EXECUTIVE SUMMARY

IARTR - ITALIAN ASSISTED REPRODUCTIVE TECHNOLOGY REGISTER

MONITORING THE ACTIVITY AND OUTCOMES OF ITALIAN ART CENTERS IN 2013.

MONITORING THE ACTIVITY AND OUTCOMES OF ITALIAN ART CENTERS IN 2013

AUTHORS

G. Scaravelli, V. Vigiliano, R. De Luca, S. Bolli, P. D'Aloja, R. Spoletini, S. Fiaccavento, L. Speziale

ART Italian National Register, National Centre for Diseases Prevention and Health Promotion, National Health Institute, Rome, Italy

INDEX

Assisted Reproduction Technology (ART) in Italy, 2013
Summary outputs generated from the National ART Register

ALL PROCEDURES (H-IUI + ART)

- **369 clinics operating or active** in 2013;
- **71.741 patients** treated;
- **91.556** treatment **cycles** performed**;**
- **15.550 pregnancies** obtained;
- **13.770** monitored **pregnancies** (11,4% pregnancies lost to follow-up);
- **10.350 deliveries;**
- **12.187 live born babies**
  2,4% of National live born babies in Italy in 2013 (514.308 live born babies, Source: ISTAT).

H-IUI ACTIVITY (ONLY WITH HOMOLOGOUS SEMEN) - 2013

- **369 clinics operating or active** in 2013;
- **17.218 patients** treated;
- **27.129** treatment **cycles** performed;
- **2.775 pregnancies** obtained;
- **10,2 pregnancies rate per cycle**;
- **2.309** monitored **pregnancies** (16,8% pregnancies lost to follow-up);
- **1.810 deliveries;**
- **1.970 live born babies**
  0,4% of National live born babies in Italy in 2013.

ART ACTIVITY (FRESH + THAWING CYCLES) - 2013

- **203 clinics operating or active** in 2013;
- **54.523 patients** treated;
- **64.447** treatment **cycles** performed;
- **12.775 pregnancies** obtained;
- **11.461** monitored **pregnancies** (10,3% pregnancies lost to follow-up);
- **8.495 deliveries;**
- **10.217 live born babies**
  2,0% of National live born babies in Italy in 2013.

ONLY FRESH CYCLES (IVF+ICSI+GIFT):

- **46.433 patients** treated;
- **55.050** treatment **cycles** performed;
- **10.712 pregnancies** obtained;
- **19,5 pregnancies rate per cycle**;
- **9.540** monitored **pregnancies** (10,9% pregnancies lost to follow-up);
- **7.125 deliveries;**
- **8.677 live born babies**
  1,7% of National live born babies in Italy in 2013.

THAWING CYCLES

- **8.090 patients** treated;
- **9.397** treatment **cycles** performed;
- **2.063 pregnancies** obtained;
- **22,0 pregnancies rate per thawing cycle**;
- **1.921** monitored **pregnancies** (6,9% pregnancies lost to follow-up);
- **1.370 deliveries;**
- **1.540 live born babies**
  0,5% of National live born babies in Italy in 2013.

Summary Table: Activity, patients treated, initiated cycles, pregnancies, pregnancies lost to follow-up, deliveries, live babies. Years 2005 – 2013

	2005	2006	2007	2008	2009	2010	2011	2012	2013
N° Clinics	316	329	342	354	350	357	354	355	369
% of clinics reporting data to ISS	91,2	100	100	100	100	100	100	100	100
ALL PROCEDURES (H-IUI + ART)									
N° Patients	46.519	52.206	55.437	59.174	63.840	69.797	73.570	72.543	71.741
N° Initiated cycles	63.585	70.695	75.280	79.125	85.385	90.944	96.427	93.634	91.556
N° Pregnancies	9.499	10.608	11.685	12.767	14.033	15.274	15.467	15.670	15.550
N° Monitored pregnancies	5.392	8.108	9.884	10.825	11.691	13.537	13.395	13.484	13.770
% Pregnancies lost to follow-up	43,2	23,6	15,4	15,2	16,7	11,4	13,4	14,0	11,4
N° Deliveries	4.033	6.148	7.513	8.319	8.896	10.387	10.065	10.101	10.305
N° Live born	4.940	7.507	9.137	10.212	10.819	12.506	11.933	11.974	12.187
H-IUI ACTIVITY									
N° clinics reporting data (with at least 1 patient treated)	275	276	275	297	303	302	298	311	307
N° Patients	15.770	18.431	18.972	19.032	20.315	19.707	20.012	18.085	17.218
N° Initiated cycles	26.292	29.901	31.551	31.268	33.335	32.069	32.644	29.427	27.109
N° Pregnancies	2.805	3.203	3.400	3.414	3.482	3.306	3.246	3.024	2.775
% Pregnancy Rate per cycle	10,7	10,7	10,8	10,9	10,4	10,3	9,9	10,3	10,2
N° Monitored pregnancies	1.464	2.296	2.703	2.652	2.699	2.793	2.659	2.506	2.309
% Pregnancies lost to follow-up	47,8	28,3	20,5	22,3	22,5	15,5	18,1	17,1	16,8
N° Deliveries	1.114	1.764	2.076	2.074	2.114	2.220	2.062	1.974	1.810
N° Live born	1.291	1.999	2.337	2.357	2.361	2.465	2.275	2.156	1.970
ART ACTIVITY (FRESH + THAWING CYCLES)									
N° clinics reporting data (with at least 1 patients treated)	169	184	181	185	180	174	179	182	178
N° Patients	30.749	33.775	36.465	40.142	43.525	50.090	53.558	54.458	54.523
N° Initiated cycles	37.293	40.794	43.729	47.857	52.050	58.875	63.783	64.207	64.447
N° Pregnancies	6.694	7.405	8.285	9.353	10.551	11.968	12.221	12.646	12.775
N° Monitored pregnancies	3.928	5.812	7.181	8.173	8.992	10.744	10.736	10.978	11.461
% Pregnancies lost to follow-up	41,3	21,5	13,3	12,6	14,8	10,2	12,2	13,2	10,3
N° Deliveries	2.919	4.384	5.437	6.245	6.782	8.167	8.003	8.127	8.495
N° Live born	3.649	5.508	6.800	7.855	8.458	10.041	9.658	9.818	10.217
INDICATORS OF THE AVALIABILITY OF SERVICES									
ART Initiated cycles per 1 million women aged 15 and 45	2.683	3.328	3.569	3.905	4.218	4.809	5.293	5.562	5.601
ART Initiated cycles per 1 million inhabitans	636	692	736	800	865	973	1.050	1.078	1.070

Summary Table: Activity, patients treated, initiated cycles, pregnancies, pregnancies lost to follow-up, deliveries, live babies. Years 2005 – 2013

	2005	2006	2007	2008	2009	2010	2011	2012	2013
ONLY FRESH CYCLES: IVF 16,7% of cycles, ICSI 83,3% of cycles, GIFT only 1 cycles in 2013									
N° clinics reporting data (with at least 1 patients treated)	169	184	181	185	180	174	179	182	178
N° Patients	27.254	30.274	33.169	36.782	39.775	44.365	46.491	46.491	46.433
N° Initiated cycles	33.244	36.912	40.026	44.065	47.929	52.676	56.092	55.505	55.050
Average age calculated	35,25	35,50	35,77	35,93	36,17	36,34	36,48	36,50	36,55
N° Aspirations	29.380	32.860	35.666	39.462	43.257	47.461	50.290	50.096	50.174
N° Transfer	25.402	28.315	30.780	34.179	37.301	40.468	42.331	41.822	40.696
N° Pregnancies	6.243	6.962	7.854	8.847	9.940	10.988	10.959	11.077	10.712
% Pregnancies rate per cycles	18,8	18,9	19,6	20,1	20,7	20,9	19,5	20,0	19,5
% Pregnancies rate per aspirations	21,2	21,2	22,0	22,4	23,0	23,2	21,6	22,1	21,3
% Pregnancies rate per transfers	24,6	24,6	25,5	25,9	26,6	27,2	25,9	26,5	26,3
% Twin Pregnancies	18,5	18,5	18,7	20,1	20,0	20,2	18,8	18,9	19,4
% Tiplet or more Pregnancies	3,4	3,5	3,6	3,4	2,7	2,3	1,8	1,8	1,6
N° Monitored pregnancies	3.603	5.464	6.793	7.728	8.453	9.806	9.572	9.535	9.540
% Pregnancies lost to follow-up	42,3	21,5	13,5	12,6	15,0	10,8	12,7	13,9	10,9
N° Deliveries	2.680	4.141	5.165	5.938	6.414	7.512	7.193	7.116	7.125
N° Live born	3.385	5.218	6.486	7.492	8.043	9.286	8.734	8.680	8.677
ONLY THAWING CYCLES									
N° Patients	3.495	3.501	3.296	3.360	3.750	5.725	7.067	7.967	8.090
N° Initiated cycles	4.049	3.882	3.703	3.792	4.121	6.199	7.691	8.702	9.397
N° Pregnancies	451	443	431	506	611	980	1.262	1.569	2.063
N° Monitored pregnancies	325	348	388	445	539	938	1.164	1.443	1.921
% Pregnancies lost to follow-up	27,9	21,4	10,0	12,1	11,8	4,3	7,8	8,0	6,9
N° Deliveries	239	243	272	307	368	655	810	1.011	1.370
N° Live born	264	290	314	363	415	755	924	1.138	1.540

THE ITALIAN ASSISTED REPRODUCTION TECHNOLOGY REGISTER (IARTR)

Assisted reproductive technology has been used in Italy since 1984 to help couples with fertility problems to have children. Only twenty years later in 2004 a specific law on the application of those techniques has been published.

The National Register of ART has been established at the Istituto Superiore di Sanità (National Institute of Health) by an order of the Ministry of Health issued on the 7 of October (G.U. n. 282 del 3 December 2005) in implementation of article n° 11 paragraph 1 of Law 40/2004 (G.U. n.45 del 24 February 2004).

The Register collects the following data:

- descriptive, technical, structural and organizational information of ART centers authorized to conduct ART;
- anonymous, aggregate data sets on the infertile couples, on created embryos and children born following the application of ART.

The National Italian Register has the following objectives:

ASSESS and REGISTER

- all the centres performing ART treatments and IUI procedures in the country
- the number of embryos created and cryopreserved

COLLECT and EVALUATE

- data regarding centres characteristics, addresses, kind of service offered (public- private or private covered by the National Health service) , kind of techniques performed
- Activity and availability
- Efficacy and safety of techniques application

PROMOTE

- Research and study on couple infertility and fertility matters
- Long term evaluation of well-being of children born after Art procedures
- Research on gametes characteristics and new cryopreservation protocols
- Monitoring the trends in assisted reproductive techniques application in order to compare different attitudes with other countries

The Register "is functionally linked with other European and International Registries, in order to exchange anonymous data, also aggregate, including electronic instruments"

The Register prepares an annual epidemiological/statistical report on the ART center's activity that afterward is sent to the Minister of Health.

HOW DOES THE IARTR WORK?

Data on efficacy, safety and outcomes of reproductive techniques including H-IUI are collected on a web site on a reserved area with a username and a password. Data collection on summary data from each centre it is organized in two different times frames, according to treatments and to treatments outcomes.

Data collection it is performed separately for H-IUI procedures (Homologous Intrauterine Insemination) and IVF-ICSI-GIFT on different electronic forms.

Data collection is made on number of cycles performed for each technique, number of patients treated, kind of infertility diagnosed, complications during treatments and results, pregnancies outcomes and babies born

The Register collect data only on a summary basis according to a national law on privacy protection (Dlg 196/2003). Task of the register it is to provide each year a complete report on all the ART treatments and H-IUI procedures performed in the country .

An annual national report on all treatments application it is provide to the Ministry of Health in order to illustrate to the Parliament the situation in ART field with a particular epidemiological overview.

The IARTR is linked to the European IVF Monitoring (EIM) Consortium which collects data on ART from about 36 European countries. In turn, the EIM sends data to the World Register ICMART (International Committee Monitoring Assisted Reproductive Technologies). The activity of IARTR is audited by Prof. Karl-Gösta Nygren, Associate Professor of Obstetrics and Gynecology at the "Karoliniska Institutet - Department of Medical Epidemiology and Biostatistics" Stockholm - Past Chairman of ICMART and Past Chairman of EIM at ESHRE.

The staff of the Registry is made up of a multidisciplinary team with expertise in epidemiology, statistics, gynecology, computer science, bioethics, sociology, biology and psychology.

THE IARTR WEB SITE

WWW.ISS.IT/RPMA

The Register web site has the goal to collect and disseminate data and information related to H-IUI and ART procedures.

It is a good tool to connect centres to the National Health Institute and to the Local Regional Authorities.

To link different professional associations, government health institutions and different stakeholders in the field of reproductive medicine.

There are different levels of interest in the web site, that give:

- A service for the citizens: they can consult the list of all the authorized centres by different regions and have information about the techniques they performs, and the availability of the service. They can find on the home page all the information regarding the and their application in Italy of ART and H-IUI techniques and their application in Italy . They can find also all the links to patient associations, government institutions , national health service, European and international registries on ART and Fertility societies; many tools to better understand problems related to infertility matters, news on reproductive and infertility issues, and a constant view on Italian legislation on reproductive field
- A service for all the centres: they can fill the forms on their activity each year and they have access to their local authority and to the national Register staff in any moment
- A service for all the 21 Italian Regions: They can see all the data relating the centres operating on their territory and they can easily monitor and elaborate data on their specific activity

The Registry's website was visited last year by approximately 50.000 users, with a daily average of about 140 hits, and is the second most visited site in the portal National Institute of Health.

THE IARTR STAFF

The staff is coordinated by Dr. Giulia Scaravelli, MD-Gynaecologist, working at the National Centre for Epidemiology Surveillance and Health Promotion at the National Health Institute.

In the staff there are a variety of skills: statistics, epidemiology, gynaecology, biology, sociology and informatics. The research group covers many areas of infertility and of reproductive medicine cooperating with Scientific Societies, Regional Authorities, Patient Associations and ART Centres:

- promote the development of knowledge in reproductive field
- provide training courses to ART operators for data flow and data recruitment
- provide information tools for ART operators and citizens in the scenario of assisted reproduction
- act as promoter on specific issues concerning information and data diffusion on reproductive techniques.

CHAPTER 1

1. ACCESS AND UTILIZATION OF ART SERVICES IN ITALY 2013

1.1. Access to the service of ART

In **Figure 1** and **Figure 2** the regional distributions of H-IUI and ART centers are represented.

The largest number of H-IUI + ART centers is concentrated in Southern Italy, (120 centers, 32,5% out of the total) and in the Northwest (97 centers, 26.3% out of the total), irrespective of the amount of activity they have carried out. The North West had the highest concentration of H-IUI centers (58; 34.9%), while the South and Islands had the highest of ART (74; 36.5%).

Figure 1: Regional distribution of H-IUI + ART active centers in 2013.

