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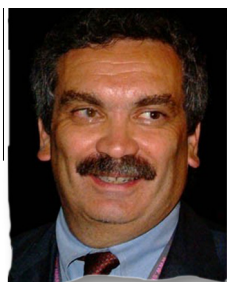
Reiterative changes in the Italian regulation on IVF: the effect on PGD patients' reproductive decisions




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Abstract National legislations represent one of the main factors influencing access to assisted reproduction treatment. The Italian situation in the last decade is an example of how the treatment of patients for preimplantation genetic diagnosis (PGD) was more dependent on regulators than on medical choices. This report analysed how the changes in Italian regulation affected the number of PGD referrals to this study centre, as well as their decision to opt for cross-border reproductive care (CBRC). The analysis showed that during the period in which PGD was actually not performed because of the restriction imposed by the Italian law on IVF (from 24 February 2004 to 7 May 2009) there was a significant decrease in the number of referrals asking for PGD (2.5% of total referrals) compared with the previous years (3.3%; $P < 0.025$) and following years when PGD was legalized (5.1%; $P < 0.001$). The number of couples opting for CBRC had an opposite trend, reaching a maximum when PGD was banned from Italian centres (55 couples), whereas after the readmission of PGD, only eight couples went abroad for treatment. Concomitantly, since May 2009, the proportion of couples performing a PGD cycle in this centre has constantly increased. 

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KEYWORDS: cross-border reproductive care, monogenic diseases, Italian law on IVF, PGD, translocations, therapeutic abortion

Introduction

Preimplantation genetic diagnosis (PGD) finds its applicability in couples at risk of transmitting a genetic disease to their offspring, or in carriers of chromosomal segmental

anomalies to prevent the transfer of embryos generated by unbalanced gametes. The clinical history of PGD started in the early 1990s when the biopsy and analysis of polar bodies from the oocyte and blastomeres from day-3 embryos were proposed as a tool to have information on

the genetic status of the corresponding oocyte or embryo (Handyside et al., 1990; Verlinsky et al., 1990). In the following years, novel applications were described (reviewed by Handyside, 2010) that made PGD a well-established technique currently performed by highly specialized centres.

Nowadays, PGD can be performed on a large spectrum of genetic diseases for which the responsible gene has been identified. More recently, new approaches have been proposed, such as preimplantation genetic haplotyping that uses panels of markers applicable to most families at risk of specific conditions, including adult-onset disorders with complete or incomplete penetrance (e.g. Huntington's disease or familial cancers; Offit et al., 2006); and human leucocyte antigen (HLA) tissue matching to select embryos HLA-compatible with an affected sister or brother needing stem cell transplants (Verlinsky et al., 2001). Whatever the indication may be, the main reason for couples at high reproductive risk asking for PGD is the desire to have an unaffected child and to avoid the trauma associated with an eventual therapeutic abortion.

With the aim of monitoring PGD treatment cycles and their outcome, including the follow up of children born, the European Society for Human Reproduction and Embryology (ESHRE) PGD Consortium was set up in 1997 to collect the data that were voluntarily contributed by major European and extra-European centres. According to the last publication, 12,388 PGD cycles have been reported resulting in 2499 clinical pregnancies with fetal heartbeat (Goossens et al., 2012). From the follow up of 6304 clinical pregnancies from PGD and PGS (preimplantation genetic screening) cycles, 5090 deliveries were reported, ending with the birth of 6304 babies. The incidence of major congenital malformations was 1.73%, which does not differ from that found in IVF/intracytoplasmic sperm injection pregnancies (Handyside, 2010).

Taken together, these reassuring data contribute to make PGD an attractive proposal for couples at high reproductive risk. From one side, gynaecologists and geneticists can offer this approach to couples that have an indication to it, and from the other side, couples have the right to choose for themselves the treatment option that they consider to meet their wishes.

