Studio Legale Gallo

Civile – Amministrativo

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Honourable EUROPEAN COURT OF HUMAN RIGHTS

SECOND SECTION

OBSERVATION OF THE THIRD INTERVENTION

Case: COSTA AND PAVAN / ITALY

Application No. 54270/10

Explanation of the facts

Mrs. and Mr. Costa /Pavan are a fertile couple affected by a severe genetic disease called "Cystic Fibrosis", they are assisted in front of the European Court of Human Rights by the lawyers Nicolò and Ginevra Paoletti. The petitioners demand permission to accede to assisted fecundation techniques so that they can carry out surgical research on the embryo, but law n. 40 from 2004 allows those techniques only for infertile or sterile couples, therefore the couple is not authorized to accede to that medical sanitary technique.

Italian Law

In Italy the law on medically assisted procreation number 40 came into force on the 10th march 2004. This regulation was issued after a long parliamentary debate with 330 rejected enhancing amendments out of 330 amendments, and it has been approved without any modification of the original text.

The law 40/04 started a debate out of the parliament in which two different line-ups were involved: science and religion. This debate arose from legislator, who introduced in Italy prohibition without any juridical nor scientific fundamentals. Therefore as provided by law in the annual reports to the Parliament from 2005 to 2009 it was stress out how harmful this regulation on a scientific level was and that it had supported both an increase of risk-pregnancies and a decrease of pregnancies. Parliament did not take into account any modification of the regulation that in 2009 was nevertheless declared unconstitutional by the Italian Constitutional Court, decision 151/09.

The decision of the Constitutional Court determined an enhancement in the application of techniques in medically assisted procreation. The limit fixed at three reproducible embryos and the obligation of a contemporary implantation in the uterus of all produced embryos was deleted, opening in this way a departure from prohibition of cryoconservation. The decision of the Constitutional Court deleting a part of law 40 applied pre-implantation diagnosis techniques, because it eliminated the limit of three producible embryos.

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Currently all Italian centers that apply advanced techniques of medically assisted procreation carry on clinical research on the embryo following the National regulation for infertile couples as carrier of genetic pathologies. Considering that in reference to the admittance of techniques, law provides for in article 1:

"1. To support the solution of reproductive problems derived from sterility or from human infertility medically assisted procreation is allowed, in terms provided by current law, that grants the rights of all involved subjects, including the conceived".

2. The resort to medically assisted procreation is allowed when there are no other efficient therapeutic procedures available to remove the reason of sterility or infertility".

Article 4 sub-paragraph 1 of law 40/ provides that the *"resort to medically assisted procreation techniques is allowed only when the impossibility to remove with alternative procedures the reasons that block procreation and it is limited to cases of unaccountable, documented by medical deed sterility or infertility as well as to cases of determined and by medical deed documented sterility or infertility."* Law 40 /04 in articles 13 sub-p. 2 and 14 sub-paragraph 5, provides that the couple can ask information about the health condition of the embryo and that on the embryo can be carried out clinical researches provide they have no eugenetic aims.

Law number 40/04 provides in article 7 *"guidelines containing indications on procedures and techniques of medically assisted procreation."*

Provided that the same guidelines in the part that regulates the admittance to medically assisted procreation techniques confirm that the admittance to medically assisted procreation techniques is allowed to infertile and sterile couplet, but extend the concept of infertility also to fertile man carrying viral sexually transmitted pathologies, caused by infection of HIV, HBV or HCV, who to prevent infection of the partner or the unborn, have to be considered infertile. In this way an administrative act extend through interpretation the concept of infertility to fertile man, carrying viral pathologies.

It must be stressed that fertile women carrying viral pathologies and couples with genetic disease are not admitted to those techniques.

Enforcing the statement of the right of procreation and the right to health of the involved subjects itself, law number 40/04 and the guidelines provide a restrictive interpretation of scientific concepts that determine inevitably an offence of the rights due to an interpretation of the examined regulations that prevent couples from the resort to medically assisted procreation techniques, who, thus not infertile or sterile, risk seriously to transmit a disease to their child. Law number 40/04 creates therefore a discrimination in the admittance to the cares based on a pathology, because the infertile person can be submitted to medically assisted procreation and also demand diagnosis on embryo and consequently avoid to transmit severe diseases to the unborn. Instead those who are not infertile but only carrier of genetically transmitted genetic pathologies have no right on pre-implantation diagnosis that can be carried out only in case of in vitro fertilization. Therefore it is clear that a discrimination takes place based on the pathology to give admittance to cares. This discrimination creates a damage to the health of the fertile

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woman who procreates in a natural way and may then be allowed to carry out prenatal diagnosis, like villocentesis, ecography and amniocentesis and then have admittance to pregnancy interruption with consequent damage on health and effects on psychological balance of the involved subject. The pregnancy interruption could be avoided by a diagnosis on embryo before it is transferred into uterus. Italy through the prohibition of the admittance to medically assisted procreation for fertile couplet carrying genetic transmitted pathologies does not allow for preventions sake to take care of woman's health.

