



Italian Journal of Gynæcology & Obstetrics

December 2020 - Vol. 32 - N. 4 - Quarterly - ISSN 2385 - 0868

Preimplantation genetic testing: comparative analysis of jurisprudential regulations

C. Casella¹, L. Carbone², A. Conforti², V. Marrone², G. Cioffi², C. Buonfantino², P. De Rosa², L. Avino², A. Capalbo³, C. Alviggi², P. Di Lorenzo¹

¹Department of Advanced Biomedical Sciences, University of Naples Federico II, Naples, Italy

²Department of Neurosciences, Reproductive Sciences and Odontostomatology, University of Naples Federico II, Naples, Italy

³Igenomix Italy, Molecular Genetics Laboratory, Marostica, Vicenza, Italy

ABSTRACT

Preimplantation genetic testing (PGT) is used to screen for genetic diseases or chromosomal abnormalities in couples at risk of transmission to the offspring. It can be applied also to determine the gender or phenotypical features of the unborn and to type the Human Leucocyte Antigen (HLA), in order to search for future potential stem cell or bone marrow donors. Aim of this review is to provide a comprehensive description of Italian jurisprudential approach on PGT, and in addition, to compare the jurisprudential orientation of other nations of West Europe and USA. PGT is allowed for almost any indication in some countries (United Kingdom and USA), but is forbidden in others (Austria). In the majority of countries PGT is authorized to prevent the transmission of genetic diseases, being considered unacceptable for gender selection for non-medical reasons.

Less frequently, PGT is allowed to provide therapeutic options for an already born sibling. In some cases, prior authorization from a health authority or a healthcare provider is requested. Social, healthcare and ethical issues underpin the request for PGT. Given the difficulty to identify a list of genetic diseases for which could be authorized the access to PGT, the European Society of Human Reproduction and Embryology (ESHRE) proposes to limit such test to cases characterized by a "high risk of a serious condition". In such a framework, it has been proposed that the access to PGT is allowed through a prior in-depth meeting between the couple and a multidisciplinary equipe of healthcare professionals (obstetrician, geneticist, psychologist, expert in bioethics, legal-medicine specialist) to evaluate the medical, but also juridical and ethical acceptability of the request.

SOMMARIO

La diagnosi genetica pre-impianto (PGT) è utilizzata per lo screening di malattie genetiche o di anomalie cromosomiche in coppie a rischio di trasmetterle alla prole. Essa può essere utilizzata anche per determinare il sesso e le caratteristiche fenotipiche del nascituro o per la tipizzazione del sistema di istocompatibilità (HLA) così da ottenere futuri potenziali donatori di cellule staminali o di midollo osseo. Scopo di questa review è di fornire un'ampia descrizione dell'orientamento giurisprudenziale italiano in materia di PGT, ed inoltre di analizzare in maniera comparata l'approccio legislativo di altre nazioni dell'Europa occidentale e degli Stati Uniti. Accanto a Paesi in cui la PGT è ammessa pressoché per qualsiasi finalità (Regno Unito e USA), in altri è vietata (Austria). Nella maggior parte dei Paesi europei la PGT è autorizzata per prevenire la trasmissione di malattie genetiche, essendo invece ritenuta inaccettabile la selezione del sesso per finalità non mediche. Meno frequentemente la PGT è autorizzata nell'interesse terapeutico di un bambino già nato. In taluni casi è richiesta la preventiva autorizzazione di un'autorità sanitaria o una attestazione medica. Problematiche di natura socio-sanitaria ed etica sottendono il ricorso alla PGT. Data la difficoltà di individuare una lista di malattie genetiche per le quali vada considerato autorizzabile il ricorso alla PGT, la Società Europea di Riproduzione Umana e Embriologia (ESHRE) propone di limitare tale metodica ai casi caratterizzati da un "alto rischio di un disturbo grave". In tale contesto, è proposto che l'accesso alla PGT avvenga attraverso un preventivo approfondito colloquio tra la coppia ed un'equipe di professionisti sanitari (ostetrico-ginecologo, genetista, psicologo, bioeticista e medico-legale) al fine di valutare l'ammissibilità medica, ma anche giuridica ed etica della richiesta.

Corresponding Author: Luigi Carbone

E-mail: drcarboneluigi@gmail.com

Copyright 2020

DOI: 10.36129/jog.32.04.03

Key words:

Preimplantation genetic testing (PGT); eugenetics; bébé médicament; genetic disease; informed consent; aneuploidies; assisted reproduction technologies (ART); in-vitro fertilization (IVF).