In many countries, IVF techniques are regulated at national level, with each country having its own specific law. In Italy on 19 February 2004, a very restrictive law on IVF was promulgated (Repubblica Italiana, 2004), which imposed, besides other limitations including PGD/PGS, three embryos as the maximum to be inseminated per cycle and the transfer of all generated embryos (Benagiano and Gianaroli, 2004). In addition, the access to medically assisted conception techniques was specifically allowed only to infertile couples.

These severe limitations were the main cause of an increasing phenomenon called cross-border reproductive care (CBRC), which refers to the travelling of patients from their country of residence to another country in order to receive fertility treatment (Ferraretti et al., 2010). Despite the difficulty of quantifying this phenomenon, it is estimated that the approval of the national law quadrupled in a few months the already-existing CBRC from Italy, causing well-known psychological and economic damage to patients (Ferraretti et al., 2010). In 2010, a study by ESHRE, based on

a survey administered to foreign patients in 46 clinics in six European countries found that 31.8% of returned forms were filled in by patients from Italy. Approximately 70% of them mentioned legal reasons as the predominant motive for CBRC, with 2% asking for a PGD/PGS cycle (Shenfield et al., 2010).

The limitations to the practice of IVF imposed by the law were felt to be especially unbearable for couples, such as many PGD couples, who had experienced traumatic reproductive histories (Karatas et al., 2010). Therefore, a number of initiatives from individual patients, fertility centres, associations and non-governmental organizations were mounted against the law, culminating, in May 2009, with the Italian Constitutional Court declaring the unconstitutionality of the Article 14 prohibiting the generation of more than three embryos (Benagiano and Gianaroli, 2010). This decision made PGD feasible again as its ban had already been formally removed 1 year earlier when the Regional Administrative Court of Latium declared the prohibition of PGD as unconstitutional (Tribunale Amministrativo Regionale del Lazio, 2007).

The aims of this report were to verify to what extent the proportion of patients asking for PGD in this study centre changed after May 2009 in comparison to the previous years and to quantify the number of PGD couples who opted for CBRC. This was done with the finality of evaluating how the reiterative changes in the national legislation interfered with the reproductive decisions of couples who, being carriers of single-gene disorders or balanced translocations, had the need to receive specialized care in infertility clinics. As one of the major reference centres for PGD since 1996 where a substantial proportion of cases underwent PGD/PGS (according to the PGD consortium data collection, this study centre has contributed 70% of the 2210 submitted Italian data; Veerle Goossens, personal communication; Figure 1), the resulting figures could provide a reliable estimation of this phenomenon that is otherwise difficult to quantify.

Materials and methods

Looking at the internal archives, the number of consultations for PGD in this study centre was calculated in relation to all the consultations performed, to estimate the proportion of PGD patients in three time periods, defined as follows: (i) pre-law period, from January 1998 to 23 February 2004, during which PGD was allowed as IVF was not yet regulated; (ii) restrictive law period from 24 February 2004 to 7 May 2009, during which PGD was not performed due to the limitations imposed by the legislation; patients had to go abroad for having a PGD cycle; and (iii) post-court decision period from 8 May 2009, when PGD was admitted again in IVF centres, to 31 December 2012. The year 1998 was selected as a starting point because PGD became a widespread and reliable technique in the late 1990s. The analysis was restricted to PGD couples while excluding PGS, since indications to PGD are more objectively detected being genetically determined. Conversely, PGS is often considered as a treatment option after some episodes of repeated implantation failures.