All this is in contrast to articles 8 and 14 of the European Chart of Human Rights.

Pre-implantation genetic diagnosis (PGD)

PGD (Pre-implantation genetic diagnosis), consists in a series of procedures that allow to detect the presence of genetic diseases and chromosome alterations, in oocytes and embryos generated in vitro from couples at high reproductive risk, prior to their implantation in uterus. To carry out this procedures a cell has be taken from embryo, that will be carefully analyzed to evaluate its chromosome system.

INDICATION TO PGD

These procedures are applied in different groups of patients:

1) Couples carrying genetic pathologies that can be transmitted to their children

2) Infertile or sub fertile patients that submit to assisted conception programms (FIVET or ICSI) with low possibilities to succeed, because their reproductive history has already shown a difficulty in both natural and assisted conception. In particular, couples whose female partners are 38 years or more or have failed three or more FIVET or ICSI treatment cycles, even if they have carried out a transfer or embryos, potentially considered able to give origin to a pregnancy; patients with an alterate karyotype due to the presence of mosaic-shaped cellular lines in their sexual chromosomes or gonosomes. More recently the indications have been extended to azoospermia patients, who takes spermatozoons from the seminal way through microsurgical techniques of MESA and TESE and who have at least failed prior a ICSI cycle.

3) Patients carrying displacements in their chromosome heritage. Displacements are anomalies that lead to the birth of children with more severe chromosome alterations than those carried by their parents. Very often these alterations lead also to frequent abortion or block both the natural and assisted conception. From a medical point of view they are distinguished in robertsonian and reciprocal displacements.

4) Patients having a history with two or more abortions, not due to "mechanical" reasons like pathologies of the uterus (sinechia, fibromas, congenital defect etc.).

There are also other pathologies that may have benefits from the above stated techniques, but lacking proved scientific data, those are not described, because they are still object of studies.

It follows a chart Elaborated by the Italian society for medical studies of re production (S.I.S.Me.R. informative pamphlet n.6 "Biopsy of the embryo and pre-implantation diagnosis).

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Table 1: Genetic diseases transmittable to own children and can be analyzed by genetic diagnosis through biopsy on oocytes and embryos.

Achondroplasia	- Early Allzheimer
- Adrenoleukodystrophy	- Metachromatic leukodystrophy
Agammaglobulinemia	- Central heart disease
- Universal congenital alopecia	- Gaucher's disease
- Genetic neuropathic amiloidosi	- Krabbe's disease
- Sickle cell anemia	- Norrie's disease
- Falcone Anemia	- Pelizaeus-Merzbacher's disease
- Hereditary angioedema, HAE	- Tay-Sachs' disease
- Spinal Muscular Atrophy (SMA)	- MELAS syndrome
- Cardioencephalomyopathy	- Myotubular Myopathy
Deficit COX2	- Mucopolysaccharidoses
- Hypertrophic cardiomyopathy	- Neurofibromatosis type 1 and 2
- Charcot-Marie-Tooth 1. And 2.	– Sipple syndrome
- Classical citrullinemia	- Holoprosencephaly
- Condrodisplasia punctata (CDPX1)	- Osteogenesis imperfecta
- Condrodisplasia metafisal (MCDS)	- Adenomatous polyposis coli
- Huntington's disease, chorea	- Polycystic Kidney Disease
- Alpha 1-antitrypsin deficiency	- Retinitis pigmentosa
- LCHAD	- Retinoblastoma
- 21-hydroxylase enzyme deficency	- Rhesus Rh D
- Mitochondrial trifunctional protein deficiency	- Tuberous sclerosis complex
- Ectodermal dysplasia (ED1) (EDAR)	- Alpers' disease
- Multiple epiphyseal dysplasia (MED)	- Alport syndrome
- Myotonic dystrophy	- Crouzon syndrome
- Becker muscular dystrophy	- Di George syndrome
- Duchenne muscular dystrophy	- Gorlin syndrome
- Emery-Dreifuss muscular dystrophy	- Hunter syndrome MPS II
- FSHD	- Lesch-Nyhan syndrome
- Haemophilia A and B	- Leigh syndrome (surf 1)
- Ohtahara syndrome (gene PNPO)	- Li-Fraumeni syndrome
- Epidermolysis bullosa	- Marfan syndrome
- Gardner syndrome	- Omenn syndrome
- Phenylketonuria	- Potter I syndrome
- Cystic Fibrosis	- Rett syndrome
- Ganglioside (GM1) (GM2)	- Stickler syndrome