INTRODUCTION

The aim of Preimplantation genetic diagnosis (PGD) can be wide. First of all, it can be used to screen, for genetic diseases or chromosomal anomalies, couples at risk of transmission of a determined inheritable condition to the offspring (1). It was introduced into ART (assisted reproduction technology) with the aim of detecting embryo aneuploidies for reducing the rate of miscarriage and increasing the pregnancy rate (2). In this sense, possible indications are advanced maternal age, recurrent implantation failure (RIF), recurrent spontaneous miscarriages, (3) severe male factor (4) and premature ovarian insufficiency (POI) or poor ovarian reserve (POR) (5-8), which are all recognized conditions associated to increased rates of chromosomal abnormalities (9). Lately, other indications have been proposed, like previous chemo-radiotherapy or the intention to perform a single embryo transfer (SET), although these do not find wide agreement (9). Indeed, cost-effectiveness of PGT has been evaluated, showing its better results in advanced maternal age (over 35 years old) and when the plan is for SET (10). However, it is recognized that cost-effectiveness may vary depending also on national legislations and regulations, as well as the experience of the center performing the test (10). Currently, the term PGD has been replaced by PGT (preimplantation genetic testing), including analysis for aneuploidies (PGT-A), for monogenic or single gene defects (PGT-M) or for structural rearrangements (PGT-SR)(11). In fact, such practice would allow to select for transfer only the embryos who are not carrying genetic anomalies, putting apart the ones who instead show any kind of abnormalities. Indeed, due to intrinsic limits of the techniques of genetic analysis of polar bodies or embryos, such test was since early considered more like a screening (PGS) and not a proper diagnostic test. In view of this, future parents could be reassured that with high probability their embryo is genetically healthy, and accordingly choose to avoid the implantation

of an ill embryo, or the subsequent request for abortion. However, such practice would not stand in for prenatal diagnosis itself, which should be carried out according to a comprehensive evaluation of overall pregnancy risks. Another purpose of PGT can be to type the HLA (Human Leucocyte Antigen) system to select donors (also said designer babies or bébé-médicament) for stem cells transplant in siblings suffering from hematological pathologies. Indeed, PGT revealed to be useful in beta-thalassemia, Sickle cells anemia and Fanconi anemia (12), which are pathologies needing HLA-matched stem cells or bone marrow for transplant, where a perfect donor-recipient molecular identity notably reduces the risks of rejection and other transplants clinical issues. Formerly, attempting to find a heal for their child suffering from one of the abovementioned conditions, couples tried naturally to conceive again, in order to make the future sibling a possible donor, and evaluating HLA matching with prenatal diagnosis, when pregnancy was already advanced. Many pregnancies were obtained for this scope, of which one led, in 1988, to the first umbilical cord stem cells successful transplant. Nevertheless, it should be considered that the chances to give birth to a healthy child, and at the same time HLA-matched with the sibling, is not so high. Many families faced repeated pregnancies, delaying transplant, risking to opt for abortion, in case of ill fetuses, or sometimes once HLA antigens were found to be not matched by prenatal diagnosis. Nowadays, the PGT associated to HLA typing may configure as a therapeutic tool, avoiding the need for prenatal diagnosis and allowing selection and following transfer of healthy embryos who are HLA-matched with the ill sibling. In addition, this resource may favor eugenics practice, consenting, as example, embryo selection for non-medical reasons, but social needs or family balancing. Such a possibility gives rise to the concern that it could be applied to create a baby "à la carte", namely to choose features of the unborn (sex, color of the iris), and then to build custom-made humans in vitro.

In light of the abovementioned, in what countries PGT is considered permissible needed to be ascertained. Where permitted, it should be identified the purposes for which it is allowed, and the assumptions (subjective and objective) that justify its application. Therefore, this review has been carried out with the aim of providing a comprehensive information on Italian jurisprudential approach to PGT. Furthermore, a comparison of Italian model with other western countries, including Europe and USA is proposed.

The Italian jurisprudential approach

Actually, in Italy it is excluded that it could be used for eugenic practices (13) or to type the HLA system to select stem cells donors for ill siblings. Obviously, the issue is ethical and not technical. Think, referring for example to the so-called “designer babies” o “bébé-médicament”, to the difficult case that could be determined if, after many years, the older sibling should need a kidney (14). It would create a serious problem: the younger sibling risks to feel as a certified donor with “presumed consent”, like a stock of body organs. The same applies for the older sibling, being the matching bilateral: it could happen that one day the younger one would need a transplant.

Putting apart the extreme cases, it could be arduous to deal with the unavoidable role-playing game of “the saved” and “the savior”. Also, parents could develop a guilt towards the younger child which might be faced in the wrong way. For example, pushing the older sibling to be grateful and to fell in obligation. Even harder is the evaluation of the case when the aim is a screening for genetic diseases or chromosomal abnormalities for couples at risk of transmitting it to the offspring (15).