According to this centre's standard procedure, during the first consultation, couples' reproductive history and

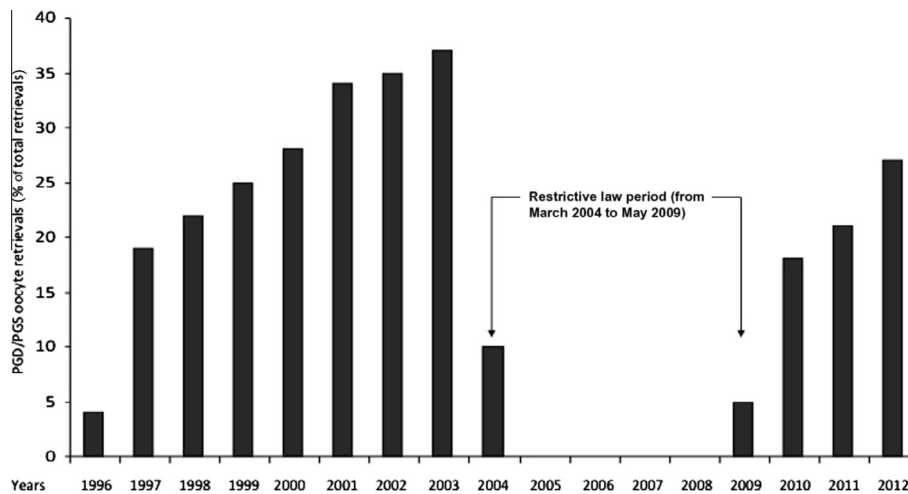


Figure 1 Proportion of oocyte retrievals in couples performing PGD/PGS cycles in this study centre from 1996 to 2012.

possible infertility conditions were documented. The genetic tests identifying the mutation and/or the translocation and the report from a medical geneticist assessing the corresponding reproductive risk were analysed and patients were informed about the need for preliminary investigations. For monogenic diseases, this consists in the confirmation of the mutations on the couple's genomic DNA and, if applicable, to affected members of the family. In the same analysis, informative markers are also investigated. For translocation carriers, if PGD is programmed by fluorescence in-situ hybridization, the adequate combination of specific probes is designed on the basis of the karyotype and then tested on the carrier's lymphocytes. The preliminary phase is not requested for couples with Robertsonian translocations or when PGD for reciprocal translocations is performed by array comparative genomic hybridization.

Details on patients' reproductive history, as well as information about PGD cycles eventually performed abroad throughout the three study periods, were collected. The latter information was mostly collected during the consultation or by qualitative phone interview, and patients were asked: (i) if they had contacted a centre in a foreign country; (ii) if they had performed a PGD cycle in a foreign country; (iii) where the PGD cycle had been performed; (iv) what was the clinical outcome; (v) how they rated this experience; and (vi) their reason for not going abroad. These data were either collected during the first consultation or in a subsequent contact with this centre, either in person or by telephone, and the data were transcribed to the patients' clinical notes. Where applicable, patients were asked why they had decided not to go to a foreign clinic.

Information provided by the couples, mainly the female partner, was duly transcribed in the patient's clinical folder and organized in a dedicated database. In this way, the data derived from the interviews could be counted and analysed independently to identify common typologies and categories (Boyatzis, 1998).

The study was approved by the study centre's Institutional Review Board on 21 February 2011 (reference no. 210211)

Results

Patients

Across the whole length of this study, 534 couples with a PGD indication attended this centre: 293 for single-gene disorders and 241 for translocations. The most common indications for single-gene disorders were thalassaemia and cystic fibrosis (45% of cases). Of translocations, 155 were reciprocal and 86 were Robertsonian.

These couples were mostly Italian ($n = 508$) coming from every region of the country. Of the remaining 26, seven were from Germany/Austria, seven from Eastern Europe, one from UK, one from France, one from the Netherlands, one from Luxembourg, six from Northern Africa and two from India.

In all, 222 couples (41%) expressed the intention to proceed with the clinical phase. At least one treatment cycle was initiated in this study centre by 148, and 68 expressed their intention to go abroad (three also performing one cycle in this centre), while 9, who repeatedly called during the restrictive law period to be updated on the current legal situation in Italy, decided to wait for a possible legislative change regarding PGD.