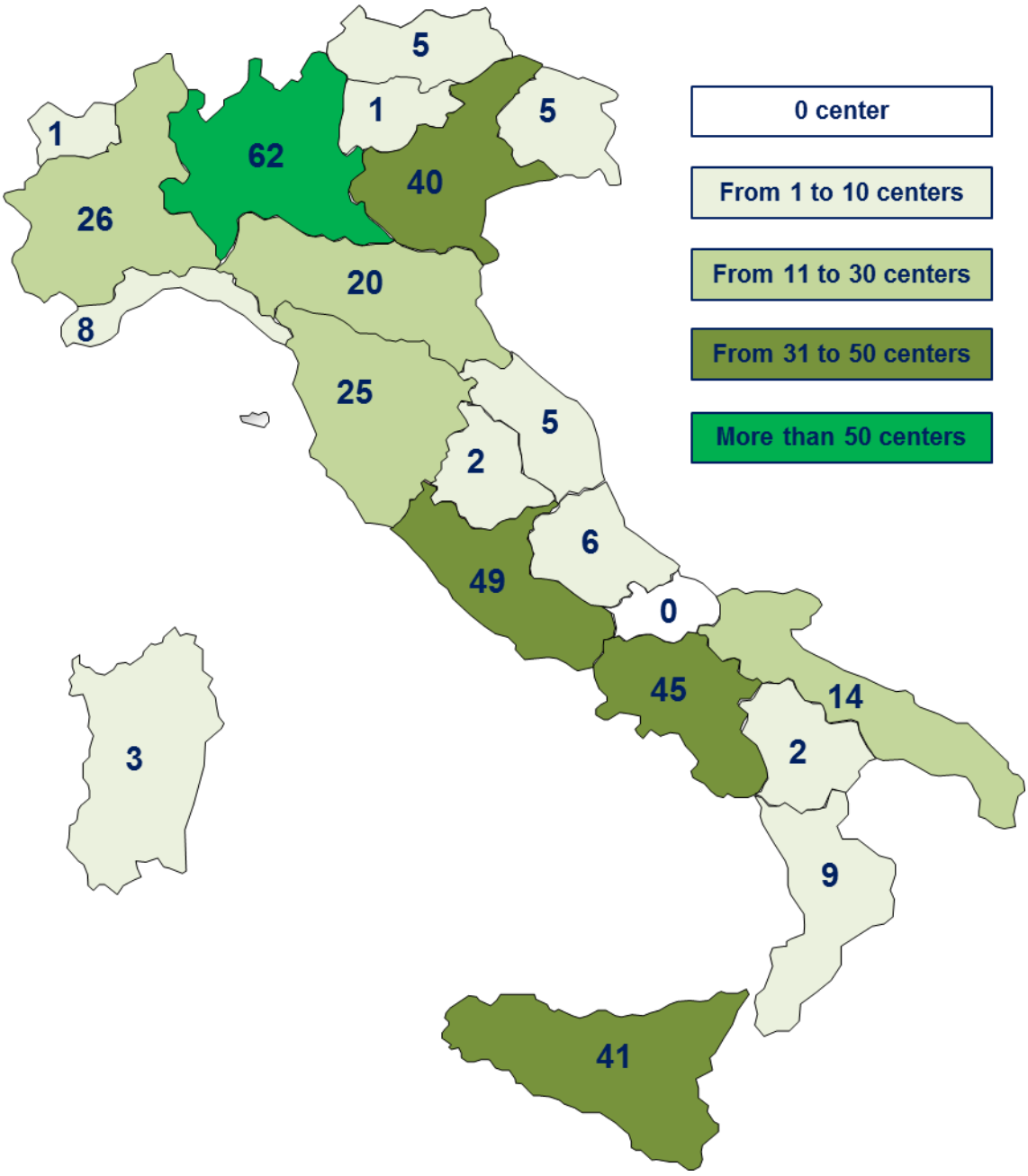
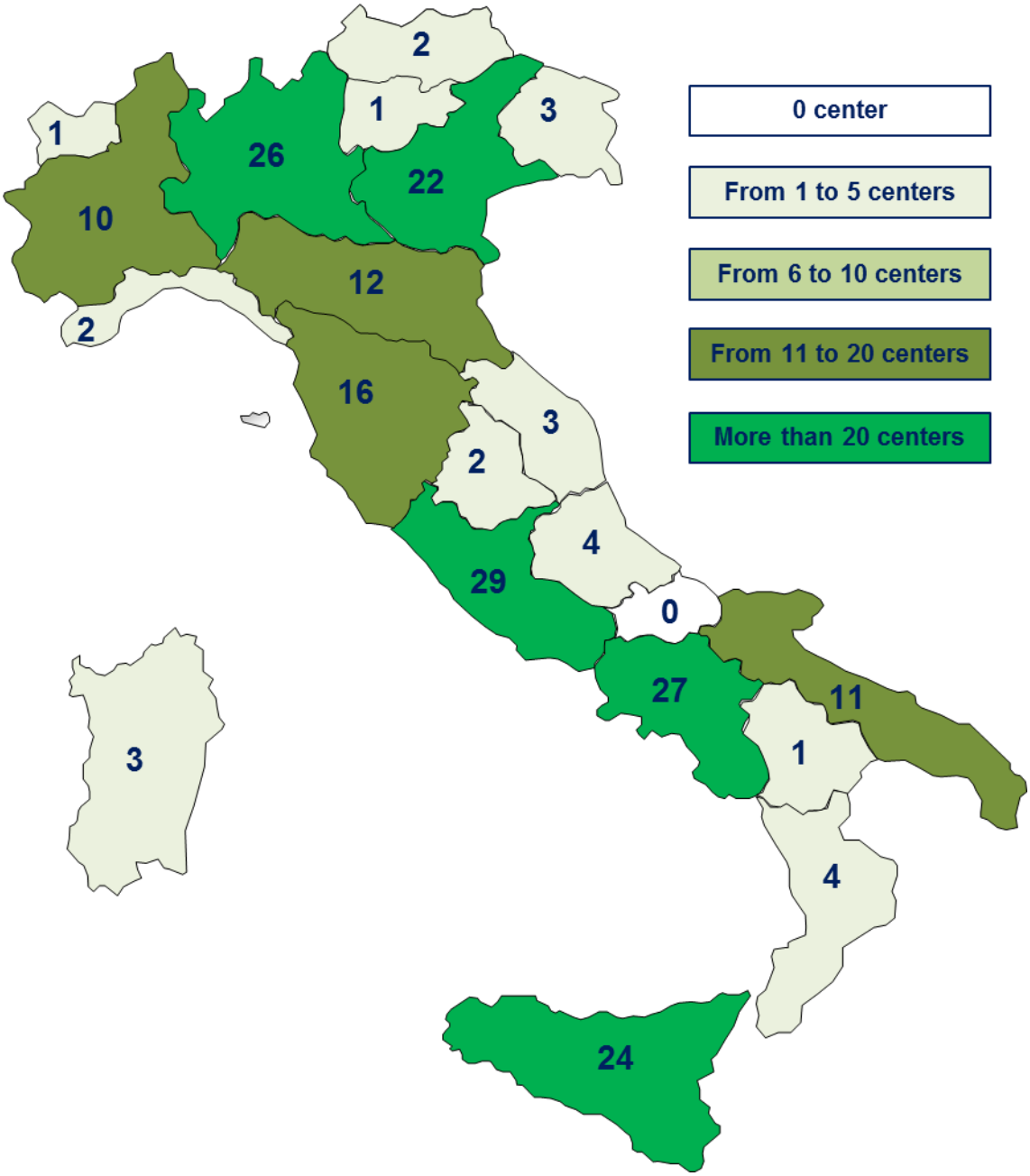


Figure 2: Regional distribution of the ART active center in 2013.



As shown in **Table 1**, in 2013 there were 166 centers that have performed only H-IUI of which only 46 operating within the National Health System (public and private 27.7%) and 120 providing private service (72.3%).

Most of public centers that performs H-IUI in Italy were in North: 31 out of 43 centers (72.1%).

Table 1: Distribution of Centers that performed only H-IUI in 2013 per type of service by Region and geographical area.

Region and Geographical Area	Total	Type of Service					
		Public		Private covered by NHS		Private	
		N	%	N	%	N	%
Piemonte	16	8	50.0	0	-	8	50.0
Valle d'Aosta	0	-	-	-	-	-	-
Lombardia	36	7	19.4	1	2.8	28	77.8
Liguria	6	2	33.3	0	-	4	66.7
Northwest	***58***	***17***	***29.3***	***1***	***1.7***	***40***	***69.0***
P.A. Bolzano	3	3	100	0	-	0	-
P.A. Trento	0	-	-	-	-	-	-
Veneto	18	6	33.3	1	5.6	11	61.1
Friuli Venezia Giulia	2	1	50.0	0	-	1	50.0
Emilia Romagna	8	4	50.0	0	-	4	50.0
Northeast	***31***	***14***	***45.2***	***1***	***3.2***	***16***	***51.6***
Toscana	9	3	33.3	0	-	6	66.7
Umbria	0	-	-	-	-	-	-
Marche	2	0	-	0	-	2	100
Lazio	20	1	5.0	1	5.0	18	90.0
Central	***31***	***4***	***12.9***	***1***	***3.2***	***26***	***83.9***
Abruzzo	2	2	100	0	-	0	-
Molise	0	-	-	-	-	-	-
Campania	18	2	11.1	0	-	16	88.9
Puglia	3	1	33.3	0	-	2	66.7
Basilicata	1	1	100	0	-	0	-
Calabria	5	1	20.0	0	-	4	80.0
Sicilia	17	1	5.9	0	-	16	94.1
Sardegna	0	-	-	-	-	-	-
South and Islands	***46***	***8***	***17.4***	***0***	***-***	***38***	***82.6***
Italy	**166**	**43**	**25.9**	**3**	**1.8**	**120**	**72.3**

Table 2 shows the geographical distribution of ART centers according to the type of services offered. Overall the number of ART centers that were active in 2013 was 203 of which 95 (46.8%) operating within the National Health Service (public and private), and 108 (53.2%) who provided only private service.

As for H-IUI centers, the majority of ART centers providing public service was concentrated in the North, i.e. in the North West 76.9% were public, while in the Centre and in the South were mostly private of Italy (58.0% and 68.9%, respectively).

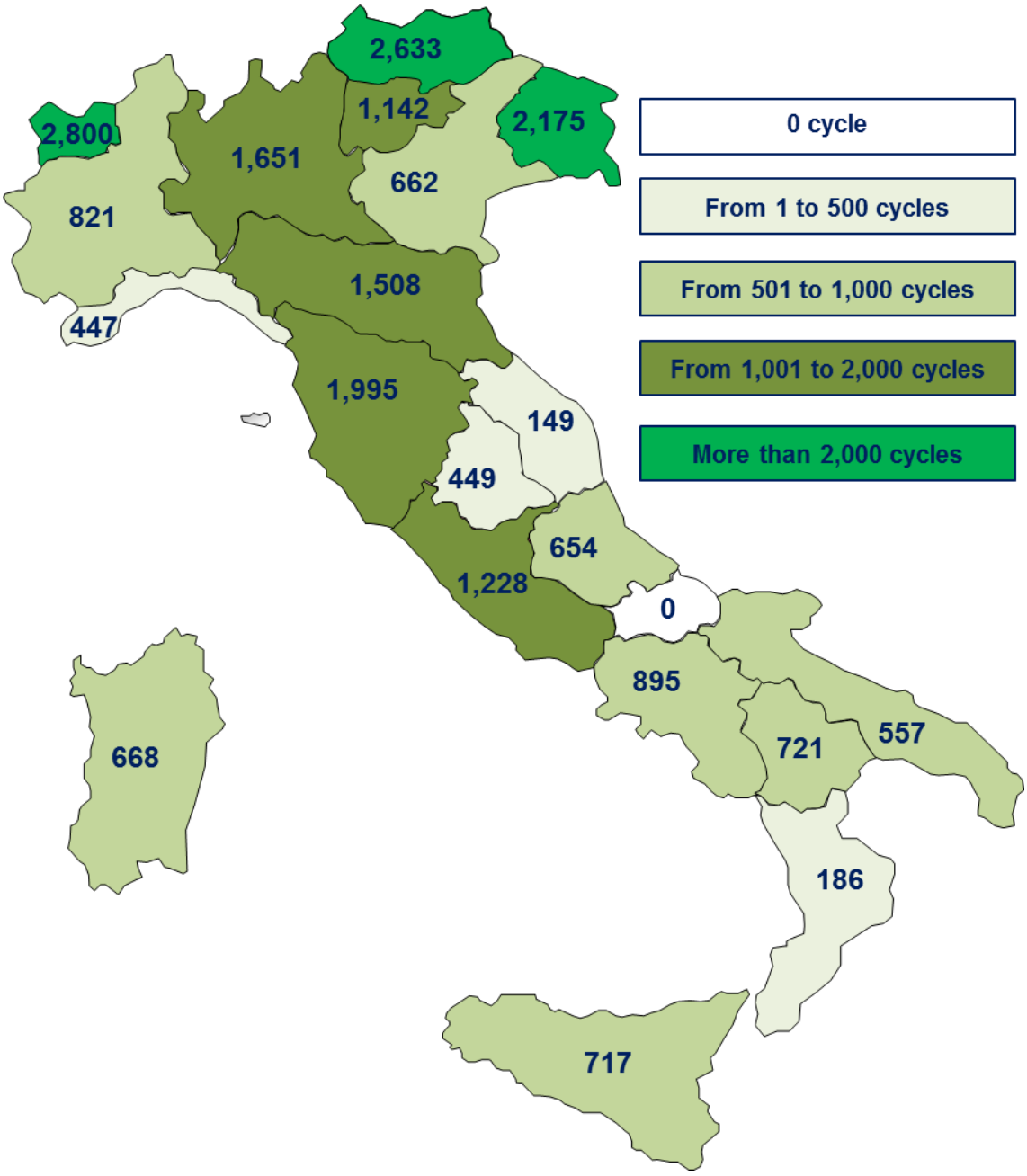
Table 2: Distribution of ART centers in 2013 by region and geographical area.