With reference to this precise scope, in absence of related provisions of the law no. 40 of February the 19th 2004, the more dating Italian jurisprudential approach recognized priority to the protection of embryo’s rights to life and integrity from conception, subordinating to them the right to conscious and responsible procreation. The jurisprudential revirement started in 2007 with two proceedings: a judgment of the Court of Cagliari (16) and a decree of the Court of Florence (17), with which, for the first time, the legitimacy of the PGT was affirmed in Italy on the basis of a constitutionally oriented interpretation of the aforementioned law no. 40/2004. Trial courts, especially the one from

Cagliari, highlighted the legitimacy of the method according to the right to health of the woman and the right of the parents to be informed about the health status of the embryos produced as ratified, and criminally sanctioned, by article no. 14, paragraph no. 5, law no. 40/2004. In view of the recognized admissibility of PGT to perform a screening of genetic diseases or chromosomal anomalies in couples at risk of transmitting them to offspring, it is necessary to question the subjective and objective requirements of applicability of this technique. With reference to the former, it should be noted that the law no. 40/2004, article no. 5, establishes that couples of adults of different sex, married or living together, of reproductive age, both living, can have access to ART. From the objective point of view, however, the art. 4, paragraph 1, limits the access to ART to those who are in ascertained conditions of sterility or infertility. About that, the guidelines adopted with Health Minister Decree of July the 21st 2004, specified that with the two words, infertility and sterility (used in the aforesaid document as synonyms), is meant “the absence of conception, beyond the cases of recognized pathology, after 12 to 24 months of regular unprotected sexual intercourse”. The 2004 guidelines also provided that the objective requirement of sterility (infertility), regardless of the reason from which it can derive, must result from a medical certification. However, after the criticisms raised against the chance of release of a real certification in special circumstances as at least for the cases of “unexplained” causes, the Italian jurisprudence clarified that the guidelines were intended to reserve to specialists working for ART centers and registered in the appropriate Register, pursuant to art. 11 of the law n. 40/2004 (and not, therefore, to any healthcare professional), the competence to certify the prerequisite for accessing the ART. Furthermore, in line with the provisions of art. 4 of Law 40/2004, only infertility from ascertained causes should have been subjected to real “certification”, while infertility from unexplained causes should have been simply “documented” by medical act. A position that makes it doubtful, in fact, that sterility is really a prerequisite for accessing ART, given that the couple’s declaration to the healthcare provider, that they had not been able to get pregnant in the previous 12 to 24 months indicated by the guidelines, would be enough to obtain a “documentation” of the state of sterility deriving from an unexplained cause, and that would legitimize, however, the request for and the access to the

ART. Moreover, the legal provision on the need to be sterile or infertile had created interpretative doubts also regarding the access or not to the ART by the “subfertile”, *i.e.* those who, although not technically sterile or infertile, are however incapable of originating or completing a reproductive process. In the absence of legal provisions, the 2004 guidelines also intervened in this hypothesis, which also granted these couples the possibility of resorting to ART. The guidelines, adopted by Health Minister Decree of July the 11th 2008, have finally extended access to the techniques in question, also to the couple in which the man is the carrier of sexually transmitted viral diseases (HIV and hepatitis B and C viruses). In addition to sterile, infertile, subfertile or suffering from sexually transmitted diseases couples, however, there are fertile couples, but carriers of genetic diseases, whose natural procreation would have the effect of giving life to a seriously ill individual. In relation to the latter, the Italian Constitutional Court (18), after a long doctrinal and jurisprudential work, with the judgment no. 96 of June the 5th 2015, (in line with what was already provided by the European Court of Human Rights with the judgment of August the 28th 2012, in the *Costa/Pavan* case (19)), considered unreasonable the indiscriminate prohibition of access to the ART, with preimplantation diagnosis, by couples fertile but affected (also as healthy carriers) from serious hereditary genetic diseases, likely to transmit significant anomalies or malformations to the unborn child (according to scientific evidence). This is because, with obvious unreasonableness, the Italian legal system allowed, however, these couples to pursue the goal of not procreating a child affected by the specific inheritable pathology of which they are carriers, resorting to the much more traumatic method of abortion (also recurrently).

Foreign approach

Once described our national current views, it is worthwhile to analyze what are the solutions adopted by foreign legal systems, without claims of absolute completeness. Each individual country faces the issue of PGT with the use of uneven, sometimes conflicting solutions, inspired in some cases by specific legislation, in others by guidelines codified by scientific societies, and yet in others by the guidance of the specialist consulted. In Austria, PGT is prohibited. In particular, such ban is inferred from art. 9, paragraph 1, of the Law of June the 4th

