



EXECUTIVE SUMMARY

IARTR - ITALIAN ASSISTED REPRODUCTIVE TECHNOLOGY REGISTER

**MONITORING THE ACTIVITY AND
OUTCOMES OF ITALIAN ART
CENTERS IN 2014.**

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Downloadable at: <http://www.iss.it/rpma>

Summary outputs generated from IARTR, 2014

	Non-donor Procedures				Gametes/embryo donation		
	IVF	ICSI	FER	FOR	Semen Donation	Egg Donation	Cryopreserved Embryos
N° Initiated cycles	7.695	48.010	9.501	1.639	42	133	34
N° Aspirations	6.898	43.896	-	-	-	-	-
N° Transfers	5.622	34.146	8.851	1.295	33	122	34
<i>with 1 embryo</i>	<i>1.173</i>	<i>9.107</i>	<i>4.676</i>	<i>344</i>	<i>10</i>	<i>16</i>	<i>8</i>
<i>with 2 embryos</i>	<i>2.880</i>	<i>15.665</i>	<i>3.315</i>	<i>688</i>	<i>12</i>	<i>59</i>	<i>17</i>
<i>with 3 embryos</i>	<i>1.426</i>	<i>8.594</i>	<i>814</i>	<i>255</i>	<i>11</i>	<i>47</i>	<i>9</i>
<i>with 4 o + embryos</i>	<i>143</i>	<i>780</i>	<i>46</i>	<i>8</i>	<i>-</i>	<i>-</i>	<i>-</i>
N° Pregnancies	1.602	9.232	2.448	273	12	57	18
Pregnancy per Initiated cycles/thawings (%)	20,8	19,2	25,8	16,7	28,6	42,9	52,9
Pregnancy per Transfer (%)	28,5	27,0	27,7	21,1	36,4	46,7	52,9
N° Pregnancies lost to follow-up	132	1.160	135	19	4	13	6
N° Pregancies losses	350	1.915	566	75	1	9	5
Pregnancy loss (%)	23,8	23,7	24,5	29,5	1/8	20,5	5/12
N° Deliveries	1.120	6.157	1.747	179	7	35	7
Twin deliveries (%)	20,0	19,7	9,8	12,3	1/7	22,9	1/7
Triplets or more deliveries (%)	0,9	1,3	0,3	-	-	-	1/7
N° Live born babies	1.358	7.490	1.929	199	8	43	10

N.B.: When fewer than 20 cycles or outcomes (transfers, pregnancies or deliveries) are reported in a given category, the rates are shown as fractions rather than percentages.

THE ITALIAN ASSISTED REPRODUCTION TECHNOLOGY REGISTER (IARTR)

The ART National Register has been established at the Istituto Superiore di Sanità (National Institute of Health), National Centre for Epidemiology Surveillance and Health Promotion, by a Decree 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 descriptive, technical, structural and organizational information of ART centers authorized to conduct ART, and anonymous, aggregate data sets on all the ART treatments, plus information on the infertile couples, on embryos created and on children born after ART. application

Main objectives of the Register are: ASSESS and REGISTER all the centres performing ART treatments and IUI procedures in the country and 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 and activity, 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 prepares an annual epidemiological/statistical report on the ART center's activity for the Minister 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.

HOW DOES IARTR WORK?

The staff is coordinated by Dr. Giulia Scaravelli, MD-Gynaecologist. In the staff there are a variety of skills: statistics, epidemiology, gynaecology, biology, sociology and informatics.

Data on efficacy, safety and outcomes of reproductive techniques including -IUI are collected on a web site on a reserved area with a username and a password. Data collection, it is based on summary data sent from each centre according to a national law on privacy protection (Dlgs 196/2003). The collection it is organized in two different times frames, according to treatments and treatments outcomes.