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- Hydrocephalus linked to X-syndrome	- Von Hippel-Landau syndrome
- Bloch–Siemens syndrome	- Fragile-X syndrome
- Malignant hyperthermia	- Wiskott- Aldrich syndrome
- Persistant hyperinsulinemic hypoglycemia	- Oro-facio-digital syndrome type 1
	- Thalassaemia

EFFECTIVENESS AND EFFICIENCY OF THE TECNIQUES

At the current state of the scientific knowledge it can be stated that those techniques can be effective in 90-93% of the cases in which they are used and that to reach 100% of effectiveness depends from the capability to develop new technologies: for this reason, up to now, these techniques cannot be considerate an alternative to the traditional prenatal diagnosis (take some chorionic villi or amniocentesis), but rather complementary to them. Their application reduces at least 90% the transfer and the eventual implantation in the uterus of embryos affected by transmitted pathologies. In case of infertile couples, they reduce the risk at least by 90% of a transfer of embryos carrying a wrong number of chromosomes into uterus. Most of them are not able to implant or provoke spontaneous abortions. In case of different results obtained after the biopsy of the embryo from those registered by prenatal diagnosis or at the birth given by word literature are extremely rare. The introduction of innovations as the application of Microarrays and of CGH (Comparative Genomic Hybridization, a technique that allows to analyze the entire chromosome system of the examined object. DNA that has to be analyzed is marked by different color fluorescent substances. Through computerized image analyzer the emitted fluorescence intensity of every chromosome measured. Fluctuation of fluorescence indicate a situation of normality or pathology) to PGD, has allowed to enhance furthermore the reliability of those techniques reducing at the same time possible risks connected to them. To enhance more the effectiveness and security of PGD techniques, in the interests of the patients based on the principles of good clinical and laboratory practices, the European Society of Human Reproduction and Embryology (ESHRE) has created a Consortium specifically dedicated to the study of these procedures, to their enhancement and the collection of connected data to be analyzed. The PGD Consortium of ESHRE has, moreover, produced a series of guidelines with binding principles for operators and centers in carrying out PGD techniques, following high quality and security standards[1].

• [1] ESHRE PGD Consortium best practice guidelines for fluorescence *in situ* hybridization-based PGD *Hum. Reprod. (2011) 26(1): 25-32*

• ESHRE PGD Consortium/Embryology Special Interest Group—best practice guidelines for polar body and embryo biopsy for preimplantation genetic diagnosis/screening (PGD/PGS) *Hum. Reprod. (2011) 26(1): 41-46*

• ESHRE PGD Consortium best practice guidelines for organization of a PGD centre for PGD/preimplantation genetic screening *Hum. Reprod. (2011) 26(1): 14-24*

• ESHRE PGD Consortium best practice guidelines for amplification-based PGD *Hum. Reprod. (2011) 26(1): 33-40*

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APPLICATION AND RESULTS

Pregnancy rates per transfer. PGD, 2008

countries	16
transfers	2080
pregnancies	657 (31.6%)
deliveries	420 (20.0%)

PGD cycles carried out in Europe in 2008 and their results as given by European data of IVF Monitoring Consortium presented at the 27th Annual Meeting of the European Society of Human Reproduction and Embryology, Stockholm 3-6th July 2011.
Common data derived from data collections (I – IX) elaborate by PGD Consortium of ESHRE

