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The Italian Experience of A Restrictive IVF Law: A Review

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Abstract

In March 2004 the Italian Parliament enacted a Law (Law 40/2004) establishing a long list of restrictions for ART procedures. The law articles were constructed around the assumption of considering the embryo as a human being, with the same or even more rights of the woman or the couple seeking treatment for their infertility-related childless. In detail, the Law obliged to use only 3 oocytes to be fertilised and all the resulting embryos had to be transferred. Embryo freezing as well as pre implantation screening (PGS) or diagnosis (PGD) and sperm or oocytes donation were forbidden. In May 2009 the Italian Constitutional Court was called to judge parts of the Law 40 and cancelled some of the restrictions since they violated women's rights to have access to the best possible treatment with the lower health risks for both her and the future children. The Constitutional Court stated that the decision on the number of oocytes to be used for insemination, the embryos to be transferred and the embryos to be frozen were a matter of good clinical practice and under the full responsibility of the reproductive specialist. PGD and PGS remains a matter of debate because the Court was not called specifically to address this subject, although a clear opinion in favour has been expressed in previous decisions. The Constitutional Court will be called only in the future to express a judgement on gametes donation that is still forbidden. The present work reviews the clinical and social effects produced by 5 years of a restrictive ART Law (2004-2009); the preliminary results after the Italian Constitutional Court decision (May – December 2009 and comments on cross border infertility treatment for procedures that are still barred.

Keywords: Assisted reproduction regulation; Assisted reproduction technology; Ethics and Law; Delivery rate; Cross border reproductive care

Introduction

On February 19, 2004 the Italian Parliament enacted a Law (Law 40/2004) [1] regulating assisted reproduction that was in effect until May 2009, when the Italian Constitutional Court cancelled most the imposed restrictions as a limitation of the couple rights to have access to the best available medical treatment and good clinical practice [2]. The Law included a very long and detailed list of restrictions: limited to 3 the number of oocytes to be used in ART (Assisted Reproduction Techniques) cycles; banned embryo cryopreservation, and imposed the transfer of all cleaved embryos (no cryopreservation) [1]. Moreover this Law banned the use of PGS (pre implantation genetic screening) for detection of embryo aneuploidies and PGD (pre implantation genetic diagnosis) for detection of genetic diseases such ß-thalassemia, an important issue in our country for the high prevalence of carriers in the Mediterranean area. Sperm and oocytes donation were also forbidden. Specialists performing treatments prohibited by the Law or even promoting these treatments in countries where they are allowed, could be persecuted and condemned, by the penal justice, to several years of prison and even radiated from the medical profession [1]. Couples, fertility centers and patient's associations appealed to the Italian Courts to modify the limit of three oocytes fertilizable at each cycle the compulsory transfer of all the embryos and the prohibition of embryo cryopreservation [2]. However, a referendum proposed by political forces and patient's associations opposing the Law in 2005, failed to reach the majority quorum (50% + 1) necessary to abolish some of its restrictive aspects. Five years after the introduction of the Law, the appeal for changes finally reached the Constitutional Court. In its ruling, the Constitutional Court declared the unconstitutionality of Article 14, Subparagraph 2 with regard to the words 'a unique and contemporary implant (transfer), at any rate, never to exceed three; and of Subparagraph 2 insofar as it does not state that embryo transfer must be performed without prejudice for the health of the woman. At the same time, it declared inadmissible all other requests of unconstitutionality. Given the complexity of the Legal situation, in part due to the fact that the Court cannot rephrase a law, but only strike out some of its parts, the situation is far from having been clarified [2]. A complete rebuttal of the law will require an intervention of the Parliament that does not seem likely in the present situation. As a result of these partial modifications, all Italian Fertility Societies approved scientific guidelines aimed at ensuring both the consistent application of the law and at defining personalized treatment plans. Basically, for each woman or couple the treating physician will individualize the optimal number of embryos to transfer for the best chance of pregnancy, while limiting to the minimum feasible the number of cryopreserved embryos. Despite these guidelines there are still areas of controversy. For example, even if most of the Italian Constitutionalists agree that PGS and PGD are allowed after the Court decision, most University and Public Institutions do not offer it fearing the uncertainty of the interpretation of the Law. Another area of conflict is represented by the persistent prohibition on the use of gamete donation (both oocytes and sperm). Initial appeals to the lower Courts by couples, patient's associations and scientific societies, claiming that the prohibition of donor treatment are unconstitutional and discriminatory against the human rights to procreation regardless of the specific pathology, have been accepted. However, nobody knows when this question will be debated by the Constitutional Court and at the moment gamete donation remains forbidden [2].