Region and Geographical Area	Total	Type of Service					
		Public		Private covered by NHS		Private	
		N	%	N	%	N	%
Piemonte	10	3	30.0	1	10.0	6	60.0
Valle d'Aosta	1	1	100	0	-	0	-
Lombardia	26	14	53.8	9	34.6	3	11.5
Liguria	2	2	100	0	-	0	-
Northwest	**39**	**20**	**51.3**	**10**	**25.6**	**9**	**23.1**
P.A. Bolzano	2	1	50.0	0	-	1	50.0
P.A. Trento	1	1	100	0	-	0	-
Veneto	22	9	40.9	1	4.5	12	54.5
Friuli Venezia Giulia	3	2	66.7	1	33.3	0	-
Emilia Romagna	12	6	50.0	0	-	6	50.0
Northeast	***40***	***19***	***47.5***	***2***	***5.0***	***19***	***47.5***
Toscana	16	4	25.0	6	37.5	6	37.5
Umbria	2	1	50.0	0	-	1	50.0
Marche	3	2	66.7	0	-	1	33.3
Lazio	29	6	20.7	2	6.9	21	72.4
Central	***50***	***13***	***26.0***	***8***	***16.0***	***29***	***58.0***
Abruzzo	4	2	50.0	0	-	2	50.0
Molise	0	-	-	-	-	-	-
Campania	27	8	29.6	0	-	19	70.4
Puglia	11	2	18.2	0	-	9	81.8
Basilicata	1	1	100	0	-	0	-
Calabria	4	0	-	0	-	4	100
Sicilia	24	7	29.2	0	-	17	70.8
Sardegna	3	3	100	0	-	0	-
South and Islands	***74***	***23***	***31.1***	***0***	***-***	***51***	***68.9***
Italy	**203**	***75***	**36.9**	***20***	**9.9**	***108***	**53.2**

1.2. Utilization of the ART service

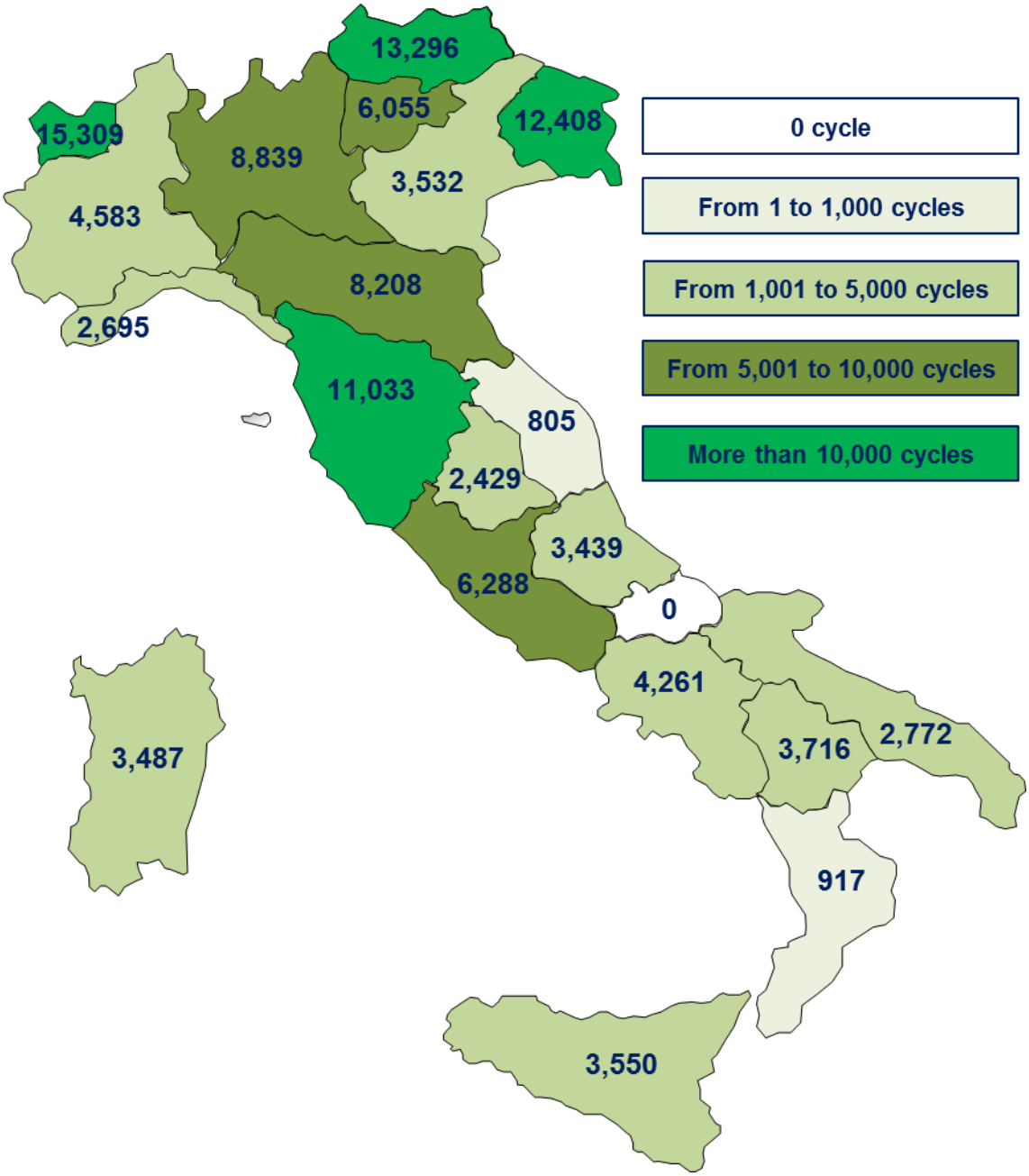
In **Figure 3** the distribution of initiated cycles per million of inhabitants per geographical region is represented. As it is shown there is a great difference in the number of cycles performed between regions ranging from 2,800 cycles offered in Valle d'Aosta to 149 cycles provided in Marche. In general, numbers of Northern and Central regions are above the national average (1,070 cycles), while in Southern regions number are below.

Figure 3: Regional distribution of the number of initiated ART cycles per million inhabitants. (Average resident population in 2013. Source ISTAT)



The same happens respect to the number of cycles initiated per million women of reproductive age (between 15 and 45 years) **Figure 4** with the Northern regions above the Italian average (5,601 cycles), and the Southern regions below.

Figure 4: Regional distribution of the number of initiated ART cycles per million women of reproductive age (15-45 years). (Average resident population in 2013. Source ISTAT)



In **Table 3** ART treatments that have been performed in Italy and in Europe were compared over time. In Italy, both the indicators, cycles per million inhabitants and per million women of childbearing age, were constantly growing, with an increase of 434 cycles (+ 68.2%) and of 2,918 cycles (+ 108.8%), respectively. It must be emphasized that, in Europe, the number of ART cycles included also Egg Donation cycles (Egg Donation - ED) that counted 2.7% in 2010. Conversely, in that period, in Italy, Egg Donation was not allowed.

Table 3: Number of initiated ART cycle per million inhabitants and per million women of reproductive age (15-45 years) in Italy and in Europe.

Years	ART Cycles/million population		ART cycles/million women (15 - 45 years)	
	Italy	Europe[a]	Italy	Europe[a]
2005	636	1,115	2,683[b]	4,008[b]
2006	692	850	3,328	3,503
2007	736	886	3,569	4,320
2008	800	947	3,905	4,661
2009	865	1,067	4,265	5,455
2010	973	1,221	4,863	6,258
2011	1,063	-	5,392	-
2012	1,078	-	5,562	-
2013	1,070	-	5,601	

a: Data for Europe refers only to those country (16) where data coverage was 100%.
b: In 2005 ART cycles are related to the number of women aged between 15 and 49 years.

The latest European data available, published in July 2014, refer to the activity of 2010. The number of started cycles per million inhabitants (calculated only for the 16 countries that have reported data of 100% of the centers) was 1,221 cycles vs. 973 in Italy.

CHAPTER 2

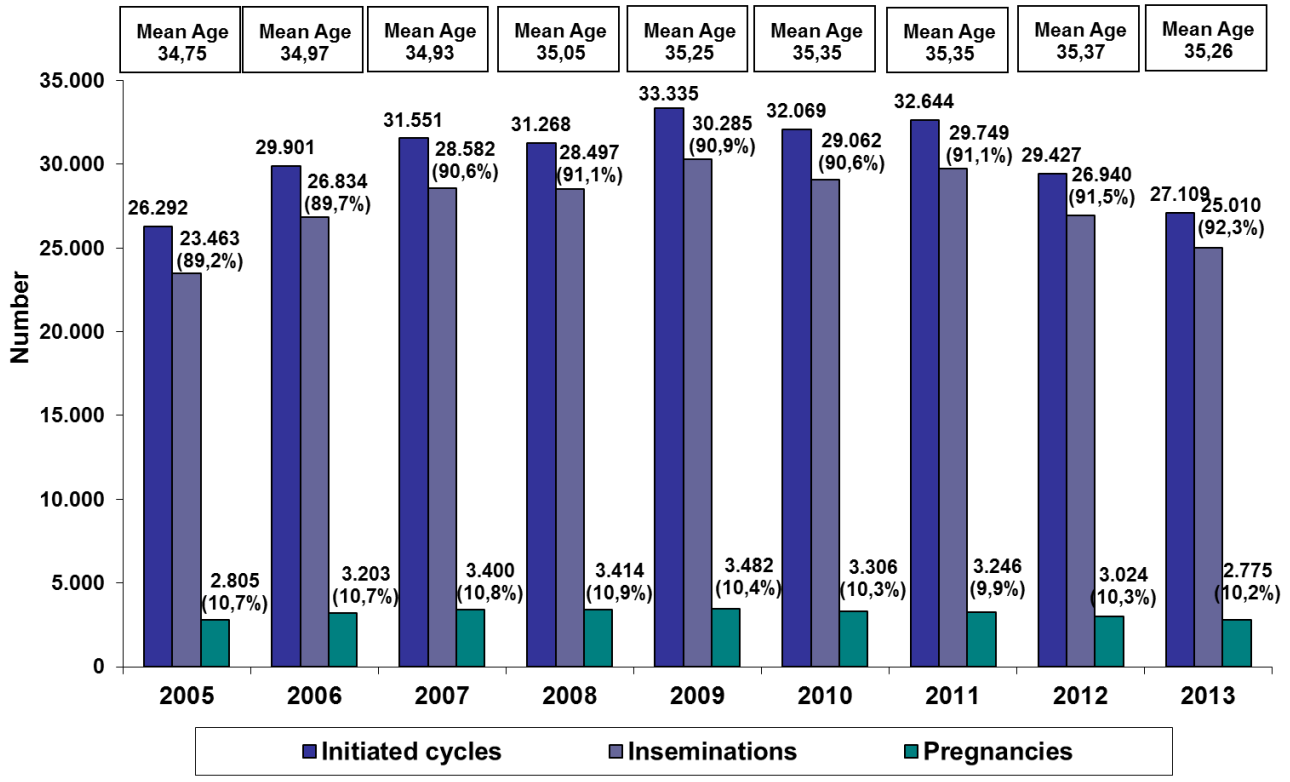
2.MAIN RESULTS OF H-IUI AND ART IN 2013 AND TRENDS 2005-2013

2.1. H-IUI cycles

2.1.1. Is the use of H-IUI increasing?

In **Figure 5** the use of H-IUI from 2005 to 2013 is represented. Number of H-IUI cycles increased from 26,292 to 27,109. There were slight changes in pregnancy rate from 10.7% in 2005 to 10.2% in 2013. Average women age increase of 0.51 year during time.

Figure 5: Trend of outcomes of H-IUI cycles, years 2005-2013.

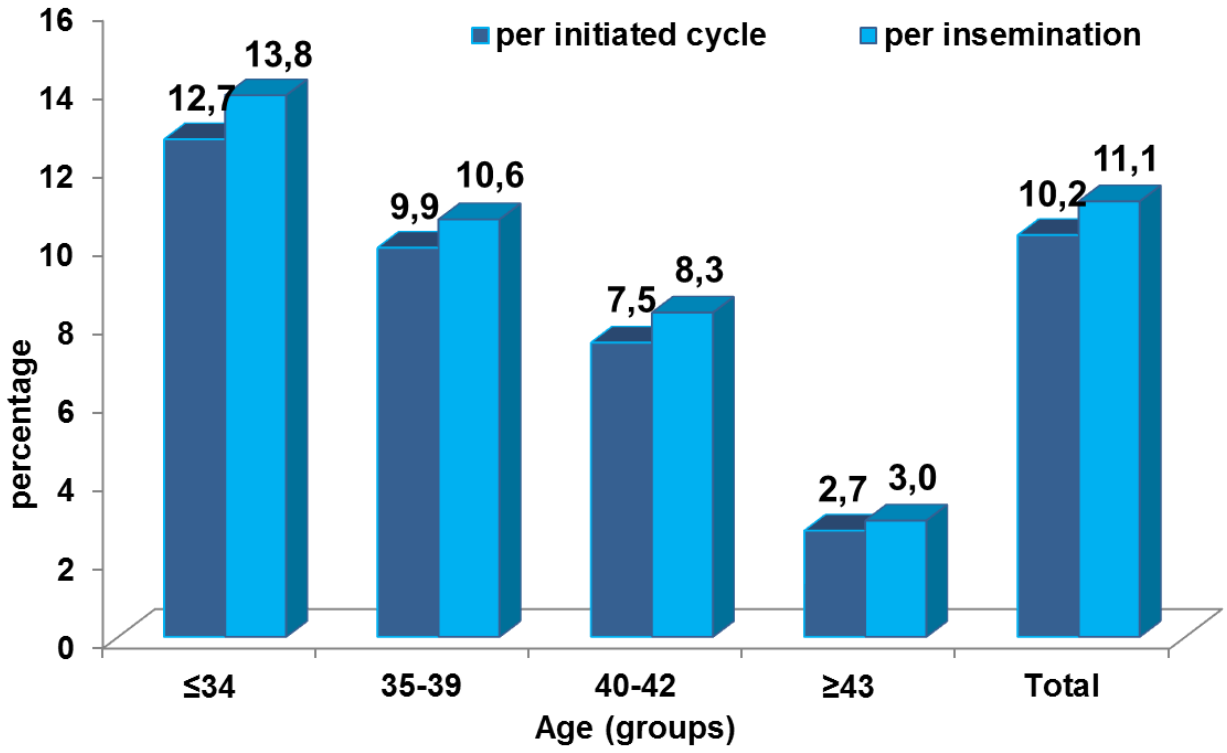


2.1.2. Do percentages of H-IUI cycles results in pregnancies, differ among women of different age groups?

Figure 6 shows percentages of initiated cycles and insemination for H-IUI that resulted in pregnancies among women of different age groups.

The probability to obtain a pregnancy in an H-IUI treatment is high related to the age of women. Numbers in older women are very small (7.5% and 8.3% in 40-42 and 2.7% and 3.0% in over 43).

Figure 6: Pregnancy rate per initiated cycle and per insemination for H-IUI cycles by age groups of female patients, 2013.



2.2. ART cycles.

2.2.1. What are the main causes of infertility among users of ART?

Figure 7 shows major causes of infertility among patients who had ART using fresh cycles in 2013. Diagnoses range from one infertility factor in the patient or partner to multiple infertility factors in either one or both.

- ***Female factor:***

- **Tubal factor -** fallopian tubes are blocked or damaged, prevent eggs from getting to the uterus and sperm from getting to the egg
- **Ovulatory dysfunction -** ovaries are not producing eggs normally. The ovaries develop many small cysts instead of ripening and maturing one egg each cycle.
- **Endometriosis -** the presence of tissue similar to the uterine lining in abnormal locations. This condition can affect both fertilization of the egg and embryo implantation.
- **Diminished ovarian reserve -** the ability of the ovary to produce eggs is reduced. Reasons include congenital, medical, or surgical causes or advanced age.
- **Multiple abortions** - when there were two or more miscarriages without any full-term pregnancy.
- **Multiple factor, female -** more than one female's cause of infertility.

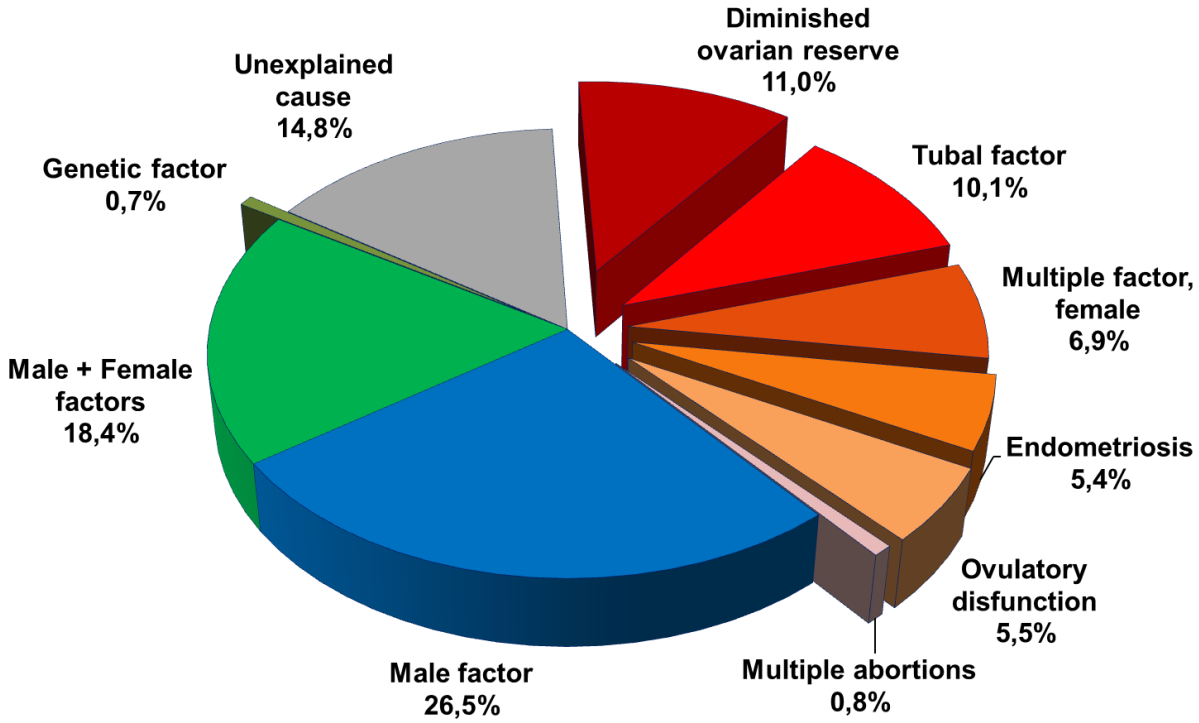
- ***Male factor*** - Low or no sperm counts, poor sperm motility (the ability to move), and abnormally-shaped sperm can all cause infertility.