1992 (20) (amended on December the 30th, 2004 (21)), where it allows the treatment and analysis of “cells capable of developing” only to the extent that it is needed to achieve pregnancy. In Belgium, PGT cannot be used to encourage eugenic practices (22). It is, however, allowed to identify the sex of the unborn child only in couples with genetic diseases linked to the sex chromosomes, and can exceptionally be authorized in the therapeutic interest of an already born child (articles 67 and 68). In Denmark, pursuant to art. 7.1 of Law no. 460/1997, PGT is allowed only in the case of “serious hereditary diseases or chromosome abnormalities” (23). It must be certified by a doctor in a multidisciplinary center for prenatal diagnosis that the couple, given the family history, is likely to give birth to a child suffering from a serious genetic disease, without known therapies at the time of diagnosis. Such law was amended by a new provision - Section 73 of Law no. 240 of April the 5th 2004 - according to which the Health Minister can license recourse to PGT in all those situations where a donor is needed for a brother or sister suffering from a serious illness. In Finland, the Law no. 1237 of December the 22nd 2006 (24) does not specifically refer to the PGT, but establishes (Section 5: “Influencing the characteristics of the child”) that it is forbidden to use in ART gametes and embryos genetically modified or used for research; the prohibition does not involve, however, cases in which embryos are subject to investigations aimed at verifying the absence of serious inheritable genetic diseases transmitted through sex chromosomes. In France, the art. 2131-4 of the “Code de la santé publique”, modified by the Law no. 814 of July the 7th 2011 (25) admits the application of PGT, subjected to authorization by the “Agence de la Biomédecine” and written consent of the couple, only when there is a risk that the unborn child may be suffering from a particularly serious genetic disease recognized as incurable at the time of diagnosis. In Germany, since February the 1st 2014, date of entry into force of the “Verordnung zur Regelung der Präimplantationsdiagnostik” (26) it is possible to access the PGT under specific conditions. As you know, the German legal system is traditionally characterized by a very strong preservation of embryo rights, in particular through the Law of 1990, significantly called Embryonenschutzgesetz (ESchG) (27), namely the law for the protection of the embryo. The strictness of this legislation was initially relieved by the intervention of the Bundesgerichtshof which, in the

court of July the 6th, 2010 (28) recalling the distinction referred to the art. 8 of the ESchG between totipotent and pluripotent cells, stated that PGT conducted on pluripotent embryonic cells, in order to search for serious genetic pathologies, does not violate the Embryonenschutzgesetz and therefore, does not represent a penal sanctionable conduct. Accordingly, in 2011 the German legislator promulgated the Präimplantationsdiagnostikgesetz which, accepting the direction of the Bundesgerichtshof, modified the ESchG by admitting, under definite conditions, the PGT. In particular, the current German regulation allows PGT if there is a high risk of transmission of serious genetic diseases to the offspring or when it is carried out to ascertain a serious pathology of the embryo, able to lead to death, miscarriage or abortion with high probability. The law, defining the boundaries of the legal regulation in the field of PGD, requires that it can only be carried out by qualified doctors at specifically authorized centers and that the written consent of the woman is preceded by adequate information and advice on possible medical, psychological and social consequences of the requested diagnosis. It is also explicitly provided that the diagnosis could be made only after an ethics committee, with an interdisciplinary composition, has verified the existence of the prerequisites required by law and has expressed its opinion on the matter. However, these exceptions to the general prohibition to PGT could not be concretely acknowledged in the absence of the aforementioned implementing regulation, the adoption of which was entrusted by the same law to the Federal Court of Justice (Bundesregierung). In this document (adopted from February 2014), the discipline was defined as regards the procedures to be observed, the issue of authorizations to specialized centers, including the title of the doctors qualified to work there and the duration of the authorizations themselves, the composition and the functioning of the committee and the management of the documentation. The decree also contains a paragraph dedicated to the definitions of cells that can be subjected to PGT. With respect to this definition, it confirms that it must be stem cells, capable of multiplying and specializing in different types of cells (so-called pluripotent cells), but not also of developing in an individual (so-called totipotent cells). In Great Britain, ART treatments and research on human embryos are regulated by the Human Fertilization and Embryology Act of November the 13th 2008 (29) which amended the Hu-

man Fertilization and Embryology Act of 1990 (30) and the Surrogacy Arrangements Act of 1985 (31). PGT is allowed for any therapeutic indication subjected to prior authorization from the Human Fertilization and Embryology Authority. In Greece (32) PGT is allowed but only if it is helpful to avoid the transmission of sex chromosomes-related genetic diseases to the fetus. In Portugal, the Law no. 32 of July 26th 2006,(33) in art. 28 paragraph 1, indicates as the aim of the PGT, the identification of embryos that are not carriers of serious anomalies, before the transfer into the womb of the woman and the subsequent art. 29, paragraph 1, establishes that such tool is intended for people deriving from families with inheritable alterations that could cause early death or serious illness, when there is a high risk of transmission to descendants. In the Czech Republic, access to ART is regulated by Law no. 227 of April the 26th 2006 (34) where with reference to the PGT it provides that “genetic examinations of embryos are permitted only by defined indications, in order to exclude risks of serious genetically conditioned diseases and defects before they are implanted into the uterine cavity” (Part three, Section 27d). In Spain, (35, 36) PGT is allowed to search for serious hereditary pathologies, with an early onset and not amenable to postnatal treatment or for the diagnosis of other diseases that may compromise the viability of the embryo (art. 12, paragraph 1); for any other purpose, including that of establishing the histological compatibility of the embryo with already born third parties, a specific authorization from the Comisión Nacional de Reproducción Humana Asistida is required (art. 12, paragraph 2). In Sweden (37) PGT is consented only to search for severe hereditary diseases, while prohibited if there would be a social reason, as for sex selection. Only the National Board of Health and Welfare can approve investigations for HLA-matching, that is, for having a child who is immunologically compatible with an already born sibling (chapter 4, paragraph 2). In Switzerland, (38) the evaluation of the genetic heritage of in vitro embryos, their sex-based selection or in relation to other characteristics are allowed only in cases where: a) the danger that an embryo carrying inheritable predisposition to severe conditions can implant in the uterus cannot otherwise be avoided; b) this serious illness is likely to occur before the age of 50 years old; c) there is no effective and appropriate therapy to counteract this serious disease; d) the couple gives written notice to the doctor that they cannot reasonably run the