The aim of the present work is to review: a) the clinical effects of 5 years with a restrictive Law; b) the clinical effects with more acceptable standards of treatment after the modifications pronounced by the

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	Pre Law	Post Law	P
Inductions	1179	1860	
Number of oocytes used	7.06 ± 3.70	2.91 ± 0.78	<0.001
Number of embryos obtained	4.66 ± 2.90	2.20 ± 0.84	<0.001
Fertilisation rate%	66.12%	75.36%	<0.001
Number of embryos transferred	2.32 ± 0.62	2.29 ± 0.69	0.736
Implantation rate %	16.50%	14.77%	0.080
Pregnancies	287	430	
Pregnancy rate/cycle	24.34%	23.11%	0.439
Pregnancy rate/retrieval	28.64%	25.65%	0.091
Pregnancy rate/transfer	31.37%	27.74%	0.056
Take home babies/cycle	19.1%	18.0%	0.48

Table 1: Characteristics of cycles according to the study period: biological data and clinical outcome.

Constitutional Court and c) to debate cross border infertility treatment for procedures that are still forbidden.

Materials and Methods

Peer reviewed journal publications (from 2005 to October 2011) as well published data from our Institution were analyzed. No data from abstracts of national or international meetings were considered, even if published as supplements of peer review journals. This work was partially funded by a specific finalized grant (Lombardy County, Italy (DGR 7255, July 3, 2008). All reported data from the Istituto Clinico Humanitas were from studies approved by the IRB. The data collection and analysis comprised pregnancy rates, live birth rates, pregnancies complications in the general population and in specific subgroups such older patients and severe male factor during the first 2 years of the full application of the Law compared to the 2 years prior to the enactment. Then we analyzed the same data during the 6 months after implementing the modifications granted by the Constitutional court. The effects of such restrictions on reproductive migration were also reviewed.

Results

In June 2007 a report was presented to the Italian Parliament from the National Institute of Health (NIH) regarding the application of the Law. Results obtained from an overall comparison of the outcome of ART from the years 2003 (before law 40/2004) to 2005, showed a drop in the percentage of pregnancies and deliveries, a higher percentage of treatments that did not reach the transfer stage, a decreased number of oocytes inseminated and an increased number of embryos transferred with a higher incidence of multiple births in younger patients [3]. Multicentre studies reported that the new Law, limiting the number of oocytes for insemination to three per ICSI cycle, significantly reduced the chance of transferring good quality embryos and thus of achieving a pregnancy in cases of severe male factor infertility [4-6]. In 2008 the Humanitas team, one of the largest ART programs in Italy in a University tertiary care hospital, reported data concerning the period 2003-2005 [7].