- ***Male and female factors*** - one or more female's and male's causes of infertility.

- **Genetic factor** - Due to chromosomal abnormalities (numerical and / or structural) or to genetic alterations. They can be both male and female factors

- ***Unexplained cause*** - no cause of infertility is found in either woman or man.

Figure 7: Distribution of principal causes of infertility among patients who had ART using fresh cycle, 2013.Total couples treated: 46,433



2.2.2. What type of ART cycles were performed in Italy in 2013?

IVF (In Vitro Fertilization): is the joining of woman's eggs and a man's sperm in a laboratory dish. The embryos created in this process are then placed into the uterus

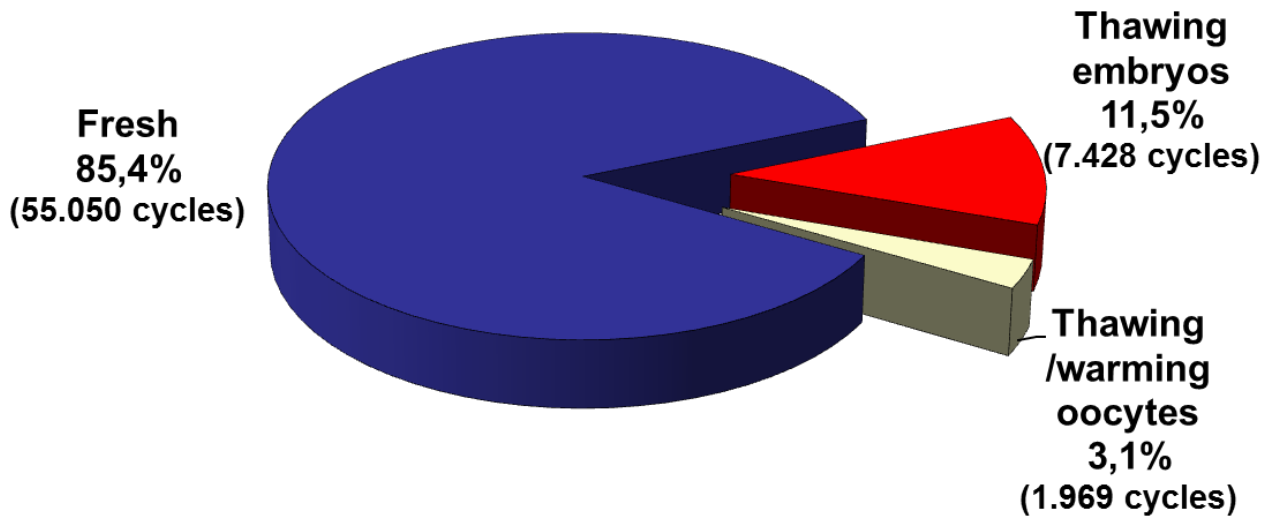
ICSI (Intra-Cytoplasmatic Sperm Injection): is a procedure in which a single sperm is injected directly into an egg. The embryo created in this process is then placed into the uterus.

GIFT (Gamete Intra-Fallopian Transfer): is the combining of eggs with sperm, using a laparoscope to place the unfertilized eggs and sperm into the woman's fallopian tube through small incisions in her abdomen

ART procedures are techniques that can be carried out in fresh or frozen cycles. During fresh cycles eggs or embryos have not been frozen. In frozen cycles eggs or embryos have been frozen. Later frozen oocytes or embryos will be thawed, in order to be fertilized or transferred.

In 2013, out of 64,447 ART cycles 85.4% were fresh cycles, 11.5% % embryo frozen/thawed cycles and 3.1% oocyte frozen/thawed cycles (**Figure 8**).

Figure 8: Type of ART cycles in Italy, 2013.



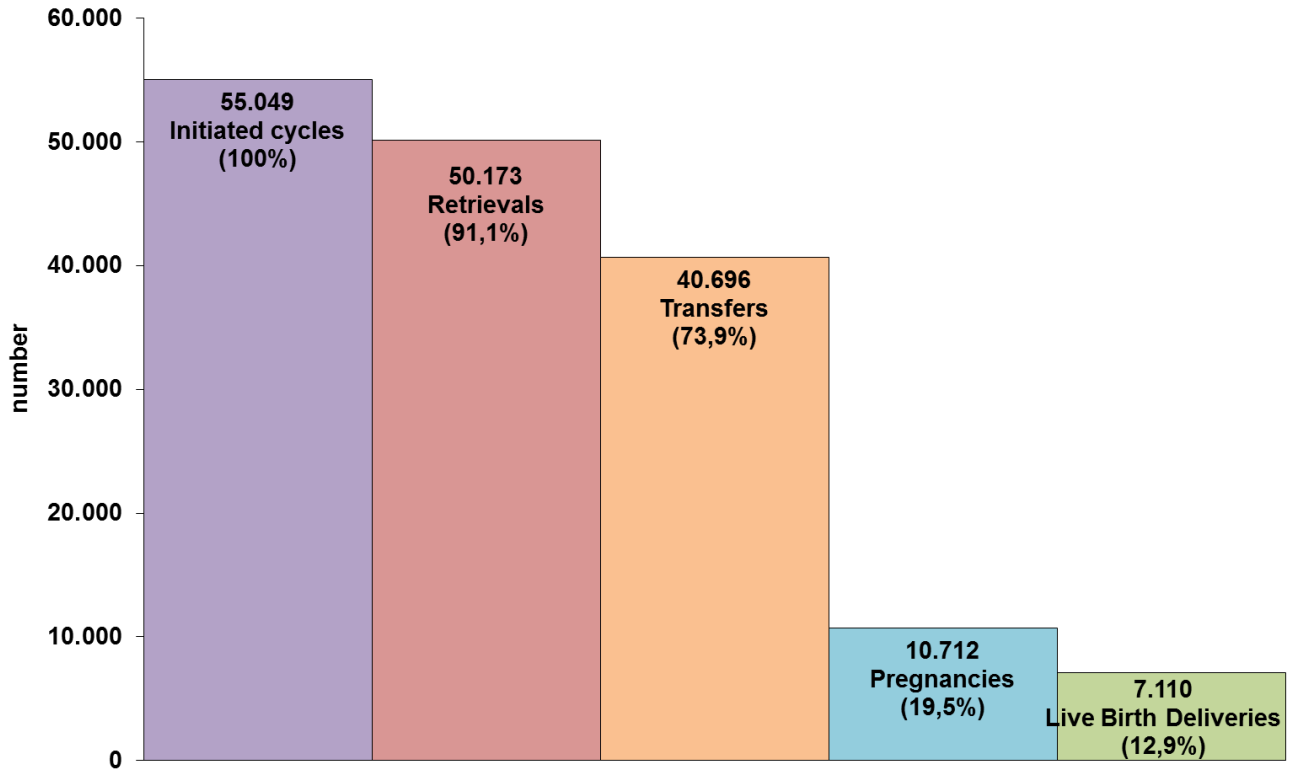
2.2.3. What are the steps for an ART treatment using fresh cycles?

An ART cycle using fresh gametes:

- begins when a woman initiates taking fertility drugs or having her ovaries monitored for follicle production. **(initiated cycle**)
- By a surgical procedure the eggs contained in the ovarian follicles are collected **(retrieval)**
- Sperm fertilize eggs in a dish with in vitro fertilization or ICSI. **(fertilization)**
- The embryo is transferred to the woman's womb **(transfer)**
- The embryo implant into the woman's womb **(implantation)**
- A clinical pregnancy occurs **(clinical pregnancy)**
- A live birth delivery occurs when at least one live born baby results from a delivery (**live birth delivery**)

In **Figure 9** outcomes resulting from various steps of fresh cycles performed in 2013 are shown. Of 55,049 fresh cycles, 91.1% resulted in egg retrievals, 73.9% in embryo transfers, 19.5% in pregnancies and 12.9% in live birth deliveries.

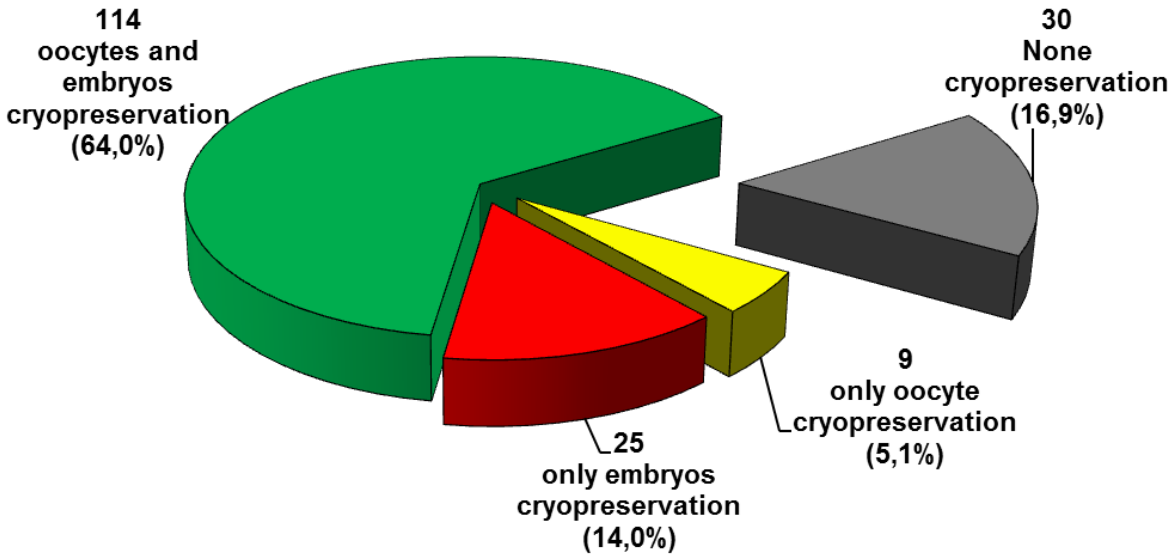
Figure 9: Outcomes of ART using Fresh cycles by stage, 2013.



2.2.4. How many centers cryopreserved embryos and/or oocytes in Italy?

In **Figure 10** the distribution of centers that have performed frozen cycles in 2013 is shown. Most of Italian centers (64.0%) performs oocyte or embryo cryopreservation whereas in 30 centers (16.9%) none cryopreservation cycle was carried out.

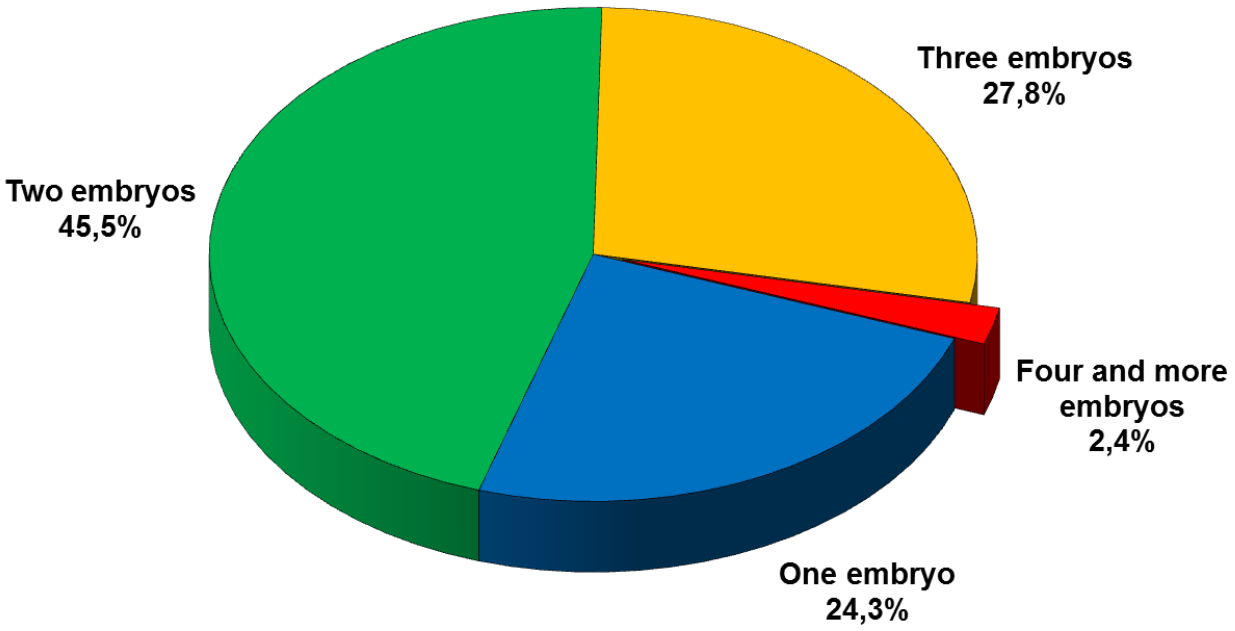
Figure 10: Distribution of centers (178) performed embryos and/or oocytes cryopreservation, 2013.



2.2.5. How many embryos are transferred in an ART procedure?

In **Figure 11** the number of embryos transferred per fresh cycle is shown (data 2013). Out of 40,696 transfers (73.9% of initiated cycles), 24.3%, of them were performed with a single embryo, 45.5% with two embryos and transfers with three embryos or more amounted nearly 30%.

Figure 11: Number of embryos transferred per each fresh cycles, 2013.