danger referred to in letter a). The examination of the genetic heritage of in vitro embryos and their selection based on sex or other characteristics are also allowed to identify chromosomal features likely to influence the development of the embryo (art. 5). In the United States, Law does not dictate specific regulation of eligibility conditions and limits of PGT. Think that, in Washington, a couple of young deaf women, Sharon Duchesneau and Candy McCullough, resorting to assisted reproduction and the following PGT, decided to have a son from a sperm donor, also affected by deafness, to make sure that the son would be born deaf like them. The two women work as therapists for deaf people and belong to a growing movement in the United States that sees deafness not as a handicap, but as a cultural identity (39). Thus, ART clinics admit the use of preimplantation genetic investigations not only to diagnose the presence of serious diseases that could develop in the early childhood (such as, for example, Tay-Sachs disease, cystic fibrosis or thalassemia), but also (and this goes beyond what is already allowed in European experience) to know if the embryo carries the risk of developing cancer in adulthood or of falling ill with neurodegenerative syndromes, such as, example, Alzheimer's disease. However, the most "disturbing" aspect of the USA experience is given by the increasingly widespread practice of asking, and obtaining, for not strictly medical reasons, but of mere parental preference, the PGT for the selection of the sex or color of the iris of the unborn child.

DISCUSSION

Overall, a somewhat uneven legal framework emerges, where alongside particularly liberal states as for example the United Kingdom and the USA, in which recourse to the PGT is admitted for almost any purpose, in Austria remains the veto for their use. In several states, the PGT is legalized to prevent the transmission of genetic diseases (Denmark, France, Germany, Great Britain, Italy, Portugal, Czech Republic, Spain, Sweden, USA), being limited in some of them to only the inherited diseases related to the sex chromosome (Belgium, Finland, Greece). The selection of sex as such is considered largely unacceptable. In some cases, the prior authorization of a health authority is required to access the PGT methods (France, Germany, Spain), or a preliminary medical certifi-

cate is required to access the ART (Italy), or which certifies the concrete risk of conceiving a child with a serious genetic disease (Denmark). To conclude, in some countries PGT can be provided (Belgium, Denmark, Great Britain, Spain, Sweden) or it can be used (USA) in the therapeutic interest of an already born child (brother or sister) (**table I**). PGT has the advantage to identify fetuses affected by genetic disorders before the embryo implantation, and then to avoid women (and more in general couples) to take difficult and painful decisions about eventual termination of pregnancy (40). Social, healthcare (mainly related to maternal-fetal health and high costs) and ethical issues (possible manipulation of genetic heritage of the unborn, increment of non-implanted embryos, selective abortion, request for abortion due to non-debilitating diseases, selection of embryos due to features not related to health status) exist, which underlie the access to PGT. In relation to the genetic diseases for which the access to PGT is considered licit, at least ethically, the European Society of Human Reproduction and Embryology (ESHRE) propose to limit such tool to cases at high risk of serious illness (41). However, to date, genetic conditions for which PGT is allowed are not only the inheritable ones but also those given by new mutations. Different variables can concur to the definition of seriousness of a given genetic disease, as for example, the risk of transmission of the condition, the penetrance, the impact on life quality, age of onset, the availability of preventive or curative therapeutic options. These variables should not necessarily all be expressed to a maximum to acknowledge the high risk of transmission of a serious illness.

In addition, personal experiences of the individual subject requesting PGT can play a non-secondary role in the definition of an illness as serious (42). Indeed, the level of difficulty to overcome the status of infertile couple, and then the concrete chance to achieve a pregnancy, can influence the opinion regarding the gravity of a genetic condition. In recent decades, indications for PGT increased, being included also diseases characterized by incomplete penetrance, adult-onset, treatable or amenable to screening (ovarian or breast cancer, hypertrophic cardiomyopathy) conditions (43). Sex selection can be morally acceptable if the goal is to avoid genetic diseases inherited by sex chromosomes, while is generally considered ethically unacceptable if used to choose the unborn gender (44). More than 400 genetic diseases, for the screening of which PGT

is practiced, have been identified (45). Someone think it could be preferable to allow the test for any detectable genetic condition, on the basis of the sole parental will, in spite of limiting PGT only to severe inheritable genetic conditions (46). Since it appears still challenging to provide a pre-determined list of all severe genetic conditions at high risk of transmission, it comes the need that the decision would be the result of a true sharing between the couple and the healthcare providers who, based on updated and correct technical knowledge, must guarantee a comprehensive information, updated and understandable (47), so to define together to detect which genetic inheritable pathology PGT should be asked for. Indeed, being a screening test and not a diagnostic one, it comes that the results of the detection of a given non-life-threatening disease would raise the issue on how to deal with the decision of the parents to be. In the era of genetic screenings, as for carrier screening tests, offering the possibility to screen for a wide list of conditions, not all of which should be necessarily considered as proper diseases, such question still remains unanswered

