub-fertility. Graphical representations of clinical categories (IT, ST, DA), geographical area of origin, and database record type were produced.

**Results:** A total of 325 studies were located in the overall search (IT=42%, ST=8%, DA=25%, irrelevant=25%). In terms of geographical location these were: UK=12%, Rest of Europe=27%, North America=52%, other=9%. In the area of IVF/IUI for male sub-fertility, 5 studies were located. The structured abstract for the most recent study (Pashayan et al., 2006) was identified in order to illustrate the structure and content of NHD EED/EURONHEED abstracts.

**Conclusions:** NHS EED and EURONHEED provide freely-available structured abstracts, including a critical commentary, of economic evaluations and are therefore valuable resources to decision-makers and researchers. Within the area of human reproduction and embryology 325 studies were located and five within the category of IVF/IUI for male sub-fertility. As illustrated by the example abstract, these resources provide evidence-based information in the field of human reproduction and embryology and other health technologies that require formal appraisal of cost-effectiveness.

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#### FREE COMMUNICATION

## Session 22: Ethics and law 1

Monday, 2 July 2007

17:00–18:00

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### O-086 Oral Pre-implantation genetic diagnosis in Europe: legal and ethical challenges for national and international regulation

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**Introduction:** In March 2005 the EU, the European Society of Human Genetics (ESHG) and ESHRE organised a workshop on the interface between genetics and reproduction in healthcare. It emerged that a full picture of PGD practice and provision in Europe was needed. Questions were raised about the impact that different regulatory frameworks between Member States might have on PGD services and to what extent couples were crossing national borders to gain access to treatment. In response, the EU commissioned this study to obtain the missing knowledge on provision and regulation of PGD services in Europe.

**Material and methods:** The first stage was an on-line questionnaire sent to European PGD and IVF clinics identified by ESHRE and through EuroGentest. The second stage was a more exhaustive analysis of PGD practice and provision in eleven countries, chosen to include countries with contrasting approaches to regulation. Some of the new EU Member States, about which little is known in this regard, were also included. Our analysis was based both on data gathered from the survey and on information obtained from interviews with experts in this field in each of the countries. The full report will shortly be available at <http://www.jrc.es/home/pages/publications.cfm>

**Results:** The study identified a wide range of clinical, scientific and quality-related findings and results. These will be separately reported: this paper focuses on the legal and regulatory results.

PGD is an expanding activity in Europe, presenting complex legal and ethical challenges. Genetic counselling and informed consent guidelines adapted to PGD may need to be developed, though the EU Human Tissue and Cells Directive should have a positive impact on quality standards.

The main reasons identified for travelling abroad for PGD are legal (usually that PGD is not allowed in the country of residence) but additional reasons for travelling to a specific country include the quality of the treatment, test availability, financial resources and manpower. The overall scale of cross-border flow is not entirely clear but it is apparent that most patients travelling abroad for PGD services come from within the EU though some come from outside Europe.

Reproductive and genetic technologies are regulated in a wide variety of ways across Europe. The relatively free movement of people and goods around the EU is a welcome development but there are disadvantages to such cross-border flow in relation to PGD if such treatment is prohibited in the family's country of origin. The evidence provided in this study suggests that doctors in certain countries are anxious about providing information to patients about suitable PGD clinics in other countries. Referral is said to be prohibited in some Member States. Patients are therefore left to identify clinics themselves and are deprived of the benefit of medical advice, counselling and support.

Secondly, the prohibition of PGD in their country of origin may complicate monitoring and follow-up. Self-referred patients may go unnoticed and clinics could be reluctant to get involved in following up families and children born as a result of a prohibited treatment. The evidence indicates some clinics are not deterred whilst others do not see it as their responsibility.

There is an apparent inconsistency in certain countries between the prohibition of PGD and the acceptance of prenatal testing and termination of pregnancy.

**Conclusions:** The rights and interests of patients seeking and receiving PGD in Europe are protected to a varied degree.

#### O-087 Oral The future (r)evolution of PGD/HLA-testing: ethical reflections

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**Introduction:** So far, preimplantation genetic diagnosis (PGD)/human leukocyte antigens (HLA)-testing takes place in the context of conceiving a 'saviour' child - PGD/HLA-testing type 1. It may well become possible, however, to perform PGD/HLA-testing outside of this context, namely in order to select matched embryos from which embryonic stem cells (ESC) could be derived and subsequently differentiated into hematopoietic stem cells (HSC) for cell therapy - PGD/HLA-testing type 2. A proactive ethical analysis is needed, focusing on HSC transplantation.

**Material and methods:** Ethical reflection on literature and practice of PGD/HLA-testing.

**Results:** No doubt, PGD/HLA-testing type 1 may well be morally justified. At the same time, however, this procedure raises various problems, both practical and moral. Practical problems include that the procedure has a moderate take home baby rate. Ethical relevant risks include that parents of a sick child in need of HSC may feel under pressure to opt for this procedure while they cannot afford another child. Moreover, there are possible health risks for the 'saviour' child, related to, amongst others, early umbilical cord clamping, which may have adverse effects especially for premature and/or very low birth weight children. It is necessary, therefore, to develop alternative strategies. One future option may be PGD/HLA-testing type 2.