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 IARTR WEB SITE

WWW.ISS.IT/RPMA

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

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 ART and -IUI techniques and their application in Italy. They can find also the links to patient associations, scientific reproductive societies, government institutions, national health service, European and international registries on ART; moreover there is a lot of information to better understand problems related to infertility matters, news on reproductive and infertility issues, and a constant view on Italian and European 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.
- A service for all 20 Italian Regions: They can see all the data relating the centres operating on their territory and they can monitor and elaborate data on their specific activity

The Registry's website was visited last year by approximately 70.000 users, with a daily average of about 190 hits, and is the second most visited site in the National Institute of Health Portal

1. ACCESS AND UTILIZATION OF ART SERVICES IN ITALY, 2014

1.1. Access to ART service

In **Figure 1** the regional distribution of ART centers is represented.

The largest number of ART centers is concentrated in Southern Italy (74 centers, 37% of the total) and in the Central area (49 centers, 24.5% of the total), irrespective of the amount of their activity.

Figure 1: Regional distribution of the ART active centers, 2014. Total = 200 centers

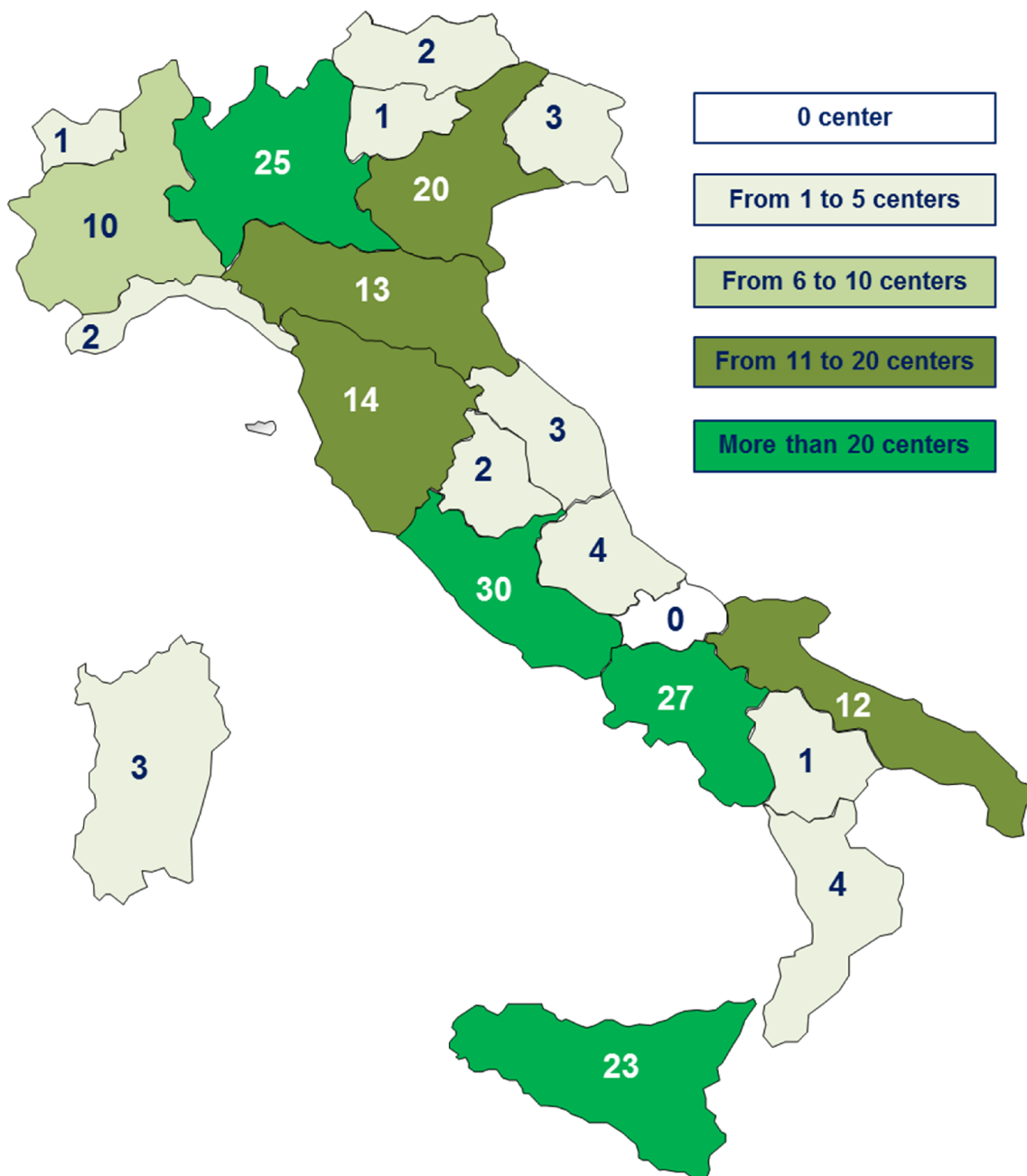


Table 1 shows the geographical distribution of ART centers according to the type of services offered. Overall, the number of centers active in 2014 was 200, 93 of which (46.5%) operating within the National Health Service (public and private), and 107 (53.5%) which provided only private service.