(48). Therefore, it seems appropriate that different healthcare professionals are involved into the decision process in addition to the reproductive medicine specialist, as the geneticist (due to his knowledge on genetics and inheritance), the psychologist (to evaluate the impact of a handicapped unborn on parental psychic health), the expert in bioethics (with the aim to dissolve ethical issue) and the legal medicine specialist (for his aptitude to highlight any fallacious conduct and harbinger of a possible judicial dispute). The need to involve in the process different professional competences is more compelling in cases in which the transmission of a given genetic disorder to the progeny can be prevented through gamete donations (49). The moral and deontological duty of the healthcare professional, not to passively comply with the couple requests and to refuse his professional work, when the health service is required in contrast with own conscience or with own technical-scientific convictions, remains firm (50). Wide international consent exists to consider not sustainable the request to access the ART procedures by couples for which the chances of birth of

Table I. Summary of the different PGD regulations in different countries.

	Access to PGD	Identify inheritable disease (also linked to sex chr.)	Sex chr. Analysis to avoid transmission of related genetic diseases	Therapeutic purposes of third parties	Sex chr. Analysis to ascertain sexual genotype
Austria	NO	-	-	-	-
Belgium	YES	-	YES	YES*	-
Denmark	YES	YES**	-	YES*	-
Finland	YES	-	YES	-	-
France	YES	YES*	-	-	-
Germany	YES	YES*	-	-	-
Great Britain	YES	YES	-	YES*	-
Greece	YES	-	YES	-	-
Italy	YES	YES**	-	-	-
Portugal	YES	YES	-	-	-
Czeck Republic	YES	YES	-	-	-
Spain	YES	YES*	-	YES*	-
Sweden	YES	YES	-	YES*	-
Switzerland	YES	YES	-	-	-
USA	YES	YES	-	YES	YES

Chr.: chromosomes. * Subject to authorization; ** Subject to medical certificate.

a child affected by a seriously disabling condition are high (43).

CONCLUSIONS

Nowadays, genetic screening tests have opened a fundamental window to the possible prevention of a wide range of diseases and pathologic conditions. In the field of reproductive medicine, prevention can be even accomplished in the pre-pregnancy period. However, different countries apply more or less different regulations to allow the access to such tests, driven by ethical, medical or legal issues, also linked to their respective jurisprudential position on the rights of the embryo and the unborn. More in-depth studies would be useful to ascertain the aforementioned issues on the basis of which foreign countries, also from Middle-East, Asiatic South-East, Africa and South-America regulate the access to PGT. At last, a multidisciplinary approach would be probably needed in order to

clarify and moreover, to uniform as much as possible between different countries, the rules and the indications to access pre-implantation genetic testing, in a “right to health” view.

AUTHORS' CONTRIBUTIONS

CC and PDL contributed to the conception and designed the manuscript. CC, PDL, and LC wrote the first draft of the manuscript. AC, VM, GC, CB, PDR, LA, AC and CA wrote sections of the manuscript. All authors contributed to manuscript revision, read and approved the submitted version. The corresponding author takes the final responsibility for the decision to submit the manuscript for publication.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