The study analysed 1179 cycles before and 1860 post Law. Basal FSH level (8.07 IU/L ± 4.02 vs. 8.03 IU/L ± 3.74), duration of infertility (3.72 years ± 2.56 vs. 3.70 years ± 2.62), number of previous IVF cycles (0.78 ± 1.08 vs. 0.78 ± 1.04), previous number of pregnancies (22.75% vs. 20.34%) were not significantly different between patients treated in the two periods. Tubal factor (25.29% vs. 23.28%), endometriosis (6.28% vs. 6.18%), unexplained (8.31% vs. 8.44%), anovulatory (1.02% vs. 1.51%), male factor infertility (28.33% vs. 31.56%), severe male factor (30.79% vs. 29.03%), and total motile count (22.33 ± 27.72 vs. 25.16 ± 42.23 millions) were also not significantly different. A statistically significant reduction in the number of oocyte retrieved, a significant reduction in the number of oocytes used (due to the law limits to use only 3 oocytes) and a reduction of the number of embryos obtained, were observed. There was no difference in the number of the embryos transferred but a significantly higher fertilisation rate post Law (Table 1). Overall, pregnancy rates and delivery rates post Law were not significantly lower while the implantation rate was lower but not statistically significant (Table 1). However, when the results were analyzed in relation to the aetiology of infertility, it was observed that patients with male factor had a significantly reduced chance of pregnancy after the Law, from 34.38% to 25.49%, prior and after the law, respectively. These data were also confirmed by other authors [4-6] (Table 2). When comparing patients that had 2 embryos transferred prior to the law to those that also had 2 embryos transferred after the Law, their pregnancy rate was lower. When comparing patients that had 3 embryos transferred prior to the law to those that had 3 embryos post Law, these latter had a higher pregnancy rate (Table 3). This apparent paradox, higher pregnancy rates post-law in those with 3 embryos and lower pregnancy rates for those receiving two embryos was explained by analyzing the data according to specific age groups. In a previous publication comparing the periods 2002-2003 we reported a direct statistically significant relation between the number of embryos transferred and the pregnancy rate [8]. In patients younger than 36 years the pregnancy rate was 55.7% with the transfer of 3 embryos and 42.5% ($p < 0.01$) with the transfer of 2 embryos. On the basis of this previous paper, we analyzed our pre and post law data divided in cycles with women younger than 36 years and ≥ 36 years, and for patients transferring 1, 2 or 3 embryos in the two classes of age (Table 3). Before Law 40 came in force our Institution policy was to transfer no more than 2 embryos in patients younger than 36 years and 3 embryos only in patients with poor prognosis or repeated failures. After the Law all embryos, up to 3 if available, had to be transferred. In younger patients the pregnancy rate was not significantly different between the 2 study- periods, but before the Law in 5.25% of the cycles there was only 1 embryo to transfer versus 11.06% of the cycles after the Law (Table 3). Prior to the law, in younger patients the elective transfer of 2 embryos was possible in 90.83% of the cycles, and this resulted in a pregnancy rate of 41.16% (Table 3). After the Law only 43% of the cycles had 2 embryos available for transfer and as a result there was a significantly lower pregnancy rate (30.90%). The pregnancy

EJACULATED TMC < 1	77/224 (34.38%)	91/357 (25.49%)	0.021
Number of embryos transferred			
1	10/73 (13.70%)	22/216 (10.19%)	0.408
2	170/476 (35.71%)	156/663 (23.53%)	<0.001
3	104/362 (28.73%)	252/671 (37.56%)	0.004

Table 2: Pregnancy rates per cycle in the two periods studied according in relation to severe male factor and according to the number of embryos transferred.

ASSISTED REPRODUCTION TECHNIQUE					
	Pre Law		**Post Law**		**p**
< 36 years					
1 embryo	2/23	(8.70%) 5.28%	11/76 (14.47%)	11.06%	0.727
2 embryos	63/396	(41.16%) 90.83%	93/301 (30.90%)	43.81%	0.005
3 embryos	8/17	(47.06%) 3.90%	151/310 (48.71%)	45.12%	1
≥ 36 years					
1 embryo	8/50 (16.00%)	10.44%	11/140 (7.86%)	16.22%	0.107
2 embryos	7/80 (8.75%)	16.70%	63/362 (17.40%)	41.95%	0.062
3 embryos	99/349 (28.37%)	72.86%	101/361 (27.98%)	41.83%	0.908

Table 3: Pregnancy rate (absolute numbers and pregnancy rate in parenthesis) according to the number of embryos transferred in women < 36 years and ≥ 36 years old and the proportion of patients before and after the law that transferred 1-3 embryos.

rates between cycles with the transfer of 3 embryos (47.06% vs 48.71%) were not different, but the percentage of cycles with the transfer of 3 embryos was only 3.90% before and 45.12% after the restrictions were introduced. Prior to the Law, in patients older than 36 years 10.44% of the cycles had only 1 embryo transferred vs 16.22% after the law and although the pregnancy rate was not significantly different due to the low sample size, a clinically relevant 50% lower pregnancy rate was observed. In 16.70% of the cycles only 2 were available for transfer before and 41.95% of the cycles after the Law. The pregnancy rate in the two periods were 8.85% and 17.40 (p=0.062). In patients ≥ 36 years of age having the goal of transferring 3 embryos, although the pregnancy rate was not significantly different (28.37% – 27.98%), 3 embryos were available in 72.86% of the cases before and only in 41.83% after the Law 40 application (Table 3).

