Journal of Intercultural Management and Ethics

JIME

ISSN 2601 - 5749, ISSN-L 2601 - 5749

published by

Center for Socio-Economic Studies and Multiculturalism
Iasi, Romania
www.csesm.warter.ro

Special Editor

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ETHICAL AND LEGAL ISSUES OF PREIMPLANTATION GENETIC DIAGNOSIS IN IVF COUPLES

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Abstract
Objectives: to describe the ethical and legal issues of the actual and predictable uses of preimplantation genetic diagnosis (PGD) for *in vitro* fertilization (IVF) couples.
Material and method: an examination of the present ethical and legal uncertainties enclosing the utilization of PGD after IVF procedures and future legal and ethical perspectives that will emerge from its clinical application.
Results: Some of the PGD are still theoretical with a great potential to drop individual`s suffering of genetic diseases which can determine disability or even death. PGD can be utilized in order to choose particular features, decreasing, over the time, genetic diversity.
Conclusions: PGD represents a technique that helps to eliminate embryos with genetic disorders before their development, being linked with *in vitro* fertilization (IVF) procedures. Therefore, the ethical and legal implications of PGD related to IVF need to be analyzed in order to ensure that the method is utilized only where is medically rightful.

Key words: Preimplantation genetic diagnosis, ethics, legal, *in vitro* fertilization.

Introduction

Four decades ago, with the IFV techniques, the scientists succeeded to "conceive" a healthy baby girl named Louise Brown who was born on 25th of July, 1978 (Ayers, 2004). The news of her birth was followed by many controversies regarding the conflict over ethical and moral aspects of the artificial technique but over the time it had proved its safety and feasibility.

The worldwide infertility prevalence rates are tough to be assessed, due to its multiple causes in both women and men. The last infertility prevalence estimation recorded that one in every four couples, living in developed countries, suffers from infertility. As a consequence of the high rate infertility couples, the number of babies that result from the IVF techniques raised all over the world, being estimated by the WHO at approximately five millions of children (Braude, Pickering, Flinter & Ogilvie, 2002).

Amniocentesis and biopsy of chorionic villus represents the main tools for prenatal diagnostic test during pregnancy, offering for high risk couples the surety of a genetically normal fetus or the consideration for termination of an affected pregnancy. For couples that undergo in vitro fertilization (IVF), the requirement of a preimplantation diagnosis test is a relevant alternative.

Preimplantation genetic diagnosis

Preimplantation genetic diagnosis (PGD) was developed as a choice for prenatal diagnose methods for affected couples that carry a substantial risk to convey a genetic disease to their child. PGD allows for the preimplantation period assessment and has proved its efficacy in preventing a large number of inherited diseases where the baby has a great risk for severe mental or physical disability, early death, or conditions that manifest rapidly in childhood and short-circuit their lifetime (table 1). The diagnosis of these diseases can be ascertained before the implantation and by highlighting the alteration within the involved gene, the chromosome that carries it can be identified by family tree or other distinctive chromosomal rearrangement can be detected (Handyside, Kontogianni, Hardy & Winston, 1990).

Table 1. Genetic diseases that were tested with preimplantation genetic diagnosis

Autosomal recessive	**Autosomal dominant**	**Sex-linked**	**Chromosomal Disorders**
Cystic Fibrosis	Myotonic Dystrophy	Duchene and Becker's Muscular Dystrophy	Chromosomal Trisomies (13, 18, 21)
Beta-Thalassemia	Huntington's Disease	Hemophilia A and B	Chromosomal Translocations
Spinal Muscular Atrophy	Charcot-Marie-Tooth disease	Fragile-X Syndrome	Monosomies (ex. Turner`s Syndrome)
Tay-Sachs Disease	Neurofibromatosis 1&2	Mental Retardation	
Rh Immunization	Marfan Syndrome	Wiskott-Aldrich syndrome	
Gaucher Disease	Osteogenesis Imperfect I&IV	Charcot-Marie-Tooth	
Sickle Cell Anaemia	Polycystic Kidney Disease 1&2	Myotubular Myopathy	
HLA Genotyping	Von-Hippel Lindau	Ornithine Carbamyl Transferase	
Epidermolysis Bullosa	Multiple Epiphyseal Dysplasia	X-lynked Hydrocephalus(OTC)	