PGD referrals in the three study periods

Table 1 describes the couples attending the centre throughout the three study periods. During the pre-law period, 6230 referrals attended S.I.S.Me.R. centres for first consultation. Of these, 203 couples (representing 3.3% of referrals in the same period) had a PGD indication for monogenic diseases ($n = 102$) or for translocations ($n = 101$). There were 102 patients (50.2%) of proven fertility (i.e. having had a pregnancy in the past). At least one PGD cycle was attempted by 86 couples (42.4%) at the study centre, while 5 (2.5%) opted to go abroad (**Table 1**).

During the restrictive law period, there was a significant decrease in the proportion of couples asking for PGD with 138 cases over 5509 referrals (2.5%; $P < 0.01$; **Table 1**). More specifically, 79 were for monogenic diseases and 59

Table 1 Description of PGD referrals in three study periods related to the national legislative situation.

| | Pre-law period | Restrictive law period | Post-court decision period |
|---|--|--|--|
| All consultations | 6230 | 5509 | 3753 |
| PGD consultations (%) | 203 (3.3) ^{a,b} (2.7 per month) | 138 (2.5) ^{a,c} (2.2 per month) | 193 (5.1) ^{b,c} (4.5 per month) |
| Monogenic diseases (% of PGD) | 102 (50.2) | 79 (57.2) | 112 (58.0) |
| Translocations (% of PGD) | 101 (49.8) | 59 (42.8) | 81 (42.0) |
| Fertile couples (% of PGD) | 102 (50.2) | 74 (53.6) | 87 (45.1) |
| Monogenic diseases (% of all monogenic diseases) | 62 (60.8) | 45 (57.0) | 54 (48.2) |
| Translocations (% of all translocations) | 40 (39.6) | 29 (49.2) | 33 (40.7) |
| Couples performing ≥ 1 cycle in S.I.S.Me.R. (% of PGD) | 86 (42.4) | 0 | 59 (30.6) + 3 with first visit in the law period |
| Couples performing cycles abroad (% of PGD) | 5 (2.5) ^d | 26 (18.8) ^{d,e} | 8 (4.1) ^e |

Values are *n* (%) unless otherwise stated. ^{a–e}Numbers with same superscripts are significantly different: ^a $P < 0.025$; ^b $P < 0.01$; ^{c,d,e} $P < 0.001$. Pre-law = from January 1998 to 23 February 2004; restrictive law = from 24 February 2004 to 7 May 2009; post-court decision = from 8 May 2009 to 31 December 2012.

for translocations. Among these 138 couples, 74 (53.6%) were fertile. Due to the aforementioned limitations in the law, none of these couples performed PGD cycles in Italy. According to the performed interviews, 26 (18.8%) decided to consult centres located in different countries to receive fertility and diagnostic treatment through assisted reproduction technology (Table 1). In the same period, 20 couples having had a first consultation in the pre-law period also decided to go abroad for treatment (Figure 2).

During the post-court decision period, the proportion of PGD couples at their first consultation increased significantly in comparison with the two previous periods ($P < 0.01$ with the pre-law period, and $P < 0.001$ with the restrictive law period; Table 1). There were 193/3753 consultations (5.1%), of which 112 for monogenic diseases and 81 for translocations. In this PGD group, 87 couples (45.1%) were fertile. In all, 59 patients (30.6%) made at least one cycle in the study centre. In the same period, also three couples, whose first visit was in the restrictive law period,

performed a cycle in the study centre, accounting for a total of 62 couples being treated in the centre during the post-court decision period. Concomitantly, the number of couples who went abroad to perform a PGD cycle decreased significantly ($P < 0.001$; Table 1). As shown in Figure 2, in the post-court decision period, 8 couples opted for treatment abroad. In addition, 9 couples with their first visit after 8 May 2009 had already performed a cycle in a foreign centre when PGD was not applicable in Italy. Therefore, the total number of couples that resorted to CBRC in the restrictive law period was 55 (central bar in Figure 2).

PGD couples' reproductive history

Considering the reproductive history of the 534 PGD couples in the three study periods, 263 were of proven fertility and 245 were infertile. For 26 couples, the condition of fertility was unknown due to the use of protected intercourses.