Our results demonstrated that older patients and younger patients with only 2 unselected embryos available for transfer and patients with severe male factor were highly penalized by the restrictions of the Law and how this effect was obscured, in the general population, by the higher pregnancy rate obtained in younger patients who transferred 3 embryos [7]. Although the more intensive selection of oocytes significantly improved the fertilization rate, the use of just a few oocytes without the possibility of selecting the most suitable embryos for transfer greatly reduced the chances of pregnancy.

However other studies showed, in contrast to ours and other authors publications, that the new legislation neither reduced success rates of assisted reproductive technologies (ART) using fresh embryos, nor increased the multiple birth rate [9,10]. Moreover La Sala et al. [2009] [11] recently published favourable data concerning the perinatal outcome after the application of the Law concluding that the 2004 Italian infertility legislation led to improved quantitative and qualitative outcomes of ART. In May 2009 the Italian Constitutional Court cancelled some of the Law 40 prohibitions leaving to the clinicians the judgment of the best interest of the women reproductive process. The number of oocytes to be inseminated, embryos to be transferred and cryopreserved relies upon the reproductive specialist. Our Institution published the results of first 6 month cycles following the removal of some restrictions, demonstrating a significantly higher pregnancy rate per started cycle compared with previous results and showing how better results could be immediately obtained using an individualised approach to treatment [12]. This retrospective observational study included all the IVF and ICSI cycles performed from January 2008 to May 2009 (when the changes ordered by the Constitutional Court came into effect), and those performed from May 2009 until the end of December 2009. A total of 3274 cycles were analyzed, 2248 before and 1026 post Law modifications. Mean women age, percentage of women > than 36 years old, basal FSH level, duration of infertility, previous ART cycles, indication to treatment, cancelled cycles, cycles with no oocytes retrieved and mean number of oocytes/cycle were not significantly different between the 2 groups [12]. The number of oocyte used was, as expected, significantly higher as the number of embryos obtained (Table 4). A significantly lower percentage of cycles had only 1 embryo for transfer and likewise cycles with only 2 or 3 embryos available were also significantly fewer than prior to the removal of some legal restrictions (see summary in Table 4). After the Law was modified the fertilization rate was significantly reduced, confirming data of our previous study [7], but the cumulative embryo score was significantly higher. Although the implantation rate was not significantly different and a significantly higher number of patients transferred less than 3 embryos, a statistically significant higher pregnancy rate per started cycle (intention to treat analysis) was obtained (Table 4). By analyzing the data according to patients ≤ 36 years and > 36 years, the younger group had a significantly lower number of cycles with only 1 embryo transferred, a significantly higher number of cycles with 2 embryos transferred and a significantly lower number of cycles with 3 embryos transferred. Older patients had a significantly lower number of transfers with one or two embryos and a significantly higher number of cycles with 3 embryos transferred (Table 5).