Indication	PGD	PGS	PGD-SS	Total
Cycles to OR	8111[1]	13063	579	21743[1]
Number infertile	3078	11304	47	14429
Female age	33	37	37	35
Cancelled before IVF/ICSI	18	2	0	20
ART method				
IVF	876	1495	146	2517
ICSI	7054	11241	416	18711
IVF+ICSI	39	225	0	264
Frozen+ICSI+IVF+unknown	106[1]	40	17	163[1]
Unknown	20	50	0	70
Cancelled after IVF/ICSI	472	442	16	930
Cycles to PGS/PGD	7623	12609	563	20795
FISH	4211	12606	381	17198
PCR	3405	3	182	3590
FISH + PCR	7	0	0	7
Zona breaching				
AT drilling	3423	3970	19	7412
laser drilling	3769	7404	131	11304
Mechanical	417	1170	413	2000
Unknown	14	65	0	79
Biopsy method				
Polar Body biopsy	121[2]	1816[2]	0	1937[2]
Cleavage aspiration	7067[2]	10093[2]	141	17301[2]
Cleavage extrusion	323	625	422	1370
Cleavage flow displacement	16	22	0	38
Blastocyst	71	2	0	73

• ESHRE PGD Consortium 'Best practice guidelines for clinical preimplantation genetic diagnosis (PGD) and preimplantation genetic screening (PGS)' *Hum. Reprod. (January 2005) 20(1): 35-48*

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Polar Body and cleavage	20	0	0	20
Unknown	16	52	0	68
Embryology				
COC's	110851	152595	7952	271398
Inseminated	94019	126398	6604	227021
Fertilised	67592	89479	4573	161644
Biopsied	50165	71440	3582	125187
Successfully biopsied	49448	70623	3455	123526
Diagnosed	44545	65181	3141	112867
Transferable	16544	23380	1241	41165
Transferred	10926	16975	860	28761
Frozen	2309	3165	290	5764
Clinical outcome				
Cycles to ET	5850	9433	419	15702
hCG positive	1970	3145	161	5276
Positive heart beat	1542	2429	120	4091
Clinical pregnancy rate (% per OR/% per ET)	19/26	19/26	21/29	19/26

OR, oocyte retrieval; AT, acid Tyrode's; COC, cumulus oocyte complexes; SS, social sexing; PGS, preimplantation genetic screening; FISH, fluorescence in situ hybridisation; ET, embryo transfer; ART assisted reproduction technology; PB, polar body

PGD column includes PGD for chromosome abnormalities, sexing for X linked disease and PGD for monogenic disorders

[1]Includes two cycles with PGD on frozen embryos only. These cycles were not counted in the cycles with OR.

[2]Twelve cycles had polar body biopsy and cleavage stage biopsy[2]

Community legislations

In the majority of the European countries PGD is allowed and is routinely carried out on patients with an anamnestic picture compatible with the indications for the application of the technique. In other countries, even if allowed, such technique is subject to restrictions. In Germany, for example, Law for the protection of the embryo that forbade PGD came into force at the beginning of the 90s ["ESchG" (abbr.): Gesetz zum Schutze von Embryonen: 13th December 1990 (BGBl. I S. 2746 and BGBl. I S. 2702, 2705]. This law is partially amended in vote by the Bundestag on 7th July 2011 (Gesetzentwurf 17/5451) following a long debate that involved also International specialists. Currently, in Germany, PGD can be carried out exclusively in selected centers on couplet that present determined anamnestic conditions (presence of severe genetic pathologies). The authorization to carry out this technique is dependent on completing of a suitable

[2] ESHRE PGD Consortium data collection X Human Reproduction, Vol.25, No.11 pp. 2685–2707, 2010
- ESHRE PGD Consortium data collection IX Human Reproduction, Vol.00, No.00 pp. 1–25, 2009
- ESHRE PGD Consortium data collection VIII Human Reproduction Vol.23, No.12 pp. 2629–2645, 2008
- ESHRE PGD Consortium data collection VII Human Reproduction Vol.23, No.4 pp. 741–755, 2008
- ESHRE PGD Consortium data collection VI Human Reproduction Vol.22, No.2 pp. 323–336, 2007
- ESHRE PGD Consortium data collection V Human Reproduction Vol.21, No.1 pp. 3–21, 2006
- ESHRE PGD Consortium data collection IV Human Reproduction Vol.20, No.1 pp. 19–34, 2005
- ESHRE Preimplantation Genetic Diagnosis Consortium: data collection III Human Reproduction Vol.17, No.1 pp. 233–246, 2002
- ESHRE Preimplantation Genetic Diagnosis Consortium: data collection II Human Reproduction Vol.15, No.12 pp. 2673–2683, 2000
- ESHRE Preimplantation Genetic Diagnosis (PGD) Consortium Human Reproduction Vol.14, No.12 pp. 3138–3148, 1999

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counselling proceding and the approval of an appropriate ethic committee.