		Deficiency	
Phenylketonuria	Familial Adenomatous Polyposis		
Congenital Adrenal Hyperplasia	Achondroplasia		
Fanconi Anemia	Li-Fraumeni (p53 gene)		
Glycogen Storage Disease	Retinitis Pigmento		

The first use of the PGD took place in the United Kingdom in the late '80s, being performed in order to eschew the conveyance of X linked mental retardation and adrenoleucodystrophy. High risk fertile couples with family history or an affected child were enrolled for IVF, where the embryos resulted in vitro were analyzed for peculiar genetic abnormalities by extracting the DNA from the single cell that was amplified through polymerase chain reaction (PCR) and tested for genetic alteration or the existence of a Y chromosome that was linked to the genetic sequence (Ried, Landes, Dackowski, Klinger, & Ward, 1992). One or two blastomeres from the pre-implanted embryo are removed at the biopsy, during the 3rd day of development, without an increased risk of affecting the embryo.

The implementation of fluorescence in situ hybridization (FISH) (Griffin, Handyside, Penketh, Winston & Delhanty, 1991), enables with the help of a microscope, to recognize individual chromosomes in order to simplify the sex selection (Scriven, Handyside & Ogilvie, 1998) but also to detect those embryos that carry imbalances in translocation types or further chromosomal rearrangements (Renwick & Ogilvie, 2007). The embryo haplotyping represents the newest technique of PGD, that does not require specific information of the genetic disorder, but only which is the implicated gene and its inheritance patterns in the family (Braude & Flinter, 2007).

Legal and ethical issues regarding the eligibility or the access to treatment

The parents that have a genetic condition or are known to be bearers and encounter infertility issues are good candidates for PGD test. Couples that have family history regarding a severe pathology have a tough option to make, if to decide for abortion of the fetus that was diagnosed with the condition in question. Others who experimented a necessary termination of pregnancy followed by a prenatal diagnosis like amniocentesis or chorionic villus sampling, or patients with emotional, moral or religious judgments who consider PGD as being the only manner to have a healthy fetus are the designate group of patients for PGD testing.

In infertile couples who went for PGD is necessary that valid embryos for the transfer to get through the biopsy with normal morphology but as well to be clear of the genetic conditions. This demand is controversial for couples since the number of embryos can significantly decrease or in many situations there may be none, making this test an alternative for amniocentesis or chorionic villus sampling in few cases (Flinter, 2001).

Armenti et al. (2016) showed in a prospective study the importance of PGD in the incidence rate of X-linked disorders (figure 1). At the same time, the authors pointed out a real ethical problem and a continuous challenge in cutting off the male descendants, with the recommendation of PGD used to identify healthy embryos in X-linked conditions.