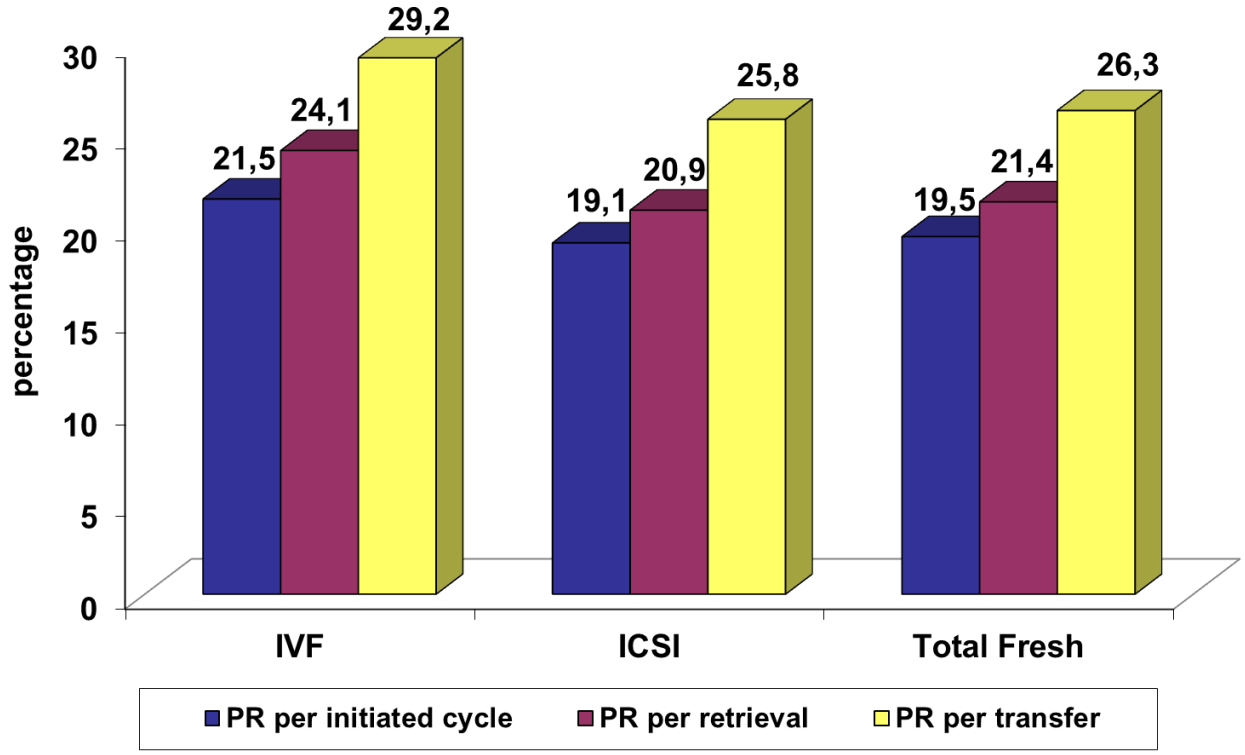


2.2.6. What is the percentage of initiated cycles, retrievals and transfers that results in pregnancies for Fresh cycles?

Pregnancy rates per initiated cycle, per retrieval and per transfer are shown in **Figure 12** (IVF and ICSI 2013). Overall, after IVF rates were significantly higher than following ICSI.

It should be noted that in the most cases patients underwent to IVF may have had a better prognosis.

Figure 12: Pregnancy Rates per initiated cycle, per retrieval and per transfer using IVF or ICSI procedure, 2013.

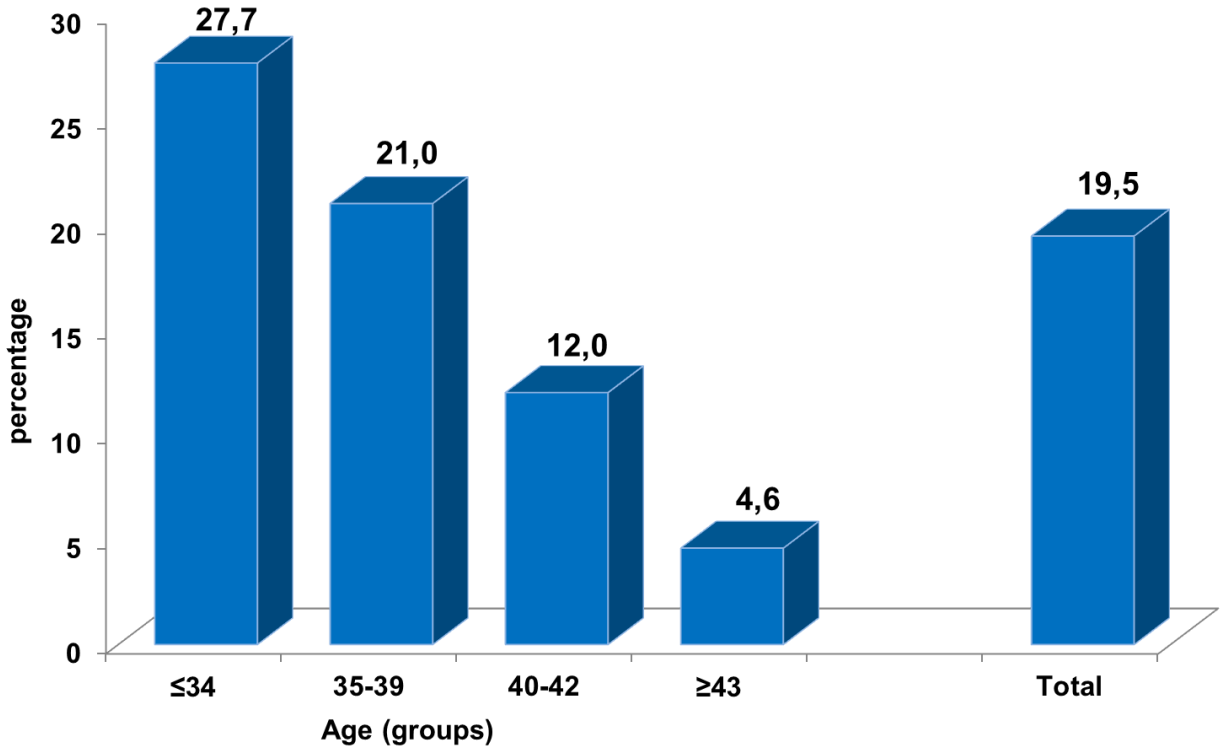


2.2.7. How percentages of Fresh cycles that result in pregnancies differ among women of different age groups?

The women's age is the most important factor predicting success during ART treatments.

In **Figure 13** pregnancy rates by woman age groups are represented (data 2013). As it is shown rates decreased as age increased.

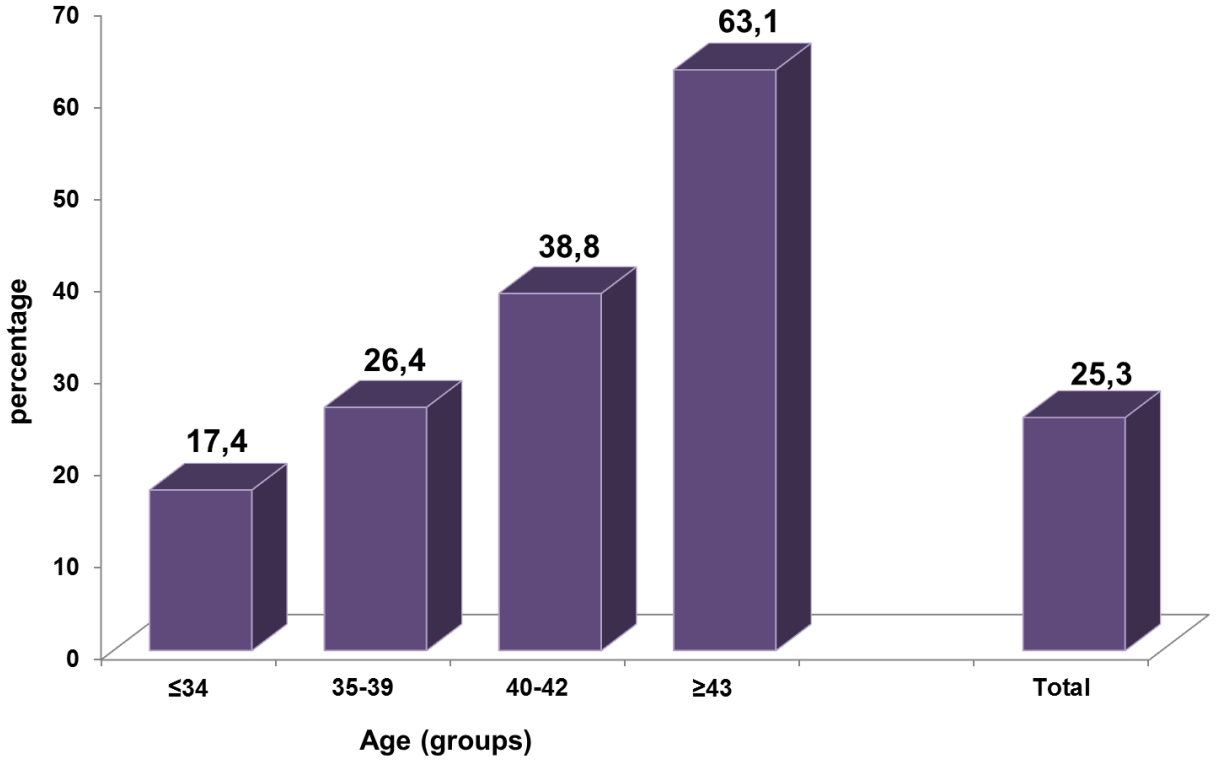
Figure 13: Pregnancy rate per initiated cycles using fresh cycles by age groups of female patients, 2013.



2.2.8. Does the risk of pregnancy losses differ among women of different age groups?

Woman age also increases the risk of negative pregnancy outcomes (spontaneous or therapeutic abortions and ectopic pregnancies). As it is shown in **Figure 14** rates of older age groups were much higher than those of youngers, i.e. 38.8% in 40-42 and 63% in over 43 years old vs. 17.4% in ≤ 34 and 26.4% in 35-39 years old.

Figure 14: Percentage of pregnancy loss using fresh cycles by age groups of female patients, 2013.

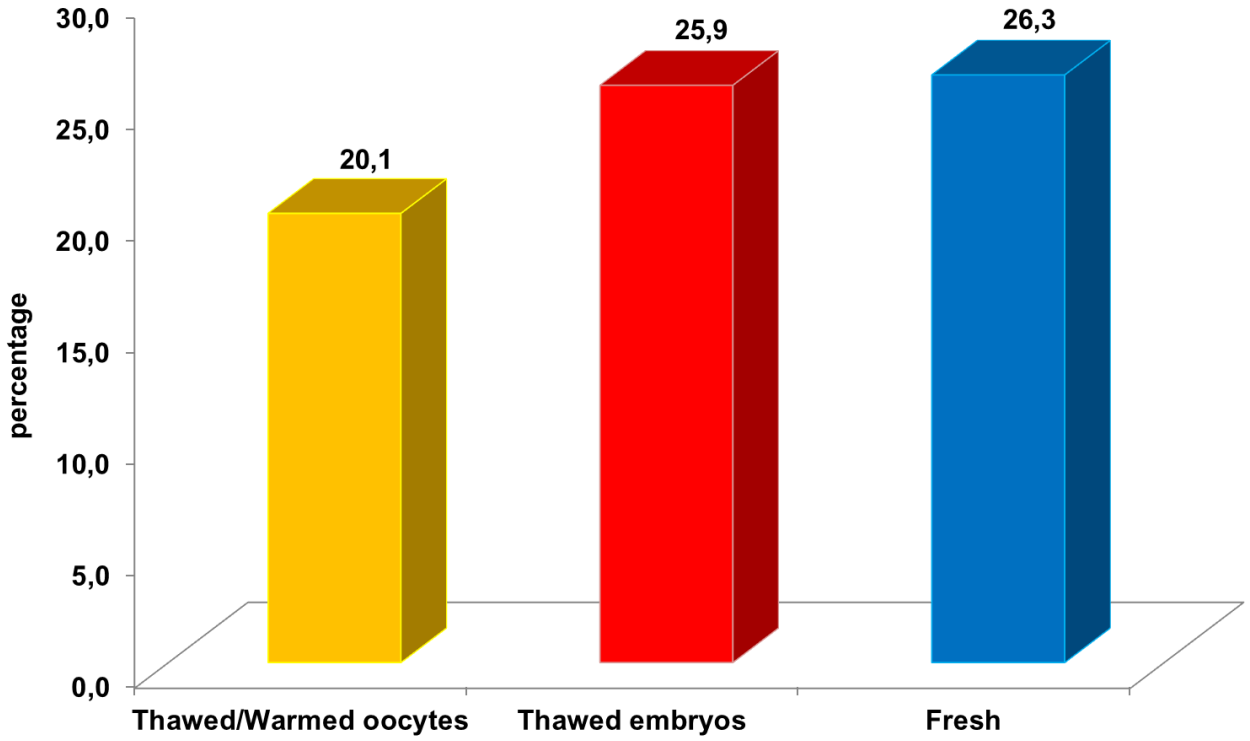


2.2.9. Which percentage of transfers result in pregnancies in ART cycles using frozen oocytes and frozen embryos vs. Fresh?

In 2013, 6,818 frozen embryo transfers (13.9% of all transfers) and 1,491 frozen oocyte transfers (3.0% of all transfers) have been performed.

In **Figure 15** pregnancy rates per transfer with frozen oocytes (20.1%) and embryos cycles (25.9%) were compared with those with fresh cycles (26.3%). This indicates that pregnancy success using frozen embryo is superimposable to that obtained with fresh oocytes.

Figure 15: Pregnancy rates per transfer with frozen oocytes (FOR), with frozen embryos (FER) cycles vs. fresh cycles, 2013.

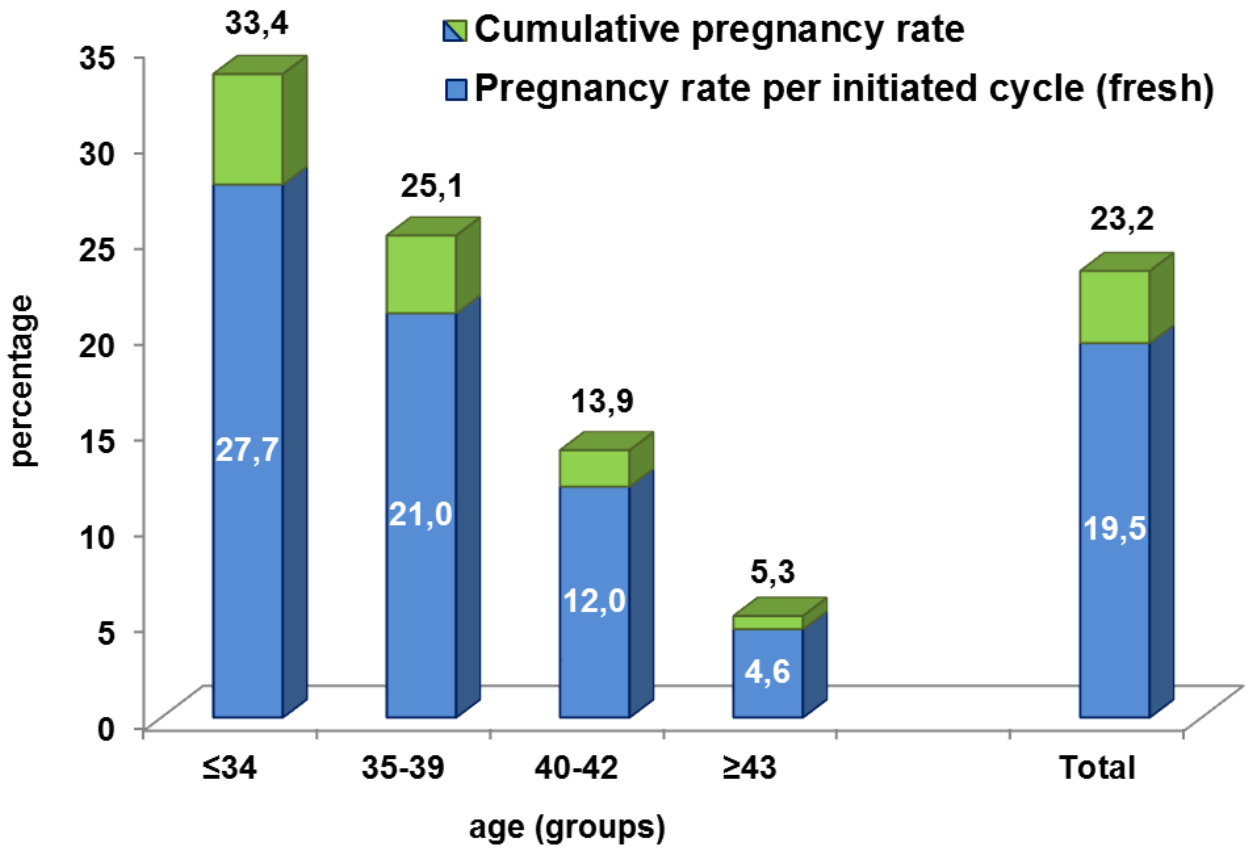


2.2.10. What is the Cumulative Pregnancy Rate?

Cumulative pregnancy rate is the overall chance of a birth, for instance, from the use of all fresh and frozen embryos from an IVF cycle, or from several cycles of treatment. To calculate cumulative pregnancy rate (CPR), individual instead that cumulative data collection would be needed. Unfortunately, IARTR as well as other Registries around the world collects information only in aggregated form. To overcome this limitations and calculate CPR using aggregated data, the number of pregnancy obtained either from fresh and frozen cycles were divided by the number of initiated cycles, per year. CPR may provide a broader view of pregnancies that are achieved in Italy, in a year of activity. Moreover, the comparison of pregnancy rates from fresh cycles vs. cumulative pregnancy rates may show the added value of embryo and oocyte cryopreservation and underline the importance of using supernumerary oocytes.