The only European state in which the technique is currently prohibited is Austria.

1. The list of the countries that decided by law in subject of pre-implantation diagnosis:
2. Austria: Prohibited, allowed only the analysis on polar corpuscles
3. Belgium: Allowed
4. Bulgaria: Allowed
5. Cyprus : Allowed
6. Czech Republic: Allowed
7. Danmark: Allowed
8. Estonia: Allowed
9. Finland: Allowed
10. France: Allowed
11. Germany: Allowed only in determined cases and in authorized centers following a suitable counselling iter and after the approval of a suitable ethic commettee
12. Greece: Allowed
13. Ireland: Allowed
14. Italy: Allowed only to infertile couples and currently carried out only in some private centres, because public structure are not suitably equipped to carry out this analysis.
15. Lettonia: Allowed
16. Lithuania: Allowed
17. Luxemburg: Allowed
18. Malta: Not regulated
19. Netherlands: Allowed
20. Poland: Not regulated
21. Portugal: Allowed
22. UK: Allowed
23. Romania: Allowed
24. Slovacchia: Allowed
25. Slovenia: Allowed
26. Spain: Allowed with some restrictions (for example in case of chromosome anomalies or monogenetic diseases)
27. Sweden: Allowed
28. Hungary: Allowed

Scientific reference bibliography published on specific sector magazines subject to an anonymous report system (Scientific reference bibliography is attached, attachment A)

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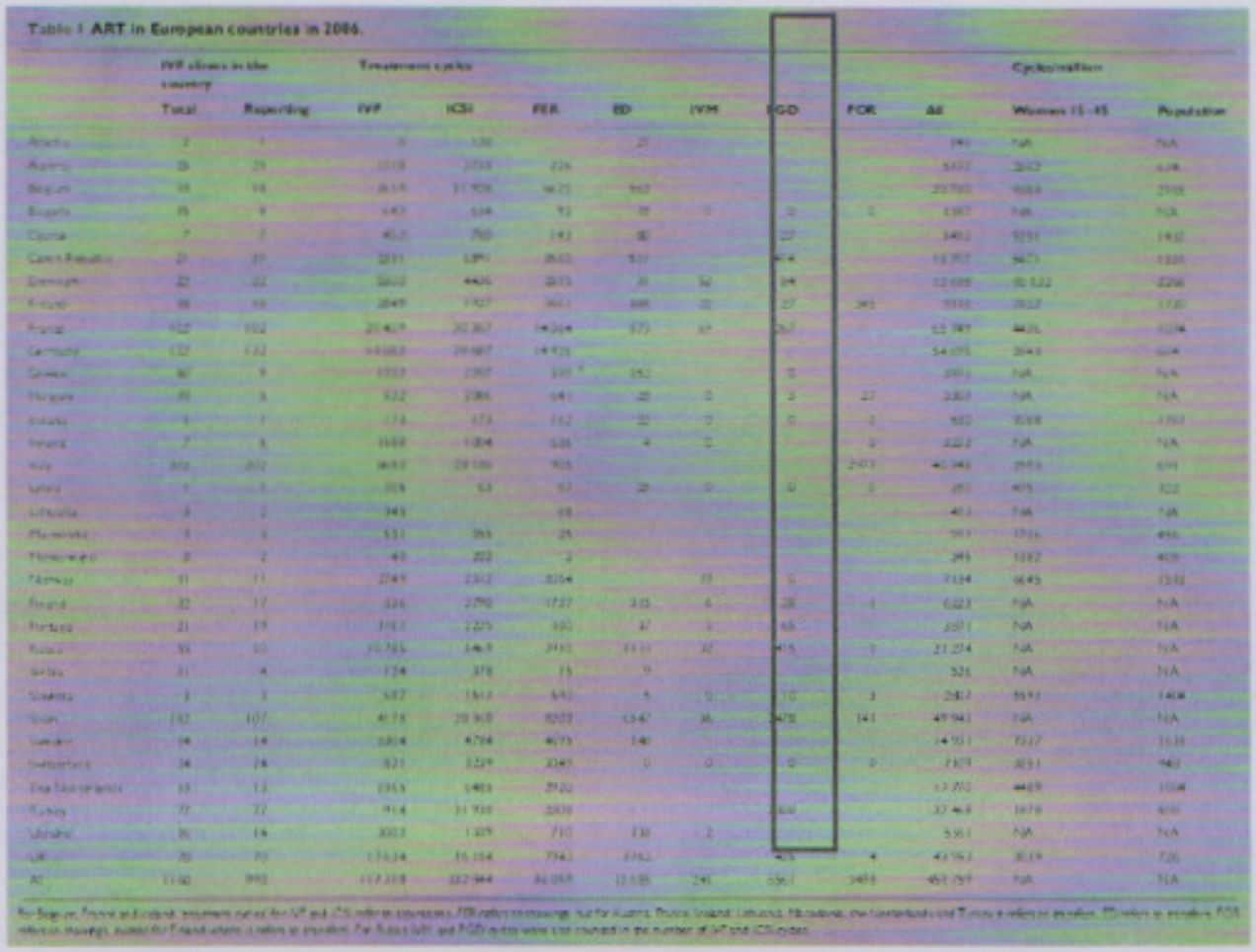
APPLICATION AND REGULAMENTATION OF THE TECHNIQUE IN EUROPEAN COUNTRIES[3]