The majority of ART centers providing public service was concentrated in the North of Italy, i.e. in the North West 76.3%, while in the Centre and in the South there were mainly private facilities (57.1% and 67.6%, respectively).

Table 1: ART centers distribution by region and type of service, 2014.

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	25	13	52.0	9	36.0	3	12.0
Liguria	2	2	100	0	-	0	-
Northwest	38	19	50.0	10	26.3	9	23.7
P.A. Bolzano	2	1	50.0	0	-	1	50.0
P.A. Trento	1	1	100	0	-	0	-
Veneto	20	8	40.0	0	-	12	60.0
Friuli Venezia Giulia	3	2	66.7	1	33.3	0	-
Emilia Romagna	13	6	46.2	0	-	7	53.8
Northeast	39	18	46.2	1	2.6	20	51.3
Toscana	14	4	28.6	6	42.9	4	28.6
Umbria	2	1	50.0	0	-	1	50.0
Marche	3	2	66.7	0	-	1	33.3
Lazio	30	6	20.0	2	6.7	22	73.3
Central	49	13	26.5	8	16.3	28	57.1
Abruzzo	4	2	50.0	0	-	2	50.0
Molise	0	-	-	-	-	-	-
Campania	27	8	29.6	0	-	19	70.4
Puglia	12	3	25.0	0	-	9	75.0
Basilicata	1	1	100	0	-	0	-
Calabria	4	0	-	0	-	4	100
Sicilia	23	7	30.4	0	-	16	69.6
Sardegna	3	3	100	0	-	0	-
South and Islands	74	24	32.4	0	-	50	67.6
Italy	200	74	37.0	19	9.5	107	53.5

1.2.Utilization of ART services

In **Table 2** the trends of ART initiated cycles per million inhabitants and per million women of reproductive age (between 15 and 45 years) are shown in comparison with the same indicators in Europe. In Italy, both the indicators were constantly growing, with an increase of 466 cycles (+ 73.3%) and of 3,172 cycles (+ 118.2%), respectively.

The latest European data available, published in June 2016, refers to the activity of year 2012. The number of started cycles per million inhabitants (calculated only for the 18 countries that have reported data of 100% of the centers) was 1,252 cycles vs. 1,078 in Italy.

Table 2: Number of initiated ART cycle per million inhabitants and per million women of reproductive age (15-45 years) annually in Italy (2005-2014) and in Europe (2005-2011).