The advantages of this alternative strategy are, at least in principle, both practical and moral. Advantages include that this procedure will increase the number of options for parents involved, that it could have substantial medical benefits for the diseased sib, as the procedure may be less time consuming and more effective, and that all the (medical and psychosocial) child-related objections and concerns regarding the type 1 case would be circumvented.

The primary normative issue regarding PGD/HLA-testing type 2 concerns the creation of human pre-implantation embryos solely for so-called 'instrumental use', more in particular to obtain ESC/HSC for cell therapy. It is important to distinguish between a legal and an ethical perspective. Many countries prohibit the creation of embryos for instrumental use. It can be argued, however, that the creation of embryos for instrumental use, just like the use of spare embryos, can be morally justified on the conditions of proportionality and subsidiarity. There can be little doubt that the use of pre-implantation embryos for life saving therapy, like in the type 2 case, is proportional. Critics might object that this procedure is at odds with the principle of subsidiarity, pointing, amongst others, to the type 1 case, which at least limits the loss of embryos - after all, the matched-and-healthy embryos will be transferred. This restrictive use of the principle of subsidiarity, however is unreasonable in view of the possible advantages of the type 2 case.

From a 'feminist' perspective, the production of embryos for instrumental use may be criticized, e.g. because the procedures involved (like hormonal stimulation) are not without risks for the oocyte donor. This criticism seems, however, to be less relevant for the ethics of PGD/HLA-testing type 2, as the risks are fully proportional in view of the benefit to be gained, i.e. the saving of the woman's child.

**Conclusions:** Though PGD/HLA-testing type 1 may be morally justified, it is imperative to develop alternative strategies. One option may be PGD/HLA-testing type 2. This strategy may be a morally justified alternative.

#### O-088 Oral Preimplantation genetic diagnosis for mitochondrial DNA disorders: a Gordian knot

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**Introduction:** Due to the absence of effective treatment, the prevention of the transmission of mitochondrial (mt) DNA disorders is of key importance. Prenatal diagnosis (PD) for mtDNA disease has increasingly been used since 1999. However, the complexities of mitochondrial genetics and the resulting lower predictive value of prenatal test results, are complicating PD. Partly in view of these complications, preimplantation genetic diagnosis (PGD) is regarded as a serious alternative. While PGD has been reported only once (for the 8993 mutation), some clinicians and patients consider the application of PGD for other mtDNA mutations. This paper aims to proactively discuss the ethics of PGD for mtDNA disorders.

**Material and methods:** Literature review and semi-structured interviews with physicians-researchers, policymakers and patients in the United Kingdom, France, Italy and The Netherlands.

**Results:** While PGD has a major advantage in comparison with PD, as it may avoid selective termination of pregnancy, it raises difficult ethical issues as well. As PD and PGD initiated as techniques to prevent single gene disorders that result in serious harm, debate about possible extension to new applications is required. After all, being the first ethical issue, most mtDNA diseases show an incomplete penetrance and variable expression. Clearly, the fact that fetuses

at risk may well develop into healthy children complicates PD and selective termination of pregnancy, both psychologically and ethically. Critics object that the incomplete penetrance and variable expression make PGD unjustified as well. In this regard, PGD for mtDNA disorders raises the same issues as PGD for predispositions to, for example, hereditary cancers. A categorical criticism of these applications seems, however, to be premature.

A second ethical issue, which is more specific for PGD for mtDNA disorders, concerns the residual health risks for the future child. In many cases, PGD for mtDNA disorders does not enable people to eliminate genetic risk, but only to reduce it. Though PGD may not be ideal in these situations, as even after a selective transfer an affected child may be born, some couples nevertheless consider PGD to be their best option. This application is controversial, also among clinicians. A first objection concerns the goals of PGD, namely to inform parents about the health of their embryo, enabling them to make informed reproductive choices. If this information is inaccurate, so some argue, the goals of PGD are lost out of sight. Furthermore, in these cases, a conflict may arise between on the one hand the prospective parents' reproductive autonomy and on the other hand the responsibility of the reproductive physician to take into account the welfare of the future child. In the literature, three evaluation standards are used to assess the welfare of the child. In this presentation, the high risk of serious harm standard will be defended. However, difficulties in putting this standard into practice will be illustrated by means of a Leber hereditary optic neuropathy (LHON)-case. Another issue may arise in case of heteroplasmic mtDNA mutations, such as the 3243A>G mutation leading to MELAS, as only embryos with residual health risks may be available. In cases like these, would it be morally justified to transfer an embryo with a low mutant load? And when would the clinicians responsibility to transfer the best possible embryo imply to start another IVF/PGD cycle in order to obtain mutant-free embryos?

**Conclusion:** Both PD and PGD to prevent mtDNA disorders raise ethical questions. While PGD may offer a valuable alternative, PGD is not a cure-all, as new issues require proactive ethical reflection and debate, in particular the transfer of embryos with residual health risks.