Table 1 ART in European countries in 2006.



Relevance of the issue

It is not possible to quantify precisely the number of citizens that go abroad to find this type of treatment, because there is a lack of complete, systems and precise data. A survey based on voluntary participation carried out by Cross Border Task Force of ESHRE (attached) on 46 Centers all over six different European states, has allowed to

[3] De Mouzon et al. Assisted reproductive technology in Europe, 2006: results generated from European registers by ESHRE Human Reproduction, Vol.00, No.0 pp. 1–12, 2010

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collect some data (given below) and estimate, that in general, the phenomenon touches at least 24-30000 cycles every year[4]

Table V Sought treatment according to the country of patients' residence.

	Infertility treatment*		Specific treatments	Donation**		
	ART	IUI	PGD-PGS	Semen	Oocyte	Embryo
Italy	76.5	32.6	2.1	17.4	17.9	2.3
Germany	90.9	90.3	8.5	10.2	44.6	6.2
Netherlands	78.1	27.4	3.4	11.4	9.4	0.7
France	46.7	61.7	2.8	43.0	20.6	3.6
Norway	62.7	41.8	1.5	38.8	1.5	1.5
UK	90.6	9.4	3.8	15.1	62.3	11.3
Sweden	37.7	62.3	0.0	42.4	3.7	1.9
Total	77.9	27.1	3.2	18.3	22.8	3.4

Percentages are computed among the total number of women coming from each country.
*The sum of ART and IUI is over 100% because some patients (4.9%) sought both.
**Some patients sought more than one type donation.

Table VIII Treatment sought according to the recipient country.

Recipient country	Forms (n)	Infertility treatment*		PGD-PGS	Donation*		
		ART	IUI		Semen	Oocyte	Embryo
Belgium	359	71.9	33.4	5.2	20.5	6.8	0.3
Czech Republic	251	98.4	1.6	3.6	9.5	32.4	11.9
Denmark	154	46.8	55.5	0.6	40.9	1.3	0.6
Slovenia	64	100	0.0	0.0	0.0	0.0	0.0
Spain	190	98.4	5.8	2.1	4.1	62.2	4.7
Switzerland	196	59.7	54.1	0.5	27.4	1.0	0.5
Total	1214*	73.0	22.2	3.2	18.3	22.8	3.4

*The total number (1214) differs from the total of received forms in Table I (1230) as this information was difficult to ascertain in 16 cases.

(Shenfield et al. Cross border reproductive care in six European countries Human Reproduction, Vol.25, No.6 pp. 1361–1368, 2010)

The first chart (Table V) shows a percentage of citizens that move abroad to benefit from treatments (data on PGD are given in red). Second chart (Table VIII) shows the percentage of treatments carried out in determined countries on citizens coming from from other countries. (PGD data are reported in the red frame).
In conclusion it is pointed out that Italy, as stressed in the writs presented in front of the court, law 40/04 determines a discrimination based on the pathology for the acceptance to cares that is a severe damage towards the basic principle of equality and respect towards familial life

Salerno, 28.11.2011

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[4] Shenfield et al. Cross border reproductive care in six European countries Human Reproduction, Vol.25, No.6 pp. 1361–1368, 2010

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