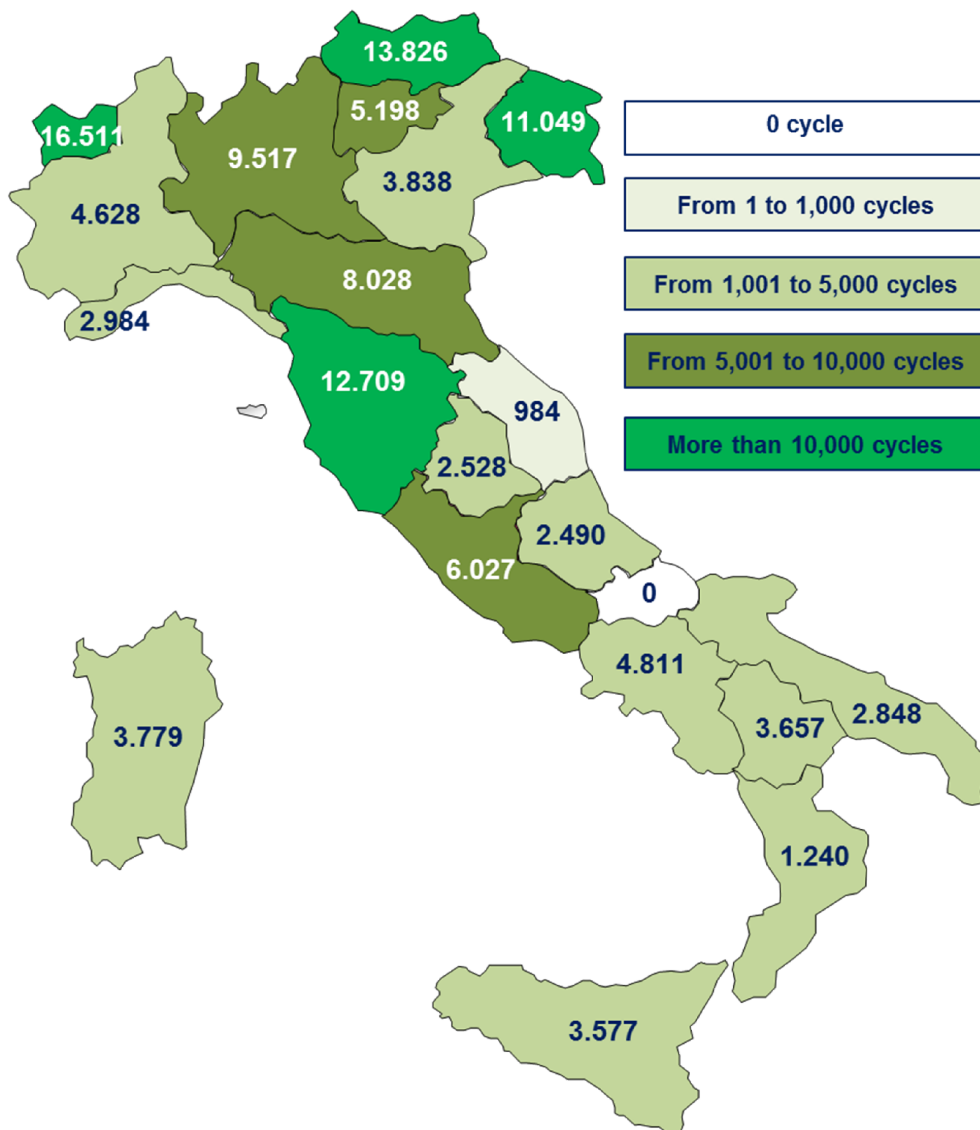
Years	ART Cycles/million population		ART cycles/million women (15 - 45 years)	
	Italy	Europe ^a	Italy	Europe ^a
2005	636	1,115	2,683	4,008
2006	692	850	3,328	3,503
2007	736	886	3,569	4,320
2008	800	947	3,905	4,661
2009	865	1,067	4,265	5,455
2010	973	1,221	4,863	6,258
2011	1,063	1,269	5,392	6,556
2012	1,078	1,252	5,562	6,519
2013	1,070	-	5,601	-
2014	1,102	-	5,855	-

a: Data for Europe refers only to those country where data coverage was 100% in every year.

b: In 2005 ART cycles are related to the number of women aged between 15 and 49 years.

In **Figure 2** the distribution of initiated cycles per million women of childbearing age per geographical region is represented. As it is shown there is a great difference in the number of cycles performed among regions ranging from 16,511 cycles offered in Valle d'Aosta to 984 cycles provided in Marche (in small regions it depends on the small number of women living there). In general, most of the region in Northern and Central area have numbers above the national average (5,855 cycles), while the majority of regions in Southern area have numbers below the average.

Figure 2: Regional distribution of the number of initiated ART cycles per million women of reproductive age (15-45 years)*, 2014.