	All cycles	*Pre Law.*	*Post Law mod.*	*p*
Inductions	3274	2248	1026	
Number of oocytes retrieved	8.26 ± 6.13	8.14 ± 6.06	8.52 ± 6.26	0.138
Number of oocytes used	3.02 ± 1.71	2.48 ± 1.03	4.22 ± 2.21	<0.001
Number of embryos obtained	2.25 ± 1.52	1.88 ± 1.07	3.08 ± 1.96	<0.001
1	479 (17.32)	374 (19.95)	105 (11.78)	<0.001
2	1052 (31.09)	691 (36.85)	169 (18.97)	<0.001
3	989 (35.76)	810 (43.20)	179 (20.09)	<0.001
>3	439 (15.84)	0	438 (49.16)	<0.001
Fertilisation rate mean ± SD	75.16 ± 28.65	76.00 ± 29.30	73.37 ± 27.15	<0.001
Cumulative embryo score	5.73 ± 2.39	5.65 ± 2.39	5.91 ± 2.39	0.022
Embryo transfers	2743 (83.78)	1863 (82.87)	880 (85.77)	0.037
Number of embryos transferred	1.88 ± 1.08	1.82 ± 1.08	2.02 ± 1.07	<0.001
1 embryo	519 (18.93)	405 (21.75)	114 (12.95)	<0.001
2 embryos	1053 (38.37)	691 (37.06)	362 (41.14)	0.040
3 embryos	1171 (42.71)	767 (41.19)	404 (45.91)	0.020
Implantation rate %	14.03 ± 27.18	13.51 ± 26.78	15.13 ± 28.01	0.107
Pregnancy rate/started cycle	701 (21.41%)	460 (20.46%)	241 (23.49%)	0.050

Quantitative data are expressed as mean ± SD. Values in parentheses are percentages

Table 4: Clinical characteristics of cycles performed before and after Italian ART Law modifications.

	All cycles	*Pre Law mod.*	*Post Law mod.*	*p*
Cycles in patients ≤ 36 years	1253	874	379	
1 embryo transferred	176 (15.88)	148 (19.45)	28 (8.07)	<0.001
2 embryos transferred	512 (46.21)	278 (36.53)	234 (67.44)	<0.001
3 embryos transferred	420 (37.91)	335 (44.02)	85 (24.50)	<0.001
Cycles in patients > 36 years	2021	1374	647	
Number of embryos transferred	1.83 ± 1.14	1.73 ± 1.11	2.04 ± 1.20	<0.001
1 embryo transferred	343 (20.99)	257 (23.34)	86 (16.14)	0.001
2 embryos transferred	541 (33.05)	413 (37.42)	128 (24.02)	<0.001
3 embryos transferred	751 (45.96)	432 (39.24)	319 (59.85)	<0.001

Quantitative data are expressed as mean ± SD. Values in parentheses are percentages

Table 5: Clinical characteristics of cycles in patients ≤ 36 years and > 36 years performed before and after Italian ART Law modifications (percentage of cyles).

The opportunity of tailoring the number of embryos to be transferred according to the mother's age and the quality of the embryo resulted in a clinically relevant reduction of multiple pregnancies. The number of triplets, although not significantly different, decreased by a 33%, as an effects of a significant reduction of the percentage of younger patients that transferred 3 embryos (Table 6). A significant reduction of twin pregnancy is anticipated as more experience and couple's acceptance of elective single embryo transfer is accumulated. Our results have been partially confirmed in a recent publication [13], with a smaller number of cycles (223 in the pre- and 308 in the post-ruling period). In this

	All cycles	Pre Law	Post Law	p
Single Pregnancies	502 (73.18)	332 (74.11)	170 (71.43)	0.451
Twin pregnancies	169 (24.64)	105 (23.44)	64 (26.89)	0.318
Triplet pregnancies	15 (2.19)	11 (2.46)	4 (1.68)	0.594

Absolute number of cycles or pregnancies. Values in parentheses are percentages

Table 6: Single and multiple pregnancies before and after Italian ART Law modifications.

	All cycles	Pre Law	Post Law	p
All cycles with cryopreservaton	977 (29.84)	607 (27.00)	370 (36.06)	<0.001
Only embryo	165 (16.89)	4 (0.66)	161 (43.51)	<0.001
Only oocytes	716 (73.29)	587 (96.71)	129 (34.86)	<0.001
Oocytes and embryos	96 (9.83)	16 (2.64)	80 (21.62)	<0.001
PR cycles with cryopreservaton	320 (32.75)	190 (31.30)	130 (35.14)	0.216
PR Only embryo	64 (38.79)	0 (0.0)	89 (39.75)	0.158
PR Only oocytes	231 (32.26)	190 (32.37)	41 (31.78)	0.898
PR Oocytes and embryos	25 (26.04)	0 (0.00)	25 (31.25)	0.010