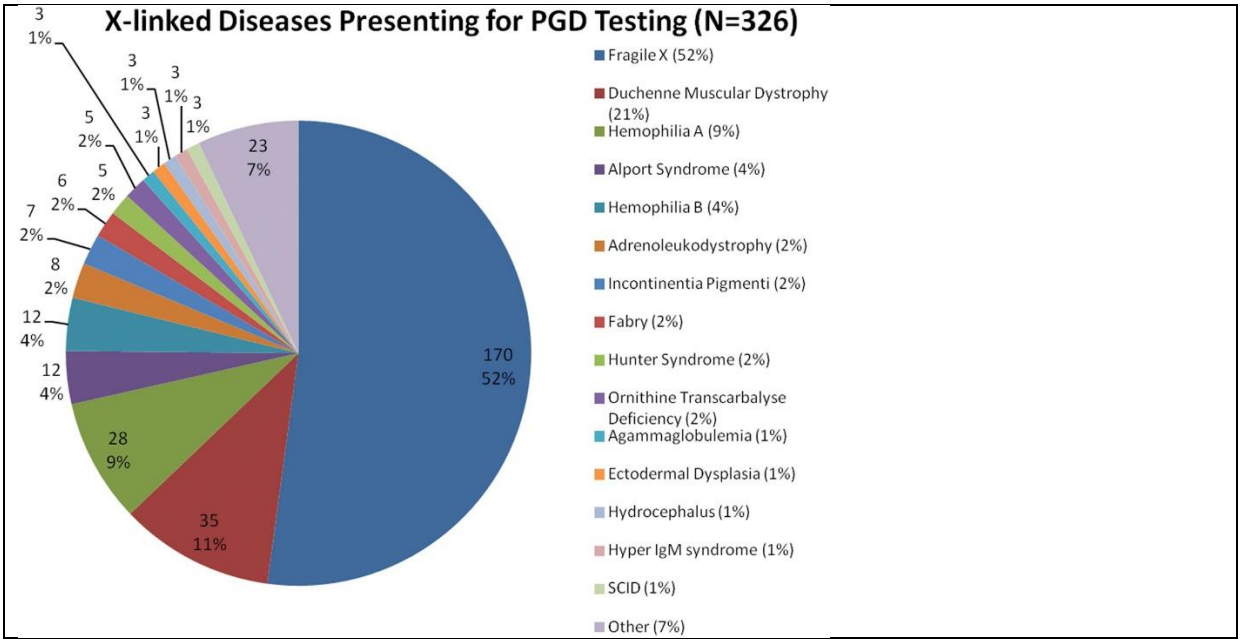

Fig. 1 The incidence rate of the X-linked pathologies followed Preimplantation Genetic Diagnose testing (Armenti et al., 2016)

At this moment, there are no a proper laws to what represents the right of a person to have treatment access. However, even some indications for PGD are established (Yang et al., 2012), in the lack of a determined legislation feasible difficulties may appear for couples who does not fit in the indicated categories and want to undergo the procedure.

In order to stop them performing an unnecessary test, it is mandatory to state clearly the prerequisites which should be accomplished for gaining the eligibility and having access to the PGD procedure.

A meta-analysis of 9 randomized controlled trials (RCT) where preimplantation genetic screening (PGS) was performed usually after IVF procedure (Mastenbroek, Twisk & van der Veen, 2011) had shown that FISH test brings no benefits on the live birth rate, instead, in women of advanced maternal age, PGS decreases it. Moreover, another RCT, in which array comparative genomic hybridization (aCGH) was performed, reported an increased rate of implantation and ongoing gestations when chromosome screening was perfomed in the 5th day (Organisation for Economic Cooperation and Development-OECD, 2007).

Under the authority of Organisation for Economic Cooperation and Development (OECD) Guidelines for Quality Assurance in Molecular Genetic Testing (International Organization for Standardization, 2012), both PGD and PGS must be performed in laboratories with an accreditation (International Standards Organisation – ISO 15189, 2019) or equivalent accreditation schemes (table 2) (European Commission Directive 2004/23/EC, 2004).

Table 2. Centers involved in ESHRE PGD Consortium

Fertility Center		Fertility Center	
1.	Sydney IVF	14.	Department of O&G, Samsung Cheil Hospital, Sungkyankwan University, Seoul
2.	University of Adelaide	15.	Instituto Dexeus, Barcelona
3.	Melbourne IVF	16.	Unitat de Biologia Cellular, Univ. Autonoma, Barcelona
4.	Center for Medical Genetics, VUB Brussels	17.	Department of Clinical Genetics, Karolinska