REFERENCES

1. Dondorp W, de Wert G. Refining the ethics of preimplantation genetic diagnosis: A plea for contextualized proportionality. *Bioethics* 2019;33:294-301. Doi: 10.1111/bioe.12534.
2. Costa M, et al. Routine karyotyping in infertile couples: Is it really mandatory? Proposal from experience on 7,196 infertile Italian couples. *Int J Gynaecol Obstet* 2017;29(1):13-8. Doi: 10.14660/2385-0868-58.
3. Bruno V, Ticconi C, Sarta S, et al. What has to be pointed out in unexplained recurrent pregnancy loss research in the unsolved fields: lessons from clinic. An Italian RPL Unit experience. *Int J Gynaecol Ob* 2019;31(2):53-62. Doi: 10.14660/2385-0868-58.
4. Harper JC, Boelaert K, Geraedts J, et al. ESHRE PGD consortium data collection V: cycles from January to December 2002 with pregnancy follow-up to October 2003. *Hum Reprod* 2006;21:3-21. Doi: 10.1093/humrep/dei292.
5. Humaidan P, Alviggi C, Fischer R, Esteves SC. The novel POSEIDON stratification of "Low prognosis patients in Assisted Reproductive Technology" and its proposed marker of successful outcome. *F1000Res* 2016;23;5:2911. Doi: 10.12688/f1000research.10382.1.
6. Conforti A, Esteves SC, Cimadomo D, et al. Management of Women With an Unexpected Low Ovarian Response to Gonadotropin. *Front Endocrinol (Lausanne)* 2019;10:387. Doi: 10.3389/fendo.2019.00387.
7. Conforti A, Esteves SC, Picarelli S, et al. Novel approaches for diagnosis and management of low prognosis patients in assisted reproductive technology: the POSEIDON concept. *Panminerva Med* 2019;61(1):24-29. Doi: 10.23736/S0031-0808.18.03511-5.
8. Esteves SC, Roque M, Bedoschi GM, Conforti A, Humaidan P, Alviggi C. Defining Low Prognosis Patients Undergoing Assisted Reproductive Technology: POSEIDON Criteria-The Why. *Front Endocrinol (Lausanne)* 2018;9:461. Doi: 10.3389/fendo.2018.00461.
9. Romanelli V, Poli M, Capalbo A. Preimplantation genetic testing in assisted reproductive technology. *Panminerva Med* 2019;61(1):30-41. Doi: 10.23736/S0031-0808.18.03506-1.
10. Somigliana E, Busnelli A, Paffoni A, et al. Cost-effectiveness of preimplantation genetic testing for aneuploidies. *Fertil Steril* 2019;111(6):1169-1176. Doi: 10.1016/j.fertnstert.2019.01.025.
11. Zegers-Hochschild F, Adamson GD, Dyer S, et al. The International Glossary on Infertility and Fertility Care, 2017. *Hum Reprod* 2017;32(9):1786-1801. Doi:10.1093/humrep/dex234.
12. Conti A, Capasso E, Casella C, et al. Blood Transfusion in Children: The Refusal of Jehovah's Witness Parents'. *Open Med (Wars)* 2018;13:101-104. Doi:10.1515/med-2018-0016.
13. Act on Rules on medically assisted procreation. 2004;40. Available at: <https://www.ieb-eib.org/ancien-site/pdf/loi-pma-italie-english.pdf>.
14. Graziano V, Buccelli C, Capasso E, et al. Suggestions on how to make suboptimal kidney transplantation an ethically viable option. *Open Med (Wars)* 2016;11(1):523-529. Doi:10.1515/med-2016-0090.
15. Fedeli P, Casella C, Buccelli C, et al. Genetic research: The role of citizens, public health and international stakeholders. *Open Public Health Journal* 2019;12(1):106-113. Doi: 10.2174/1874944501912010106.
16. Court of Cagliari, Sentence no. 2508/2007. Available at: <https://archivioldpc.dirittopenaleuomo.org/upload/1354806458ordinanza%20Tribunale%20Cagliari.pdf>.
17. Court of Florence, Ordinance of December 17, 2007. Available at: <https://www.unionediritiumani.it/wp-content/uploads/2012/07/Tribunale-di-Firenze-sentenza-17.12.2007-fecondazine-assisitita.pdf>.
18. Casella C, Niola M, Graziano V, et al. Assisted reproductive technologies in the relationship between the Legislator and the Constitutional Court. *Rivista Italiana di Medicina Legale e del Diritto in campo sanitario* 2017;4:1441-1456.
19. Di Lorenzo P, Casella C, Niola M. The regulations relating to heterologous artificial insemination following the ruling of the Constitutional Court. *Rivista Italiana di Medicina Legale e del Diritto in campo sanitario* 2015;1:25-43.
20. Act on Reproductive Medicine of June 4, 1992, "Fortpflanzungsmedizingesetz". Available at: http://www.ris.bka.gv.at/Dokumente/BgblPdf/1992_275_0/1992_275_0.pdf.
21. Act on Reproductive Medicine, Amendment of December 30, 2004, "Fortpflanzungsmedizingesetz-Novelle 2004". Available at: http://www.ris.bka.gv.at/Dokument.wxe?Abfrage=BgblAuth&Dokumentnummer=BGBLA_2004_I_163.
22. Law on Medically assisted procreation and the destination of surplus embryos and gametes of July 6, 2007. <https://www.ejustice>.