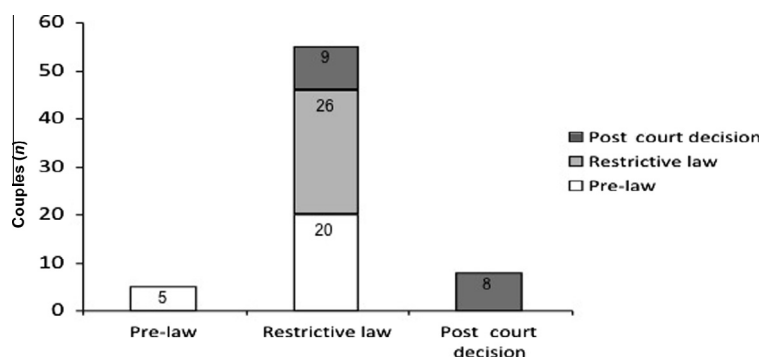


Figure 2 Number of PGD couples opting for cross-border reproductive care (CBRC) at this study centre in the three studied periods according to time of first consultation. During the restrictive law period, CBRC was decided by 20 couples having had a first visit in the pre-law period; by 26 couples with the first visit done during the restrictive law period; and by eight couples that later attended this centre after the post-court decision. Pre-law = from January 1998 to 23 February 2004; restrictive law = from 24 February 2004 to 7 May 2009; post-court decision = from 8 May 2009 to 31 December 2012.

Table 2 Reproductive history of 161 fertile couples carrying a monogenic disease.

| <i>Monogenic disease</i> | <i>Spontaneous pregnancies</i> | <i>Affected children</i> | <i>Dead children</i> | <i>Therapeutic abortions</i> | <i>Miscarriages</i> |
|---|--------------------------------|--------------------------|----------------------|------------------------------|---------------------|
| Achondroplasia | 1 | — | — | 3 | — |
| Adult syndrome | 1 | — | — | 1 | — |
| Adrenogenital syndrome | 2 | 2 | 1 | 3 | — |
| Alport syndrome X-linked | 1 | — | — | — | 1 |
| Androgen insensitivity syndrome | 1 | 1 | — | — | — |
| ATR-X syndrome | 2 | 2 | — | 1 | 1 |
| Carbamoyl phosphate synthetase I deficiency | 1 | — | 1 | 1 | 1 |
| Charcot-Marie-Tooth disease | 4 | 1 | 1 | 2 | 1 |
| Citrullinaemia | 1 | 1 | — | — | — |
| Connexin | 1 | 1 | — | — | — |
| Cystic fibrosis | 26 | 9 | — | 15 | 13 |
| Emophilia | 1 | — | — | — | 1 |
| Facioscapulohumeral muscular dystrophy | 1 | — | — | 1 | — |
| Fragile-X syndrome | 3 | 1 | — | 5 | 2 |
| Gaucher disease | 1 | 2 | 1 | — | 1 |
| Glaucoma congenital | 2 | 2 | — | — | — |
| Glycogen storage disease (type II) | 2 | 2 | 2 | — | — |
| Haemophilia | 6 | 2 | — | 5 | 1 |
| Heterotopia periventricular | 1 | 1 | — | — | — |
| HLA | 1 | 1 | — | — | — |
| HLA + specific diseases | 5 | 6 | — | 1 | 1 |
| Huntington chorea | 2 | — | — | 1 | 1 |
| Hydrocephalus X-linked | 1 | — | — | 1 | — |
| Ipx X-linked | 1 | 1 | — | — | — |
| Incontinentia pigmenti | 1 | — | — | — | — |
| Leigh disease | 1 | 1 | — | — | — |
| Lesch–Nyhan syndrome | 1 | — | — | — | 1 |
| Marfan syndrome | 1 | 1 | — | 1 | 1 |
| Meckel–Gruber syndrome | 1 | — | — | 4 | — |
| Menkes disease | 2 | — | 1 | 1 | — |
| Methylmalonic aciduria (cblB type) | 1 | 1 | 1 | — | — |
| Mucopolysaccharidosis | 2 | 2 | — | 1 | — |
| Muscular dystrophy (BMD-DMD) | 18 | 6 | — | 15 | 6 |
| Myotonic dystrophy (DM1) | 4 | 1 | — | 2 | 4 |
| Myotonic dystrophy (DMPK) | 1 | 1 | — | — | — |
| Myotubular myopathy | 2 | 3 | 3 | — | 2 |
| Neurofibromatosis I disease | 2 | 1 | — | 1 | 1 |
| Osteopetrosis | 1 | — | 1 | 1 | — |
| Polycystic kidney disease | 2 | 1 | 1 | 2 | 1 |
| Potter syndrome | 1 | 1 | 1 | 2 | — |
| Salla disease | 1 | 1 | — | 1 | 1 |
| Spastic paraplegia, (Strumpell disease) | 1 | — | — | — | — |
| Spinal muscular atrophy | 5 | 5 | 3 | 2 | 2 |
| β-Thalassaemia [+ HLA] | 36 [5] | 6 [4] | 1 [0] | 42 [1] | 17 [4] |
| Tuberous sclerosis | 1 | 1 | — | — | — |
| Wiskott–Aldrich syndrome | 2 | 2 | 2 | 2 | 1 |
| Wolf–Hirshhorn syndrome | 1 | 1 | — | — | 1 |
| Total | 161 | 74 | 20 | 118 | 66 |