			Hospital, Stockholm
5.	ULB Erasme, Brussels	18.	Sahlgrenska University Hospital, Gotenborg
6.	Centre for Preimplantation Genetic Diagnosis, Aarhus University Hospital, Aarhus	19.	Assisted Conception Unit, St Thomas`s Hospital, London
7.	Hospitaux Beclere et Necker, Paris	20.	Department of O&G, University College, London
8.	Institut de Genetique et de Biologie Moleculaire et Cellulaire, Strasbourg	21.	Institute of O&G, RPMS, Hammersmith Hospital, London
9.	St. Sophia`s Childrens Hospital, University of Athens	22.	Department of O&G, Baylor College of Medicine, Houston, Texas
10.	IVF and Genetics, Athens	23.	Jones Institute for Reproductive Medicine, Norfolk, Virginia
11.	SISMER, Bologna	24.	New York University Medical Center, New York
12.	PGD Working Group, Maastricht	25.	Institute of Reproductive Medicine and Science, St. Barnabas Medical Center, New Jersey
13.	Stichting Klinische Genetica Zuid-Oost Nederland, Maastricht		

In the United Kingdom, the Human Fertilisation and Embriology Authority (HFEA) holds over which fertility clinic obtains the license to perform PGD and for what is indicated. Any other supplementary PGD procedures may be possible only with the HFEA approval as long as the clinic has the necessary qualification for performing the technique.

Discussion

Assisted reproductive technologies (ART) and reproductive genetics are growing fast nowadays, bringing rapidly umpteen novel procedures in clinical practice, although, in various situations, clinical feasibility, safety, efficacy, advising or legal / ethical viewpoints of this progress need to be analyzed in details. All the basic research requires to be ensured, attended by RCT and studies that approve its safety and efficacy, beyond its initiation into current medical practice. Also, the follow up period of children born by ART must become compulsory.

Even if the legal aspects concerning the medically assisted reproduction procedures are constantly revised in Europe, consistent disparity lingers and encourages cross-border reproductive care (CBRC). The European Union (EU) directives (European Commission Directive 2006/17/EC, 2006; European Commission Directive 2006/86/EC, 2006; Willemen, D'Hooghe, Knoops, De Neubourg & Spiessens, 2012) brought an essential effect on ART by implementing latter quality and safety norms for laboratory and clinical techniques assisted by IVF.

Cross-border reproductive care patients are those who travel borders in order to seek for reproductive care in other different countries, being motivated by legal restrictions in their countries of origin, where various procedures are banned to all or for some population categories like homosexual couples or single women. The limited access in their countries and the restricted availability of a particular procedure, long waiting lists for treatment or age limitations, improved technique quality or a decreased payment for it in other countries or even the previous failures in their countries of origin convince the patients to travel across the borders in order to find new hopes for obtaining a pregnancy.

A serious ethical matter is with consideration to embryos that are not eligible for implantation. There are ethical and also religious complaints to these embryos being utilized for experimental and research intends.

In the past decades, the counseling of infertile patients has gained better improvement, since the genetic considerations are better acknowledged. The need for providing more acquaintances for patients counselling should be recognized for those who have ART or PGD

recommendations, as well as the particular needs of each person. The need for PGD should be detailed during the genetic counselling in all cases that have an indication for this technique.

Moreover, medical societies like European Society of Human Genetics (ESHG) or European Society of Human Reproduction and Embryology (ESHRE), provided guidelines for clinical practice that reflect a general comprehension of the legal, social, scientific and ethical problems in order to obtain a normative legal significance. Using PGD only to eschew conveying a genetic susceptibility or a particular feature that is considered unpleasant or to choose the sex of the fetus is inadmissible.

Conclusions

In the last several years, various European countries have approved or changed the laws that referred to ART and / or genetic testing. Even if they become more permissive there are still some European countries which prohibit PGD testing, situation that favors choice of CBRC worldwide. The legal issues related to PGD must be correlated with those related to IVF as they are interconnected.

PGD should be consider a matter of choice in terms of avoiding the transmission of a genetic disease, in the couples with genetic risks who undergo IVF because of infertility issues. The practitioner must be aware of all potential risks and difficulties and take all the measures in order to provide these procedures in a safe manner.

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