#### **O-089 Oral** How autonomous can the choice of parents asking for a saviourbaby be?

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**Introduction:** One can define the normative and descriptive frame of the genetic counseling for preimplantation genetic diagnosis (PGD) by on the one hand the concepts of autonomy and non-directiveness and on the other hand by the notions of parenthood and responsibility for the welfare of the child. In this paper we focus on the autonomy of patients asking for PGD with HLA typing. Preimplantation tissue typing is a method for creating a tissue matched child that can serve as a haematopoietic stem cell donor to save its sick sibling in need of a stem cell transplant. In clinical practice the concept of autonomy is made operational as psychological and social autonomy (descriptive) and as self-determination (normative). Psychological autonomy encompasses the intra-psychic processes in an individual. Not only conscious intentions but also unconscious motives have an effect on the moral justifications of the patient/consultant. If one's psychological autonomy decreases, a person's ability to self-determination can be questioned. If it comes to that, the ethical concept of autonomy as self-determination should be reconsidered. In the ethical literature, evaluating PGD with HLA typing, an important argument focus attention on the intention of the parents to have a new child for its own sake and not as a mere instrument to save another sick child in need of a transplant. Several authors (Pennings, 2002; Devolder, 2005) pointed out how difficult and complex the reasons for parents wanting a child are.

**Material and methods:** Using the method of participant observation, we collected the data of fifteen intake-interviews with parents asking for preimplantation genetic diagnosis with HLA typing. It concerns the psychological in-depth interview that is taken by the psychologist in the Centre for Medical Genetics in the hospital of the Free University of Brussels during three months (November, December 2006 and January 2007). The participant observer, trained as a philosopher-ethicist and psychologist, analyzes the data on ethical issues.

**Results:** The most important finding is the experience of a lack of freedom in the majority of the parents with a sick child in need of a transplant, not to choose the PGD/HLA treatment. Some people express it implicitly when

saying that they will repeat the treatment (IVF) as many times as necessary, even '100 times if needed: we have no choice'. Others explicitly state that 'it is not that we have emotionally no choice, but also rational: without a saviourbaby our (sick) child will die'. The context in which these sentences are voiced is often one of parents in preoccupation with the treatment of a very sick child (giving up work to go to the hospital with the child; traveling abroad for treatment).

**Conclusions:** Where genetic counseling in the ethical and psychological literature highlights autonomy, non-directiveness, self-determination, psychological autonomy, we see in daily practice of PGD/HLA counseling desperate consultants who feel themselves bound hand and foot to try this treatment often as a last resort to save their child, or at least, to have tried 'everything to save their child'. Ethical theory and practice presupposes actors who are free to choose. Genetic counseling aims at enhancing the autonomy of their consultants. When intrapsychic forces compel actors, it's more difficult to judge them morally. The intentions of the parents to create a saviourbaby are psychologically constrained. The ethical argument that can play a major role in the debate is the wellbeing of the future saviourbaby. The love of the parents for the sick child might be a good indication that they will love all their children?

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#### INVITED SESSION

### Session 23: Are there new paradigms in ovarian germ cell biology?

Tuesday, 3 July 2007

08:30–09:30

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#### **O-090** The numerus fixus hypothesis revisited

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A central dogma of female reproductive biology has long held that oogenesis ceases around birth in almost all mammals. Consequently, after that time the ovarian reserve will continuously decrease until depleted around menopause in humans. In 2004, Johnson et al. and Bukovsky et al. claimed that female mice and women, respectively, produce new oocytes during adult life, a phenomenon we will term neo-oogenesis. In a publication in *Cell* in 2005, however, Johnson et al. suggested that if neo-oogenesis is present during adult life, the new germ cells do not come from the ovary itself, but rather from germinal stem cells generated in the bone marrow. On the other hand, Eggan et al. (2006) showed that mice connected through their vascular system exchange blood cells, but not germ cells. Their results do not support the claim that oocytes can arise from blood stem cells in vivo. However, this does not exclude that stem cells within the adult ovary may generate new oocytes, as first suggested by Johnson et al. in *Nature* (2004).

Some issues raised by the assumption that a functional neo-oogenesis is acting in the adult ovary can be addressed.

- The paradigm of neo-oogenesis during adult life is based on calculations showing that the rate of follicular atresia is so high that mice fertility should be strongly compromised early after onset of puberty if no oocyte replacement takes place. However, when adult rats were injected with BrdU, 57% labelled intermediary (transitory) follicles were still present 150 days after BrdU removal (Meredith et al., 2000). Consequently, we challenge the criteria used to calculate the number of atretic follicles and that this calculation leads to an overestimation of the rate of follicular atresia.
- Some antibodies used to detect primordial germ cells in the adult ovary are not germ cell-specific.
- In the article in *Cell* (Johnson et al., 2005), it is assumed that follicles appear in the ovary as soon as 24 h after injection of blood progenitor germ cell. This seems inconsistent with the time (4 - 7 days) needed for a mouse oogonium to transform into an oocyte and further into a primordial follicle as seen during normal fetal development. In addition, we have studied oocyte