HLA = human leukocyte antigen.

As presented in **Table 2**, 161 fertile carriers of monogenic diseases had experienced a spontaneous pregnancy in the past, resulting in 118 therapeutic abortions and in

the birth of 74 affected children, 20 of whom had died because of the disease. The most common indications in this subgroup of patients were thalassaemia (41 cases), cystic

Table 3 Reproductive history of 102 fertile couples carrying a balanced translocation.

| <i>Translocation</i> | <i>Spontaneous pregnancies</i> | <i>Affected children</i> | <i>Miscarriages</i> | <i>Therapeutic abortions</i> |
|----------------------|--------------------------------|--------------------------|---------------------|------------------------------|
| Reciprocal | 72 | 3 | 137 | 31 |
| Robertsonian | 30 | | 57 | 9 |
| Total | 102 | 3 | 194 | 40 |

fibrosis (26 cases) and muscular dystrophy (BMD-DMD) (18 cases).

As presented in **Table 3** for 102 fertile translocation carriers, the occurrence of miscarriages was especially high (1.9 mean events per fertile couple, namely 1.9 for both reciprocal and Robertsonian translocations) as well as that of therapeutic abortions (0.39 mean events per fertile couple, namely 0.43 for reciprocal translocations and 0.30 for Robertsonian translocations).

The condition of the 245 infertile couples could be summarized as follows: 68 couples with male infertility, 39 with female infertility and 24 with both infertility factors. The remaining 114 couples did not have any specific factor of infertility beside the presence of an altered karyotype.

Cycles performed abroad

As shown in **Figure 2**, 68 couples opted to contact foreign centres: 39 were carriers of monogenic diseases and 29 of balanced translocations. In all, 15 of these couples were fertile having experienced the birth of 8 affected children and 12 terminations of affected pregnancies. Information on the clinical outcome and treatment received was provided by 35 couples, with the achievement of 2 term pregnancies.

The most frequently selected countries were Belgium (45%), followed by the USA and Greece (40%) with a few cases opting for Turkey and Czech Republic. Twenty-one couples also investigated the possibility of overcoming PGD by resorting to gamete donation. In this case, Spain and Switzerland were the most popular choices for oocyte and sperm donation respectively.

The general impression reported was positive, professionalism and quality of care being rated at high levels. Only one complaint was recorded although no specific reason was given beside 'negative impression'. According to the patients' reports, the main difficulty encountered was due to the language barrier. In addition, the discomfort related to staying abroad for several days and the feeling of loneliness in the face of the need to organize their treatment in a foreign environment were felt as especially heavy.