Absolute number of cycles or pregnancies. Values in parentheses are percentages

Table 7: Percentage of cycles with cryopreservation and pregnancy rate (PR) per transfer in the fresh cycle in patients with cryopreservation before and after Italian ART Law modifications.

study there was a significant increase in the number of oocytes used, the number of embryos obtained, and the number of embryos transferred in patients over 36 years of age. Pregnancy rate per ovum pick-up and per transfer in the pre- and post-ruling periods showed an improvement of 17% and 19%, respectively, but such differences were not statistically significant on the overall population studied, likely due to the reduced number of patients enrolled. Nevertheless, in the subgroup analysis based on age groups, in patients >36 years of age, both pregnancy rates per oocyte retrieval and per transfer were significantly higher in the second study period (p=0.0314 and p=0.0313, respectively).

After a so long period of restrictions in the number of oocytes to be used and with the prohibition of embryo's cryopreservation, now many options are available and time will be needed to establish a new standard of care. The possibility of inseminating more than 3 oocytes and the possibility of freezing supernumerary embryos has finally allowed flexibility of choice among the reproductive options. Infertile couples can now benefit of oocyte cryopreservation, if they oppose for personal or ethical reasons, to embryo cryopreservation, or they can choose to cryopreserve embryos or both [14,15]. In our preliminary, six month experience, where for some couples an individualized (according to patient's age, etiology of infertility) number of oocytes were fertilized and for others all the oocytes were used, we decided to cryopreserve only day 5-6 embryos (blastocyst-stage). In Table 7 is shown that after the decision of the Constitutional Court 36.06% (370/1026) of cycles had embryos or oocytes stored. In 161 out of 370 (43.51%) only embryos were cryopreserved, 129/370 (34.86%) had only oocyte and 80/370 (21.62) had both embryos and oocytes cryopreserved.

Even with the modifications of the Law cross border migration of Italian couples to less restrictive countries (mainly for use of donor gametes) remains very high. Cross border health care, and more specifically reproductive care, is of concern to patients, practitioners and policy makers alike. This 'exile' prejudiced European regulatory Institutions and national Parliament's positions leaving them only a symbolic role [16].

The publication of a collaborative study between two ESHRE groups, the European IVF Monitoring (EIM) and the Taskforce on Ethics and Law reported the cross border phenomena studying six countries: Belgium, the Czech Republic, Denmark, Switzerland, Slovenia and Spain. The study reported an estimated a minimum annual number of 24,000-30,000 cycles in these 6 countries and 31.8% of the couples were Italians [17]. Although the search for a better quality was one of the elements supporting couple's desire to search treatment abroad, gamete donation ranged from 51% to 76% and this percentage will grow if oocyte and sperm donation will continue to be forbidden in our country.

Discussion

Despite possible limitations due to potential biases of retrospective studies, it is clear that restrictive laws in ART have a negative impact on IVF outcomes and penalize infertile couples. The impact of five years of a restrictive in Italy legislation affected mainly older patients that represent today the majority of our infertile population, while international data on ART showed, between 2001 and 2009, a clear tendency to higher success rate with the improvement of ART [18]. The last report publishing results from ART treatments in Europe during 2006 showed an overall clinical pregnancy rate and an overall delivery rate per cycle of 29% and 21.5 % respectively for IVF cycles. When the pregnancy and delivery rate per cycle were computed for Italy, the percentage declined to 21.4% and 13.4% respectively [19], in accordance with our results for the same period [7]. The loss of both patient and physician's autonomy and rights to procreation has severely compromised the opportunities of many infertile citizens to creating families and has led to the flourishing of the humiliating form of reproductive tourism. In May 2009 the Constitutional Court cancelled most of the restrictions of the Italian Law regulating ART in Italy. Oocyte and sperm donation remain forbidden. As a direct consequence of these prohibitions many couples, at great personal expenses and sacrifices, still travel cross border to fulfil their desire for a family. It is possible that this issue will be submitted in the near future to the Constitutional Court.

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