In **Figure 16** pregnancy rate per fresh cycle and cumulative pregnancy rate by woman age groups are shown. Overall, embryo and oocyte cryopreservation increased the chances of achieving a pregnancy per initiated cycle, of about 20%.

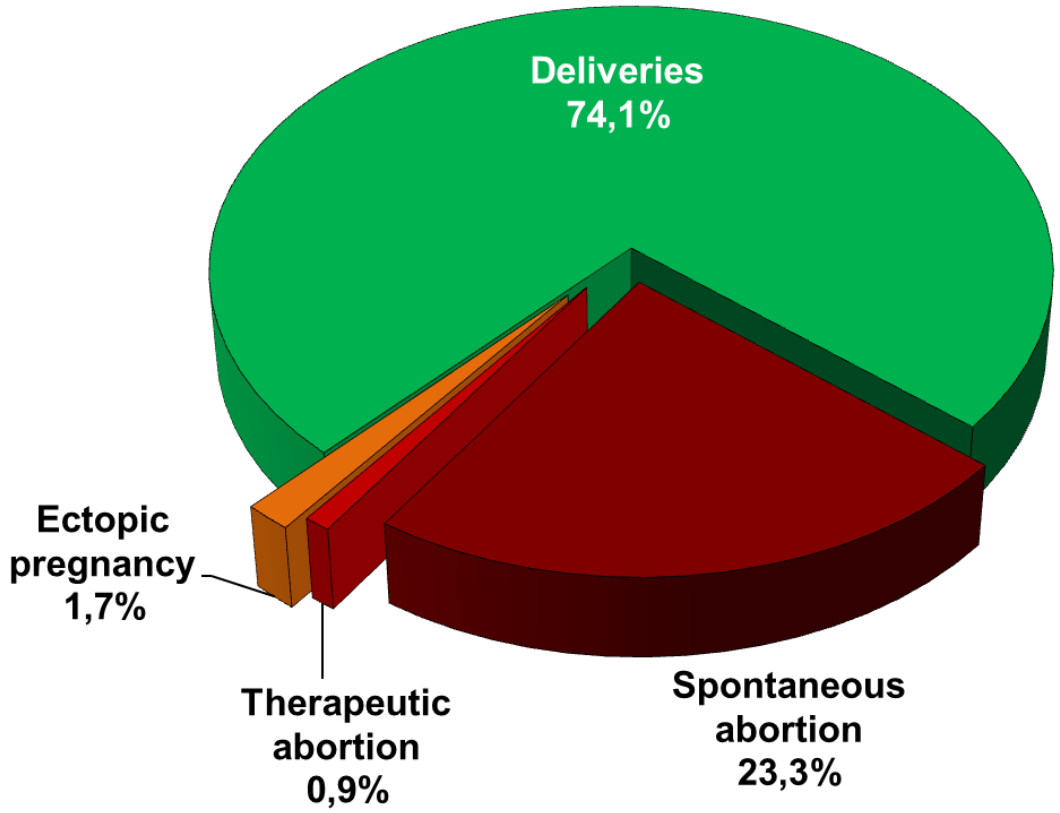
Figure 16: Pregnancy rate per initiated cycle for fresh and Cumulative Pregnancy Rate per initiated cycle, by age groups of female patients, 2013.



2.2.11. What percentage of ART monitored pregnancies result in deliveries?

In 2013, 12,775 pregnancies were obtained from both fresh and frozen embryo/oocyte cycles. Of the 11,461 monitored pregnancies, 8,495 end in deliveries (74.1%), 2,666 (23.3%) in miscarriages, 192 (1.7%) were ectopic pregnancies and 108 (0.9%) were therapeutic abortions.
The number of pregnancies lost to follow-up was 1,314 (10.3%), value close to the European average.
In 2013, 10,216 were babies born alive and 39 died at birth (0.4% out of all babies born).

Figure 17: Outcomes of monitored pregnancies from ART cycles using fresh, frozen embryos (FER) and frozen oocytes (FOR), 2013.



2.3. Trends 2005-2013.

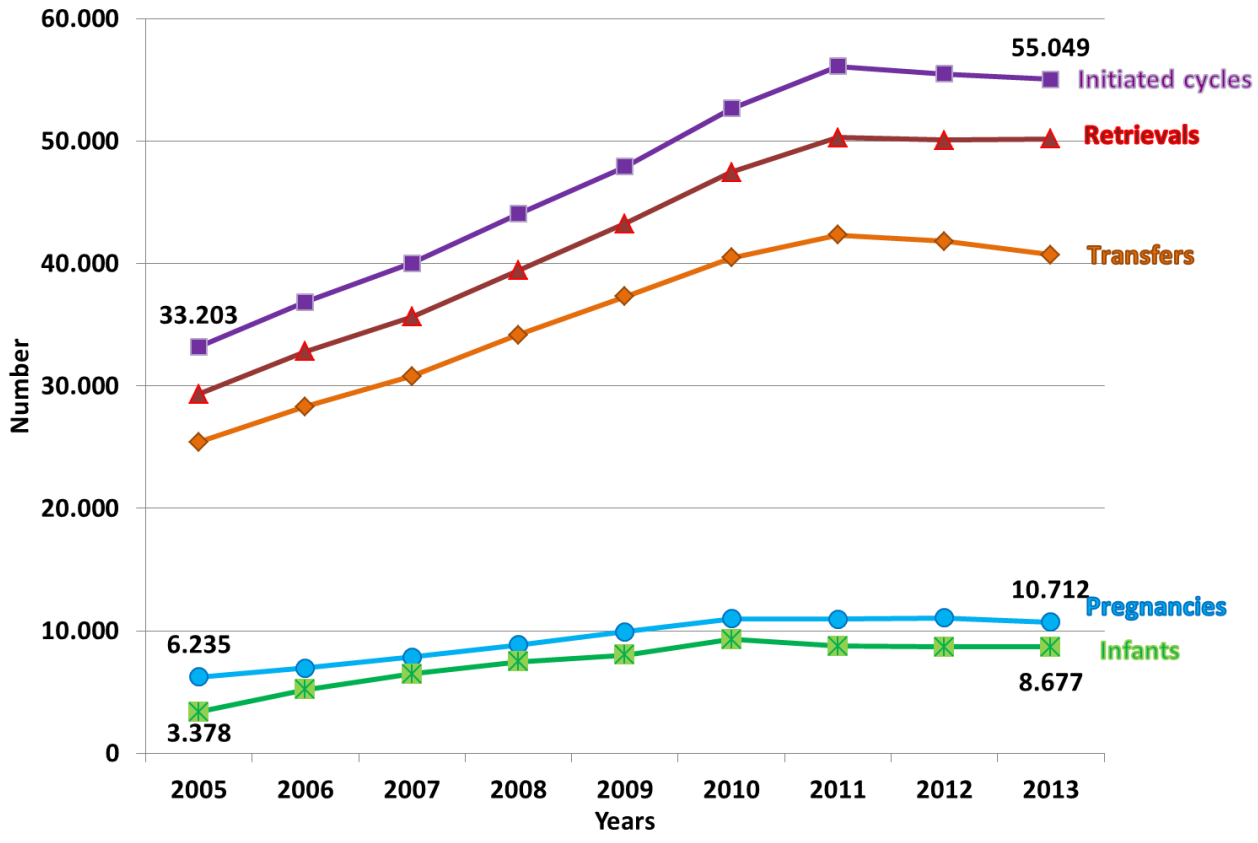
2.3.1. Is the use of ART increasing?

Figure 18 shows the number of cycle, retrievals, transfers, pregnancies and infants born using fresh cycles from 2005 to 2013.

The numbers of initiated cycles and pregnancies increased by 66% and 72%, respectively, over time. In detailed, from 33,203 cycles and 6,235 pregnancies in 2005 to 55,049 cycles and 10,712 pregnancies in 2013

The number of infants born after fresh cycles in 2013 was one a and half times higher than in 2005. However, data on infants must be considered with some caution because of pregnancy loss to follow-up that varied from 40% in 2005 to 10.3% in 2015.

Figure 18: Trend of the initiated cycles, retrievals, transfers, pregnancies and deliveries obtained from fresh cycles. Years 2005–2013.



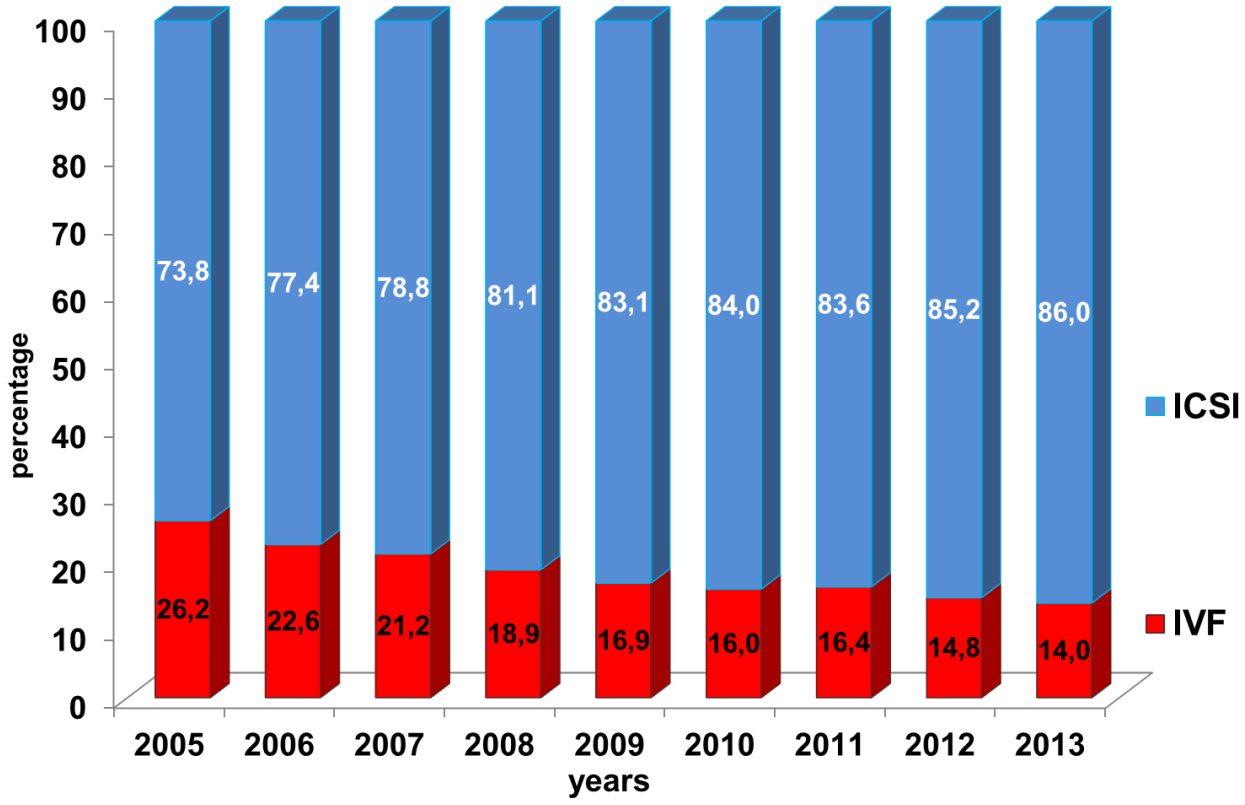
2.3.2. Did the use of ICSI increase respect to IVF?

Intra-cytoplasmic sperm injection (ICSI) was originally developed to improve fertilization rates with indication of severe male factor infertility. Today, this procedure is widely used even without a reported diagnosis of male factor infertility.

Figure 19 shows percentage of retrieval with fresh cycles performed using ICSI and IVF procedures from 2005 through 2013.

The number of ICSI cycles increased from 21,670 in 2005 to 43,165 in 2013, while IVF cycles decreased from 7,675 to 7,008. The proportion of ICSI retrieval increased from 73.8% in 2003 to 86.0% in 2013.

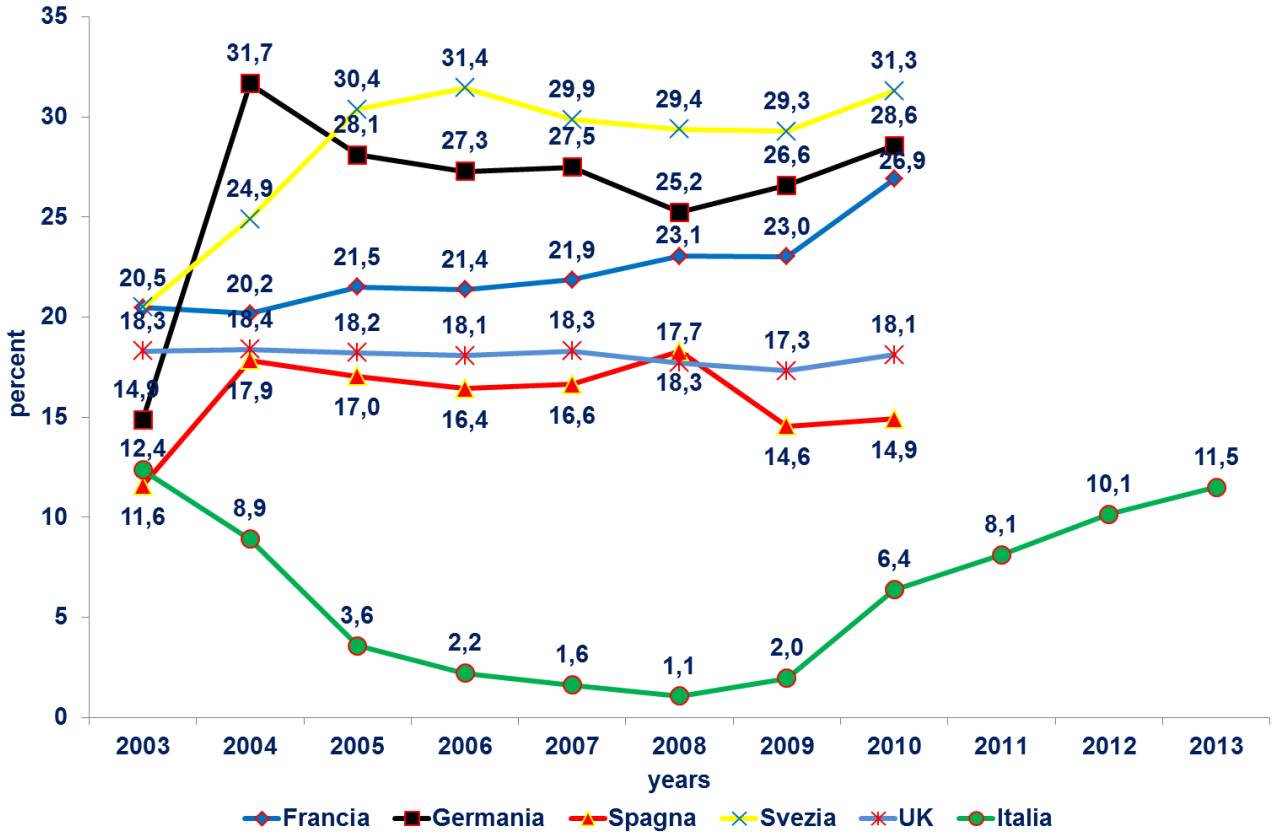
Figure 19: Trend of retrievals IVF versus ICSI. Years 2005-2013.