The reasons for couples to search for treatment abroad even when PGD was applicable in Italy are reported as follows. Of the 5 CBRC couples in the pre-law period, 2 in need of HLA typing and 1 carrier of Huntington disease were put in contact by S.I.S.Me.R. with the centre in USA having the largest experience in these conditions (Verlinsky and Kuliev, 2003; Verlinsky et al., 2001). Of the remaining 2 couple carriers of cystic fibrosis and Becker dystrophy, respectively, the first coming from the UK tried a third cycle in USA after

failing two cycles with us, while the other opted directly for another European centre.

In the post-court decision period, out of the 8 CBRC couples (6 monogenic disorders and 2 translocations), 2 had already established connections with foreign centres when PGD was not feasible in Italy, 3 opted for gamete donation and the remaining 3 preferred to perform a PGD cycle abroad.

Sixty-seven patients decided not to perform any attempt in a foreign centre, irrespective of their initial intention of going abroad. The main reasons given were the difficulty related to the overall organization of the treatment itself, including the contact with an unknown environment with a different language ($n = 67$, 100%), the high expenses related to travel and long-term accommodation ($n = 42$, 63%) and the interruption of employment ($n = 67$, 100%). In addition, approximately one-third of these couples ($n = 21$) did not inform their own family about their decision to refer to an IVF centre to undergo PGD, making the organization of a treatment abroad even more difficult.

Discussion

Data collected by the European IVF-monitoring of ESHRE show that the proportion of couples asking for PGD/PGS is extremely low in relation to the number of cycles (0.5%, Ferraretti et al., 2012). Nevertheless, in centres offering PGD/PGS such as S.I.S.Me.R., the percentage of cycles undergoing these techniques can be relevant (27% of total treatment cycles performed in this centre in 2012, **Figure 1**).

The impossibility of undergoing PGD is one of the reasons for CBRC, a complex phenomenon that expresses the patients' intention to exercise their reproductive choice. It involves several controversial aspects of assisted reproduction, including PGD, and is quite inhomogeneous due to several reasons and dissimilarities among different countries (Culley et al., 2011; Grtin and Inhorn, 2011). Major differences still remain in Europe regarding the regulation of pre-implantation genetic diagnosis (PGD), which is banned in Austria and Switzerland, whereas severe limitations affect practice in Germany, Ireland and Italy (Shenfield et al., 2010). This diversity maintains the need for CBRC from those countries where PGD is not allowed, although this is assumed rather than established in fact (Pennings, 2009).

Quantification of the phenomenon is not easy, but it is necessary to promote public discussion and analysis of the consequences related to this situation. As well as the discomfort derived from the need to travel and stay abroad for 10–15 days, concerns arise on the safety and the quality

of the treatments as well as on the financial implications (Pennings et al., 2008).

The data presented here, although covering periods of different length (74 months in the pre-law period versus 43 months in the post-court declaration period), provide an estimation of how the law on IVF in Italy and its following changes affected the number of PGD referrals to this study centre. The main limitation of this study with respect to CBRC includes the fact that participants were self-selecting and that the information was provided by the patients themselves. As there are no reliable data on the extent of CBRC for PGD from Italy except those published by Shenfield et al. (2010), it is impossible to estimate to which extent these results could be representative of the national situation. Nevertheless, as one of the major reference centres in Italy for PGD since the 1990s, the data reported here could provide a general view of the situation for PGD couples throughout the studied periods.

As shown in Table 1, the impossibility of performing PGD in the country reduced significantly the proportion of PGD couples calculated over the total number of referrals in the same period. This trend was reversed when, after the decision of the Constitutional Court in May 2009, PGD was reintroduced, resulting in a proportion of PGD referrals to this centre that is now higher (5.1%) compared with the pre-law period (3.3%). This corresponds to an average of 4.5 versus 2.7 per month, respectively. Similarly, the number of PGD cycles increased, although some time was necessary to have patients becoming aware of the possibility to perform treatment in Italy again and for the centre to reactivate and reorganize the whole procedure. Concomitantly, there was a reduction in the number of couples travelling abroad to receive the desired PGD treatment (Figure 2).