- just.fgov.be/cgi_loi/change_lg.pl?language=fr&la=F&cn=2007070632&table_name=loi.
23. Faber BA. Assisted reproduction, the law and public attitudes: a Danish perspective. *Eur Rev* 2013;21(1): S80–S84.
 24. Act on Assisted Fertility Treatments, No 1237 of December 22, 2006. Available at: <https://www.finlex.fi/en/laki/kaannokset/2006/en20061237.pdf>.
 25. Act on Bioethics, No 814 of July 7, 2011. Available at: <https://www.legifrance.gouv.fr/jorf/jo/2011/07/08/0157>
 26. Regulation on the Preimplantation diagnostics, 2014. Available at: <http://www.gesetze-im-internet.de/pidv>.
 27. German Embryo protection Act, 1990. <http://www.gesetze-im-internet.de/eschg>.
 28. German Federal Court of Justice, 2010. <http://juris.bundesgerichtshof.de/cgi-bin/rechtsprechung/document.py?Gericht=bgh&Art=en&sid=c25252bf7b1bfc1ff432dc9f0032b17&nr=52897&pos=8&anz=19>.
 29. Human Fertilization and Embryology Act, No 22, 2008. Available at: <http://www.legislation.gov.uk/ukpga/2008/22/contents>.
 30. Human Fertilization and Embryology Act, No 37, 1990. Available at: <http://www.legislation.gov.uk/ukpga/1990/37/contents>.
 31. Surrogacy Arrangements Act, No 49, 1985. Available at: <http://www.legislation.gov.uk/ukpga/1985/49>.
 32. Law on Medically assisted human reproduction, No 3089 of December 23, 2002 and Law on Enforcement of Medically Assisted Reproduction, No 3305/2005. Available at: <http://www.bioethics.gr/index.php/en/dikaio/nomothesia/138-medically-assisted-human-reproduction>.
 33. Law on Medically assisted procreation, No 32 of July 26, 2006. Available at: http://www.pgdlisboa.pt/leis/lei_mostra_articulado.php?nid=903&tabela=leis.
 34. Act on Research on human embryonic stem cells, No 227/2006. Available at: <https://www.lexadin.nl/wlg/legis/nofr/eur/lxwecze.htm>.
 35. Law on Assisted Human Reproduction Techniques, No 14, May 26, 2006. Available at: <https://www.boe.es/buscar/pdf/2006/BOE-A-2006-9292-consolidado.pdf>.
 36. Law on Biomedical Research, No 14, July 3, 2007. Available at: <https://www.boe.es/buscar/pdf/2007/BOE-A-2007-12945-consolidado.pdf>.
 37. Act on Genetic Integrity, No 351 of May 18, 2006. Available at: https://www.riksdagen.se/sv/dokument-lagar/dokument/svensk-forfattningsamling/lag-2006351-om-genetisk-integritet-mm_sfs-2006-351.
 38. Federal Act on Medically Assisted Reproduction of 18 December 1998 (Status of 1 September 2017). Available at: <https://www.admin.ch/opc/it/classified-compilation/20001938/index.html>.
 39. Savulescu J. Deaf lesbians, “designer disability,” and the future of medicine. *BMJ* 2002; 325(7367): 771–773. Doi: 10.1136/bmj.325.7367.771.
 40. Piras M, Delbon P, Bin P, *et al.* Voluntary termination of pregnancy (medical or surgical abortion): forensic medicine issues. *Open Med (Wars)* 2016;11(1):321-326. Doi:10.1515/med-2016-0062.
 41. De Wert G, Dondorp W, Shenfield F, *et al.* ESHRE task force on ethics and Law 22: preimplantation genetic diagnosis. *Hum Reprod* 2014;29(8):1610-1617. Doi: 10.1093/humrep/deu132.
 42. Paternoster M, Saccone G, Maruotti GM, *et al.* Ethical challenges in pregnant women with brain injury. *J Mater-Fet Neonat Med* 2018;31(17):2340-2341. Doi: 10.1080/14767058.2017.1339271.
 43. Van der Schoot V, Dondorp W, Dreesen JCFM, *et al.* Preimplantation genetic testing for more than one genetic condition: clinical and ethical considerations and dilemmas. *Hum Reprod* 2019; 34(6):1146–1154. Doi: 10.1093/humrep/dez059.
 44. Sueoka K. Preimplantation genetic diagnosis: an update on current technologies and ethical considerations. *Reprod Med Biol* 2016; 15: 69-75. Doi: 10.1007/s12522-015-0224-6.
 45. Kuliev A, Rechitsky S. Preimplantation genetic testing: current challenges and future prospects, *Expert Review of Molecular Diagnostics* 2007;17(12):1071-1088. Doi: 10.1080/14737159.2017.1394186.
 46. Lee VCY, Chow JF, Yeung WSB, Ho PC. Preimplantation genetic diagnosis for monogenic diseases. *Best Practice Research Clin Obstet Gynaecol* 2017;44:68-75. Doi: 10.1016/j.bpobgyn.2017.04.001.
 47. Di Lorenzo P, Casella C, Capasso E, *et al.* The Central Importance of Information in Cosmetic Surgery and Treatments. *Open Med (Wars)* 2018; 13:153-157. Doi: 10.1515/med-2018-0024.
 48. Mastantuoni E, Saccone G, Al-Kouatly HB, *et al.* Expanded carrier screening: A current perspec-

- tive. *Eur J Obstet Gynaecol Reprod Biol* 2018; 230:41-54. Doi: 10.1016/j.ejogrb.2018.09.014.
49. Casella C. "Gestazione per altri" e interessi in conflitto. *Biolaw J* 2020; 1: 321-337. Doi: 10.15168/2284-4503-530.
50. Casella C, Niola M, Di Lorenzo P, Buccelli C. The legal protection of people with debilitating illness even in the light of the law n. 219/2017. *Rivista Italiana di Medicina Legale e del Diritto in campo sanitario* 2018, 1:143-161.