2.3.3. Did the use of FER procedure change over time?

In 2004 the Italian Parliament approved a restrictive law (40/2004) regulating ART. In 2009 Italian Constitutional Court removed some limitations set out in the law, including the practice of embryo freezing, now permitted under specific conditions. For this reason the use of FER has declined consistently after 2004. When the Constitutional Court changed rules the use of FER procedure steadily resumed. As it shown in **Figure 20** in 2003 (before the Law) number of FER cycles were very similar to those in 2013 (12.4% vs. 11.5%). In the comparison with some of the largest European countries, Italy showed the lowest number of FER cycles performed

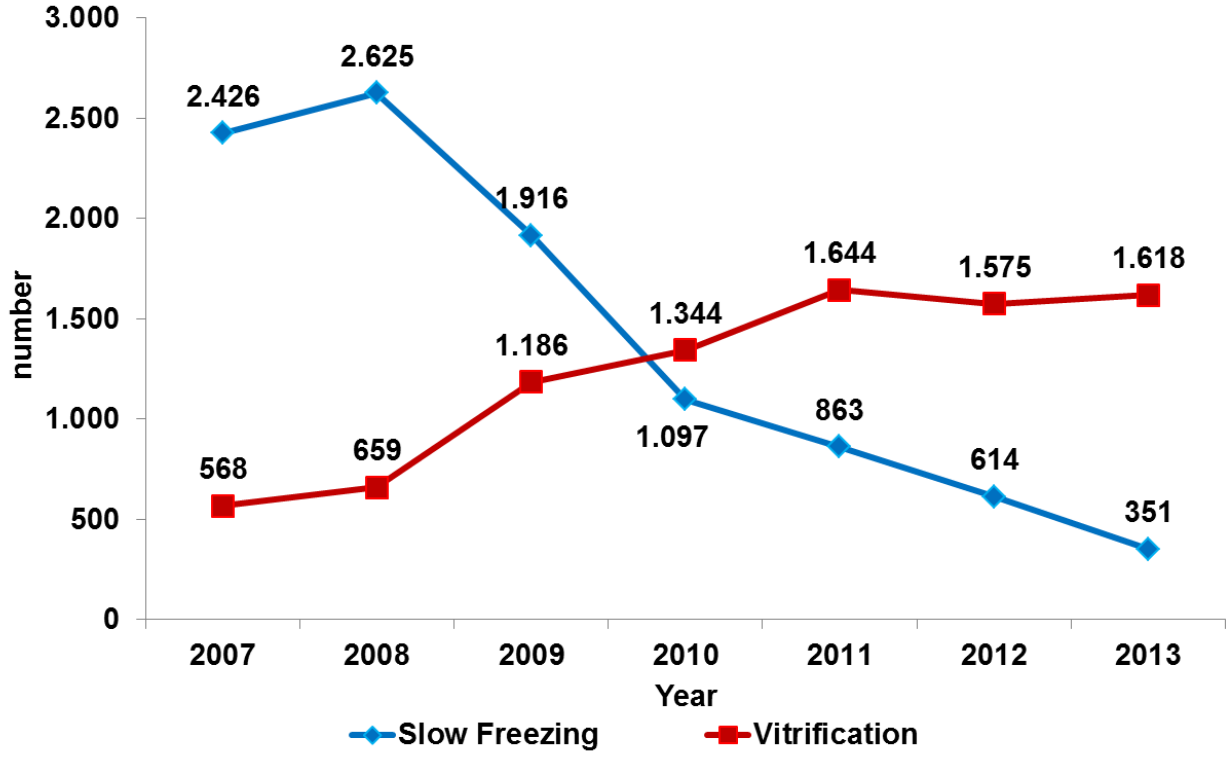
Figure 20: Trend of the application of FER procedures in Europe. Years 2003-2013.



2.3.4. Did the use of slow freezing and vitrification, in oocytes cryopreservation, changed over time?

When the Constitutional Court removed some restrictions from Italian Law on ART (2009), including embryo freezing procedure, in some specific conditions, the use of oocyte cryopreservation decreased. In detail, as it is shown in **figure 21,** slow freezing (SF) diminished over time while vitrification (VT) steadily increased (SF vs. VT from 2,426 vs. 568 cycles in 2007 to 351 vs. 1,618 in 2013)

Figure 21: Numbers of cycles performed by slow freezing or vitrification 2007-2013

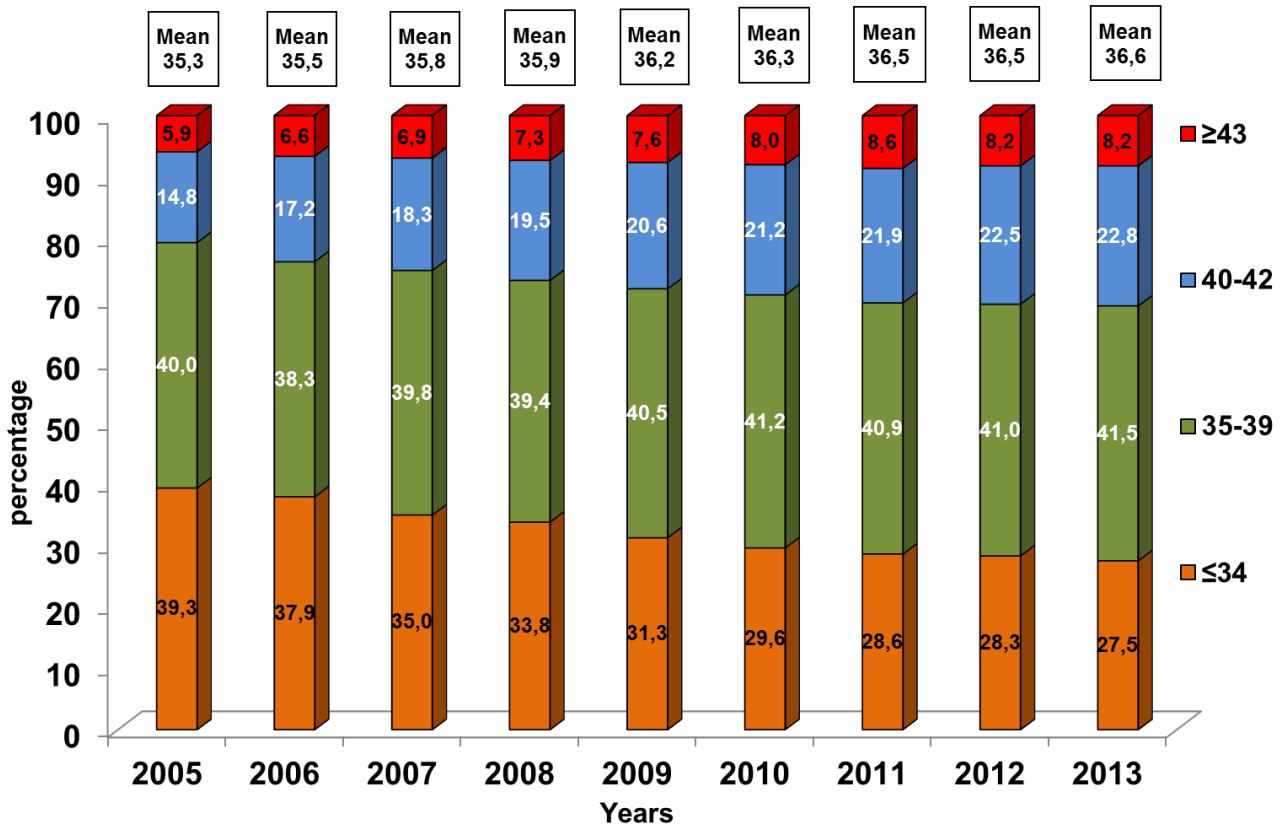


2.3.5. . Has the age of ART patients changed over time?

Figure 22 shows distribution of fresh cycles by women age groups, from 2003 to 2013.

For women aged 40-42 and older than 43 the percentage of fresh cycles increased from 14.8% and 5.9% in 2005 to 22.8% and 8.2% in 2013. The percentage of fresh cycles in women ≤34 years old decreased from 39.3% in 2005 to 27.5% in 2013. Overall, the mean age of women who had fresh cycles increase from 35.3 to 36.6 years.

Figure 22: Trend of the distribution of fresh cycles by age classes of female patients. Years 2005-2013.

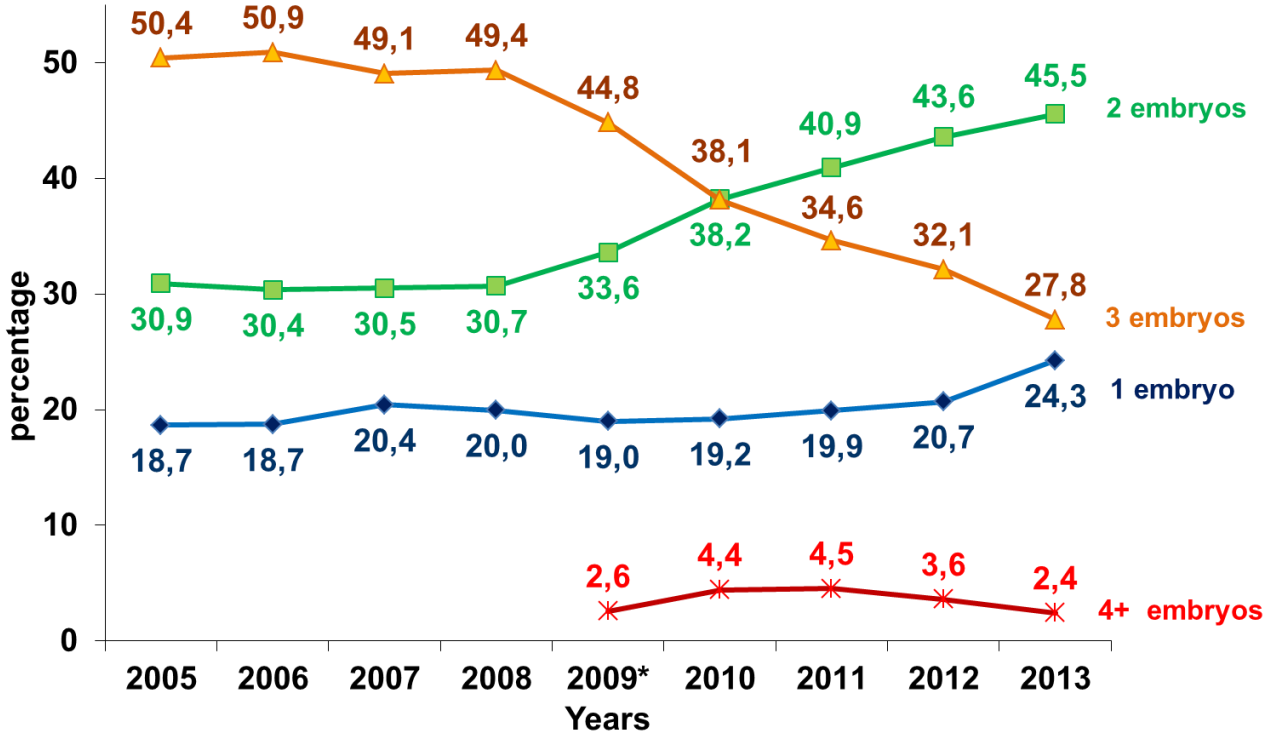


2.3.6. Has the number of embryos transferred changed in fresh cycles?

Figure 23 shows trends with the number of embryos transferred in fresh cycles.

From 2005 to 2013 cycles with one and two embryos increased from 18.7% and 30.9% to 24.3% and 45.5%, respectively. On the other hand transfers with 3 embryos dramatically decreased from 50.4% to 27.8%. As it shown in the **Figure 23** values of transfers with four or more embryos were available only from 2009, when Law 40/2004 changed the limit to transfer maximum three embryos. These values were quite stable during the time, from 2.6% in 2009 to 2.4% in 2013. The average number of embryos transferred decreased from 2.3 embryos per transfer in 2005 to 2.1 in 2013.

Figure 23: Trend of transfer by number of embryos transferred. Years 2005-2013.



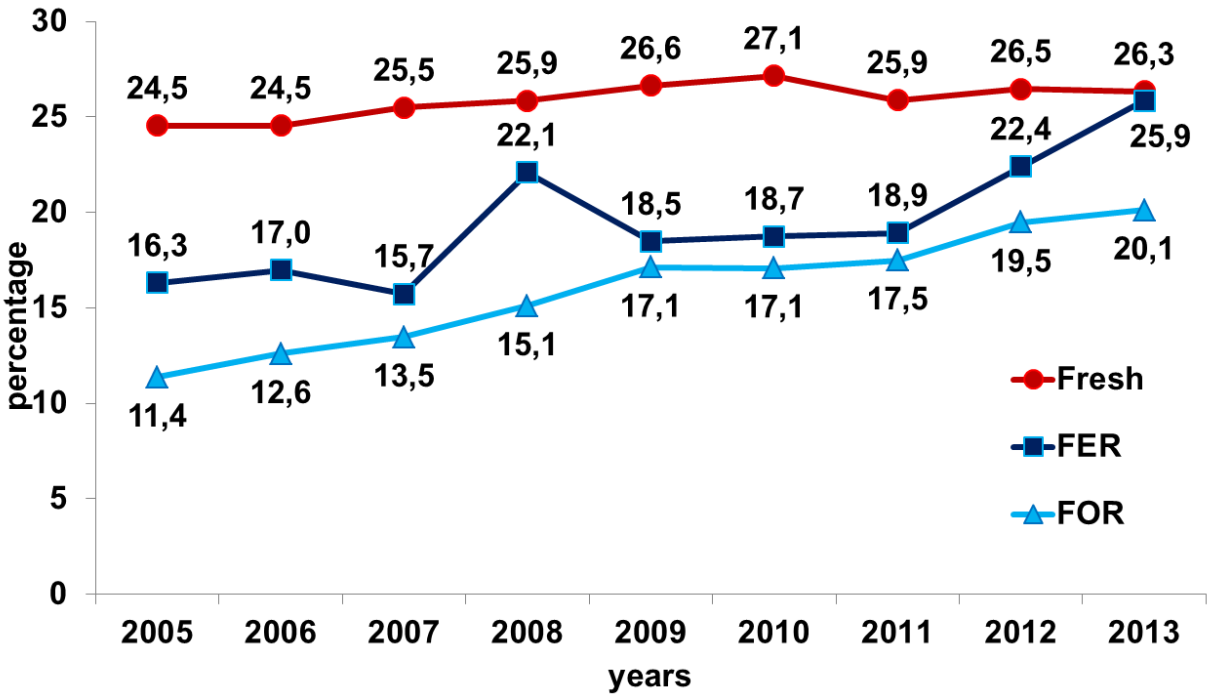
*year of the Costitutional Court sentence 151/2009.

2.3.7. Did pregnancy rates per transfer changed during the time among different ART procedures ?

Figure 24 shows pregnancy rates per transfer in order to compare cycles with fresh oocytes vs. those using frozen embryos (FER) or frozen oocytes (FOR).

Overall, fresh cycles showed the best rates increasing from 24.5% in 2005 to 26.3% in 2013, those with frozen embryos increased from 16.3% to 25.9%, and those with frozen oocytes from 11.4% to 20.1%.