During the restrictive law period, the number of patients opting for CBRC ($n = 55$, Figure 2) was slightly more than half the number of PGD cycles performed in the previous years ($n = 86$, Table 1). These data demonstrate how difficult was for these patients to take the initiative of searching for a specific medical treatment in a foreign environment.

As expressed during the interviews with patients, even when having such a strong motivation for a specific cure, as most PGD couples do have, many of them, when faced with the impossibility of being treated in their own country, gave up in view of going ahead. Although communications and achievement of information is much easier nowadays through the widespread use of the internet, full understanding of the implications related to such complicated treatment, as PGD is, still remains an important issue. In addition, the rigors of travel are troublesome in many cases, including interruption of employment, high expenses related to travel and long-term accommodation and the need for multiple forms of documentation (Inhorn and Patrizio, 2012). Even more critical is the situation of couples that already have children, especially if affected by a severe pathology, as reported by the 8 couples with an affected child who decided to go abroad. It is easily understandable that, as underlined by these patients, most of these couples feel a sense of abandonment by the Italian State, which was accused of not taking care of their needs and, even worse, of promoting discrimination on the basis of their health condition (Zanini, 2011). In many cases, these feelings triggered the necessity to find solutions at

all costs, transforming CBRC into a form of resistance to an unfair situation with the firm intention of claiming the own reproductive rights.

In summary, the present data permit the quantification of how the reiterative changes in national regulation affected the reproductive decision of PGD couples in this centre. Especially relevant is the decrease of referrals (approximately 60 cases) in a 5-year period (203 in the pre-law period versus 138 in the restrictive law period, Table 1). In addition, 55 couples considered having treatment abroad due to the impossibility of doing it in Italy (Figure 2). These figures give another relevance to CBRC for PGD compared with what was reported by Shenfield et al. (2010), where only 2.1% of 391 couples opting for CBRC had a PGD indication.

In a more general view, two main conclusions are reported. First, for patients who chose to go abroad, most were positive about their experiences, although some clearly described some negative aspects of the process. Second, many patients chose not to go abroad, despite a great need for the treatment, leading to a highly negative outcome for these couples.

till questionable in Italy is the treatment of fertile patients which is actually forbidden by the national law on IVF (Benagiano and Gianaroli, 2010). Nevertheless, the decision of the Italian Court in January 2010 allowing a non-infertile couple to undergo PGD because of the risk of disease transmission to the offspring opened the way to reconsider the situation of these couples as well. On 28 August 2012, the European Court of Human Rights (ECHR) declared the prohibition of treating healthy, non-infertile carriers of monogenic diseases as violation of Article 8 (right to respect for private and family life) of the European Convention on Human Rights. According to the current statute of the Convention, any party has the right to request, during the 3-month period following its delivery, that the case is referred to the Grand Chamber of the Court. This was requested by the Italian Government (no. 54270/2010) on the last day available before the deadline (28 November 2012), claiming the need to protect the integrity and validity of the national judicial system (Costa and Pavan v. Italy, 2012). On 11 February 2013, the ECHR rejected the appeal of the judgment. This implies that, according to the Chamber judgment of 28 August 2012, Italian legislation should provide access to medically assisted fertilization techniques also for fertile couples. Therefore, differently from the Austrian case (no. 57813/00) where the ban of gamete donation with IVF was not reversed (S.H. and Others v. Austria, 2011), in the Italian case the ECHR backed the decision in favour of good clinical practice and welfare of patients. Hopefully, the pronouncement by the ECHR represents the last act of an unfair and discriminating regulation to which Italian PGD couples have been subjected for too many years.

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