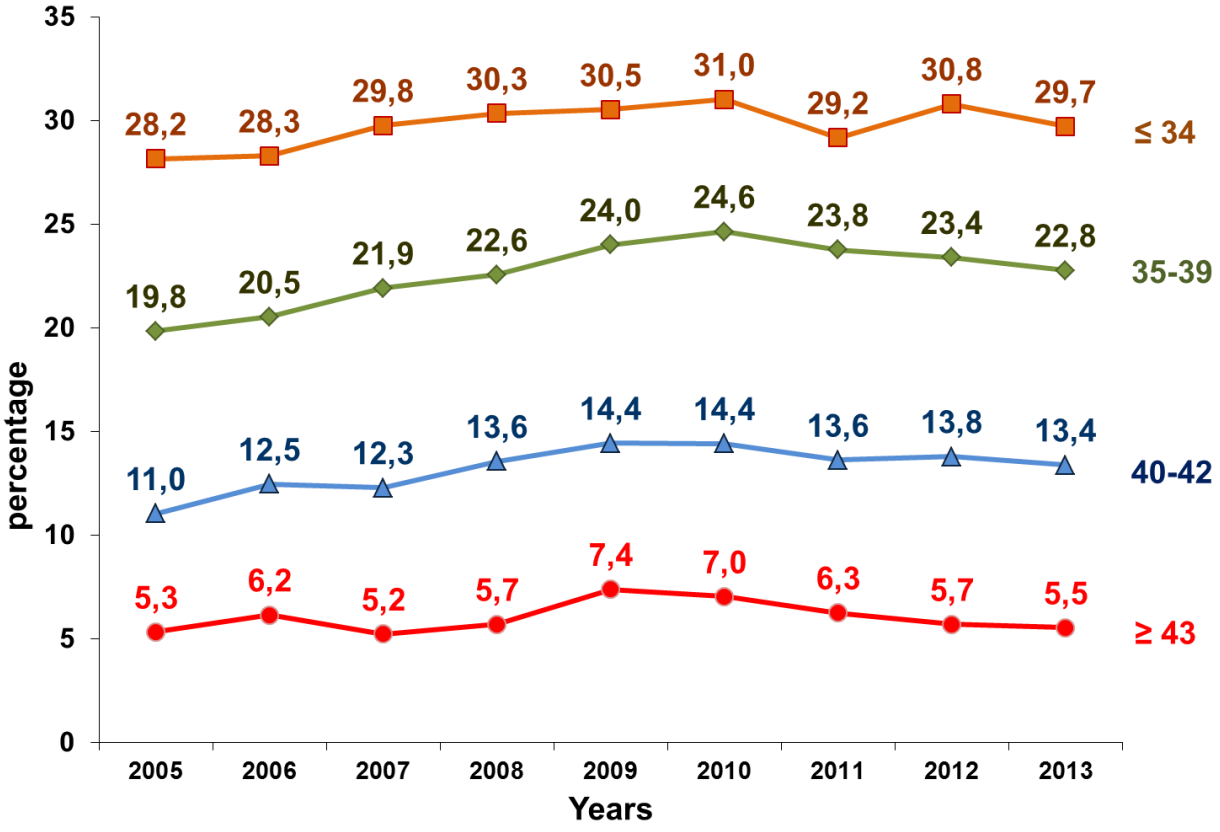
Figure 24: Trend of pregnancy rate per transfer for fresh, thawed embryos (FER) and thawed/warmed oocytes cycles (FOR). Years 2005-2013.



2.3.8.Did pregnancy rates per retrievals change across age groups?

Figure 25 shows pregnancy rates per retrieval according to women age groups, after fresh cycles. From 2003 to 2013 pregnancy rates per retrieval increased from 28.2% to 29.7% for women aged less than 34, from 19.8% to 22.8% for women aged 35-39 and from 11.4% to 13.4% for women aged 40-42. Percentages are fairly stable concerning women aged more than 42 years.

Figure 25: Trends of pregnancy rate per retrievals with fresh cycles by age group of female patients. Years 2005-2013.

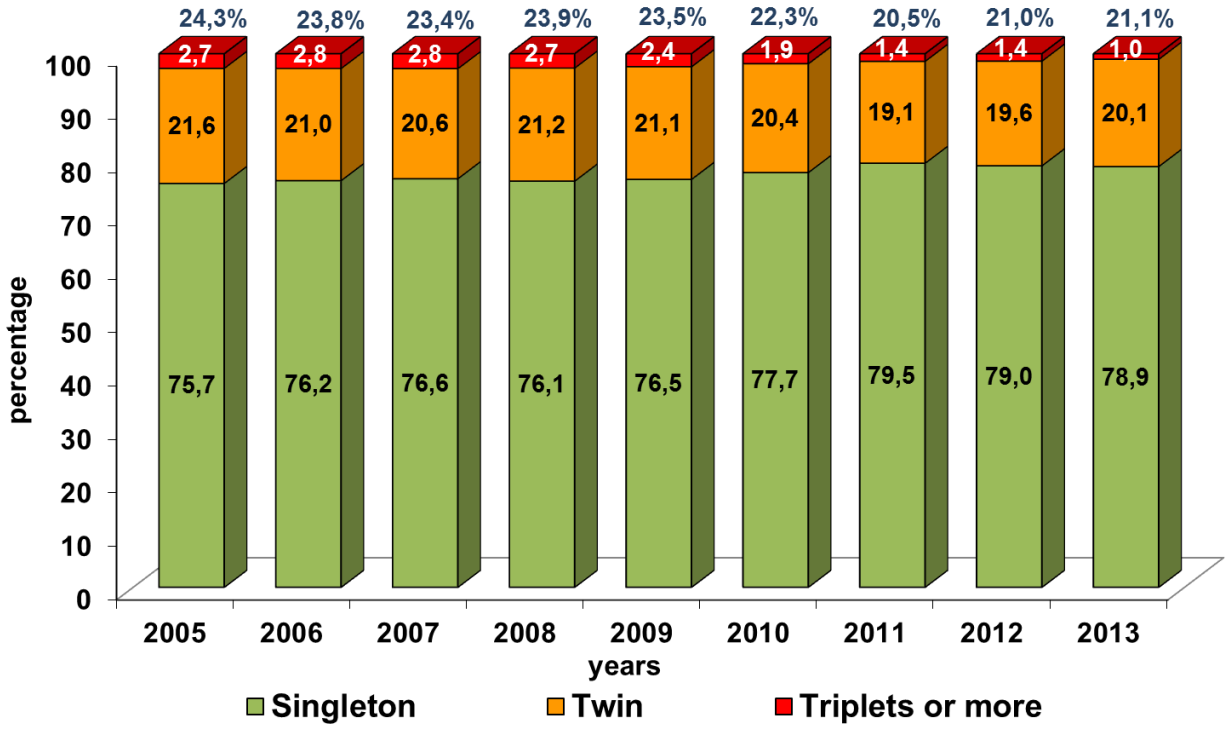


2.3.9. Did percentages of singletons, twins and triplets or more deliveries change for fresh cycles?

Figure 26 shows trends for singleton and triplet deliveries in fresh cycles.

From 2005 to 2013 twin delivery rates decreased from 21.6% to 20.1% while numbers of triplets and more deliveries decreased from 2.7% to 1%, reaching the average value in Europe, as reported in 2010 EIM data.

Figure 26: Trends of multiplicity of deliveries from fresh cycles. Years 2005-2013.



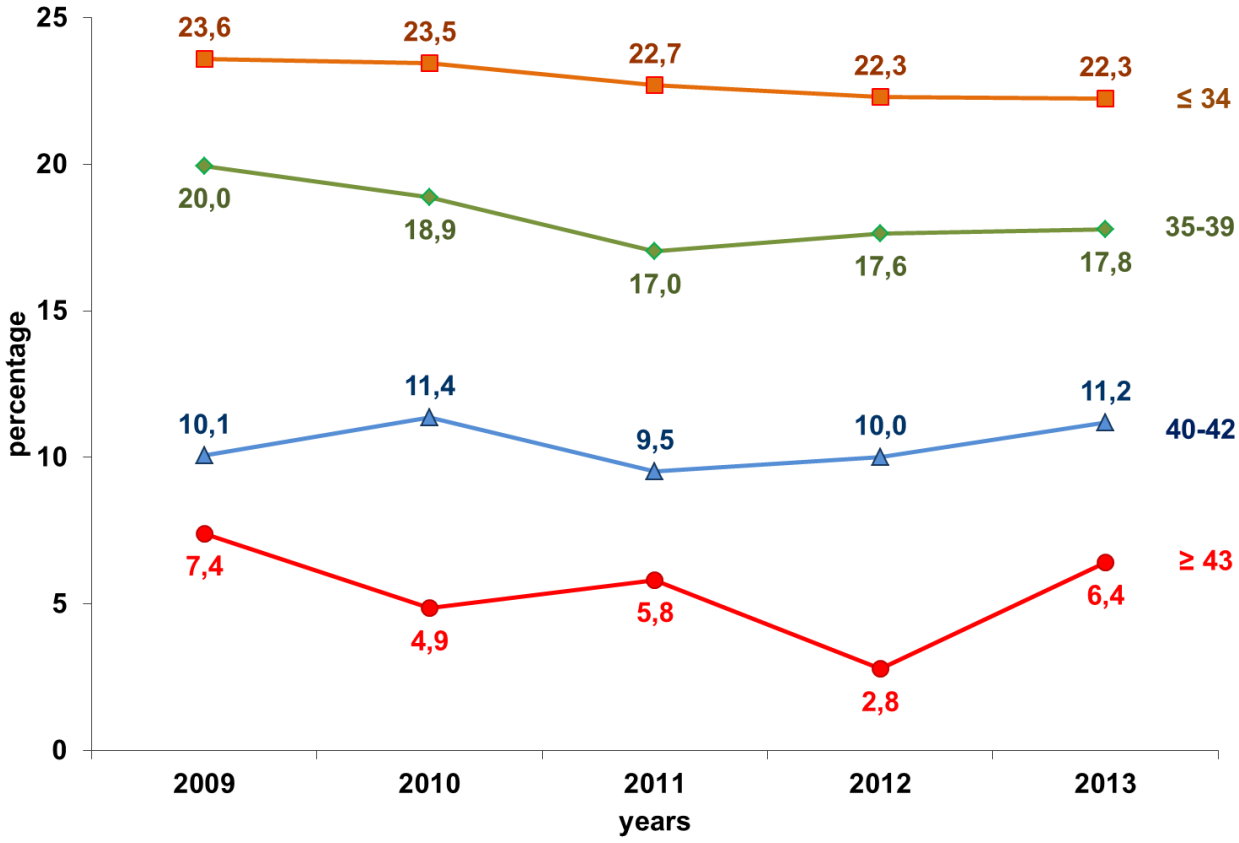
2.3.10. Did percentages of twin deliveries after ART cycles change across age groups?

Figure 27 shows the percentages of twin deliveries by woman age groups for ART cycles.

The percentage of twin deliveries decreased by 5.5% in women aged less than 35 years, by 11% for women aged 35-39 and by 13.5% for women aged more than 42 years.

Data on older women (>42 years old) need to be interpreted carefully taking into account that percentages are calculated on small number of cycles.

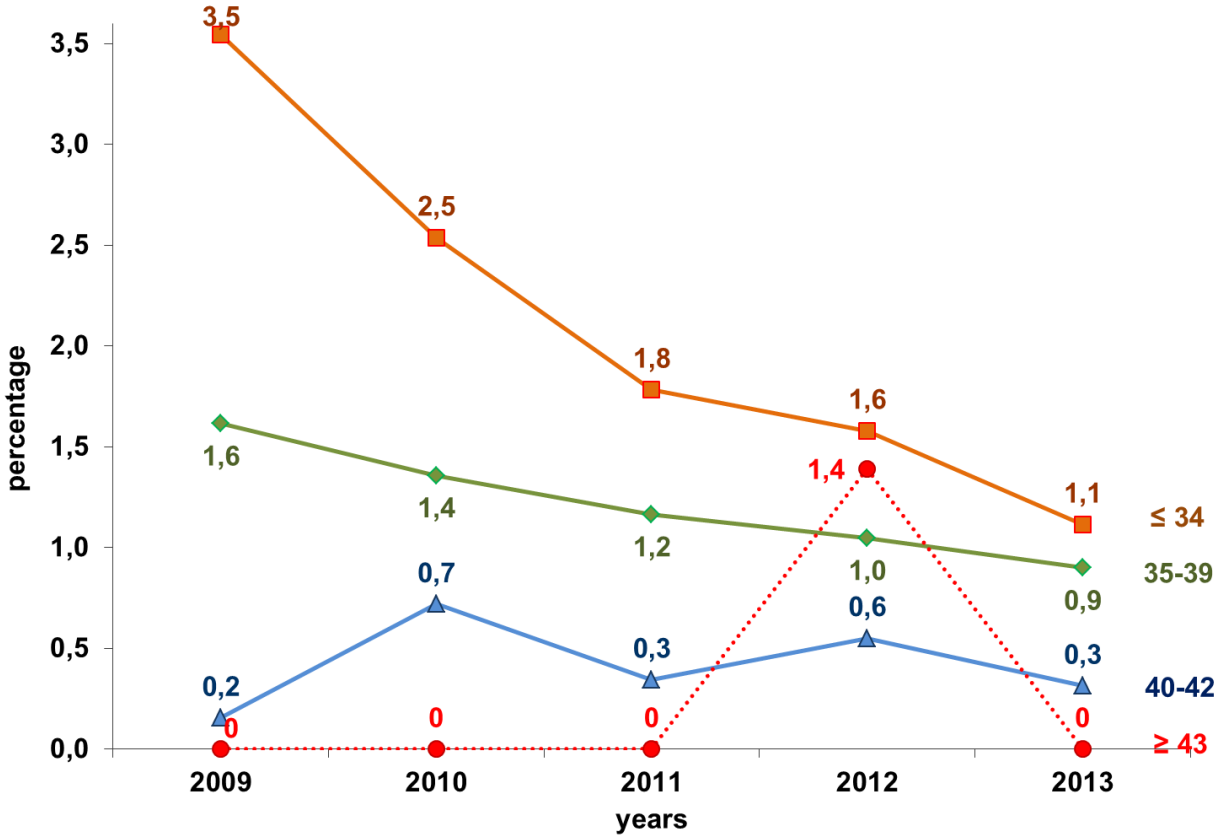
Figure 27: Trend of twin deliveries from ART, by age groups of female patients. Years 2009-2013.



2.3.11.Did percentages of triplets deliveries or more after ART cycles change across age groups?

Figure 28 shows percentage of triplets and more deliveries by woman age groups, for ART cycle. Since 2009 percentage decrease by 68% for women aged less than 35 years and by 43% for women aged 35-39. Percentages for women aged 40-42 and more than 42 need to be interpreted cautiously because of the small number of cycles performed.

Figure 28: Trend of the percentage of triplet or more deliveries from ART by age groups of female patients. Years 2009-2013.



2.3.12. Did percentages of H-IUI and ART live-born babies change over time?

Figure 29 shows percentages of live-born babies conceived by ART were compared with the national births in Italy. From 2003 to 2013 the percentage infants born with ART procedures increased 3 times and with H-IUI by 65% .

Since its establishment, IARTR collected data on 91,215 infants, of which 72,004 from ART and 19,211 from H-IUI cycles, nevertheless, for the analysis of these data some caution may be required because of the number of pregnancies lost to follow-up that changed from 40% in 2005 to 10.3% in 2013.

Figure 29: Trends of the percentage of ART infants live born babies respect to the national births in Italy. Years 2005-2013.