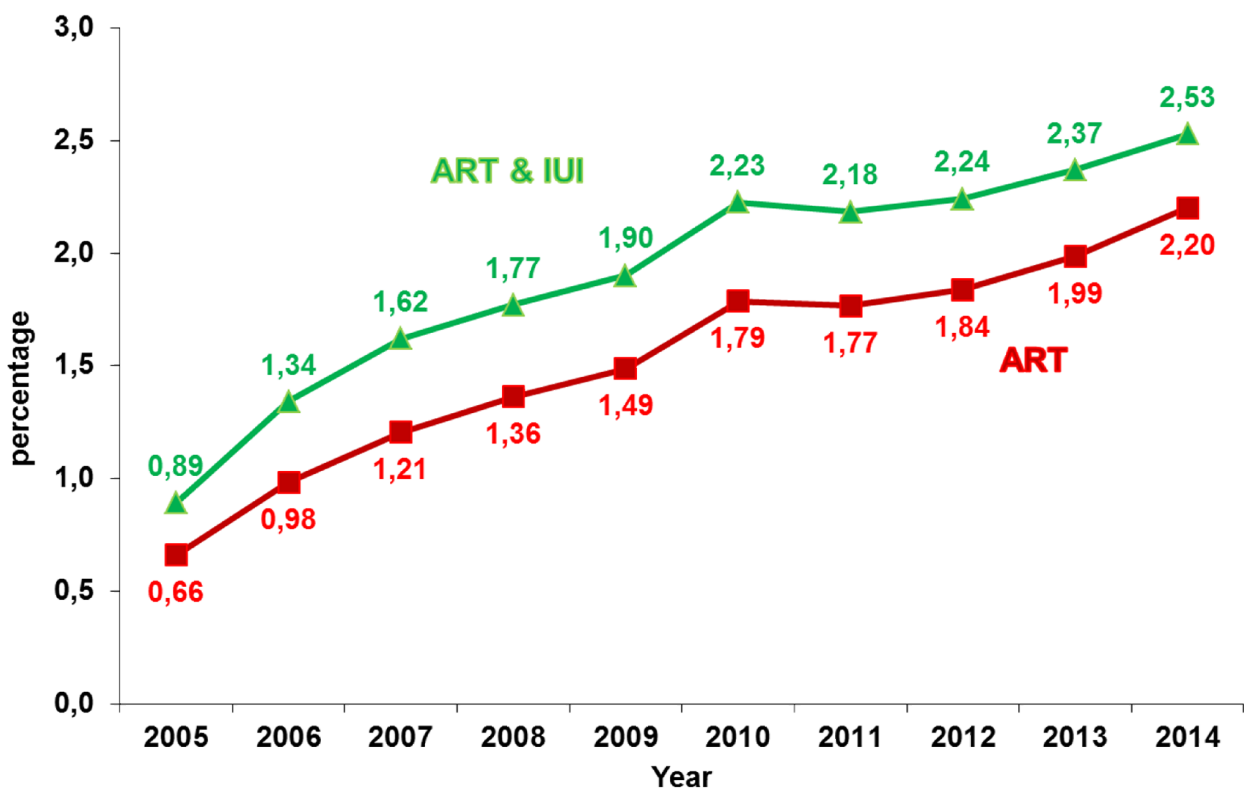


*Average resident population in 2014: Source ISTAT.

Figure 3 shows the percentages of live-born babies conceived by ART compared with the national total number of children born in Italy. From 2005 to 2014 the percentage of infants born with ART procedures increased 3 times.

Since its establishment, IARTR collected data on 103,935 infants, of which 83,041 from ART and 20,894 from IUI cycles. For the analysis of these data some caution may be required because of the proportion of pregnancies lost to follow-up, that however changed to the better: from 41% in 2005 and 21.5% in 2006 to 10.7% in 2014.

Figure 3: Trends of the percentage of ART live born babies in relation to annual national number of children born in Italy, 2005-2014.



2.EFFICACY OF ART AND TIME TRENDS

2.2. ART non-donor cycles.

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

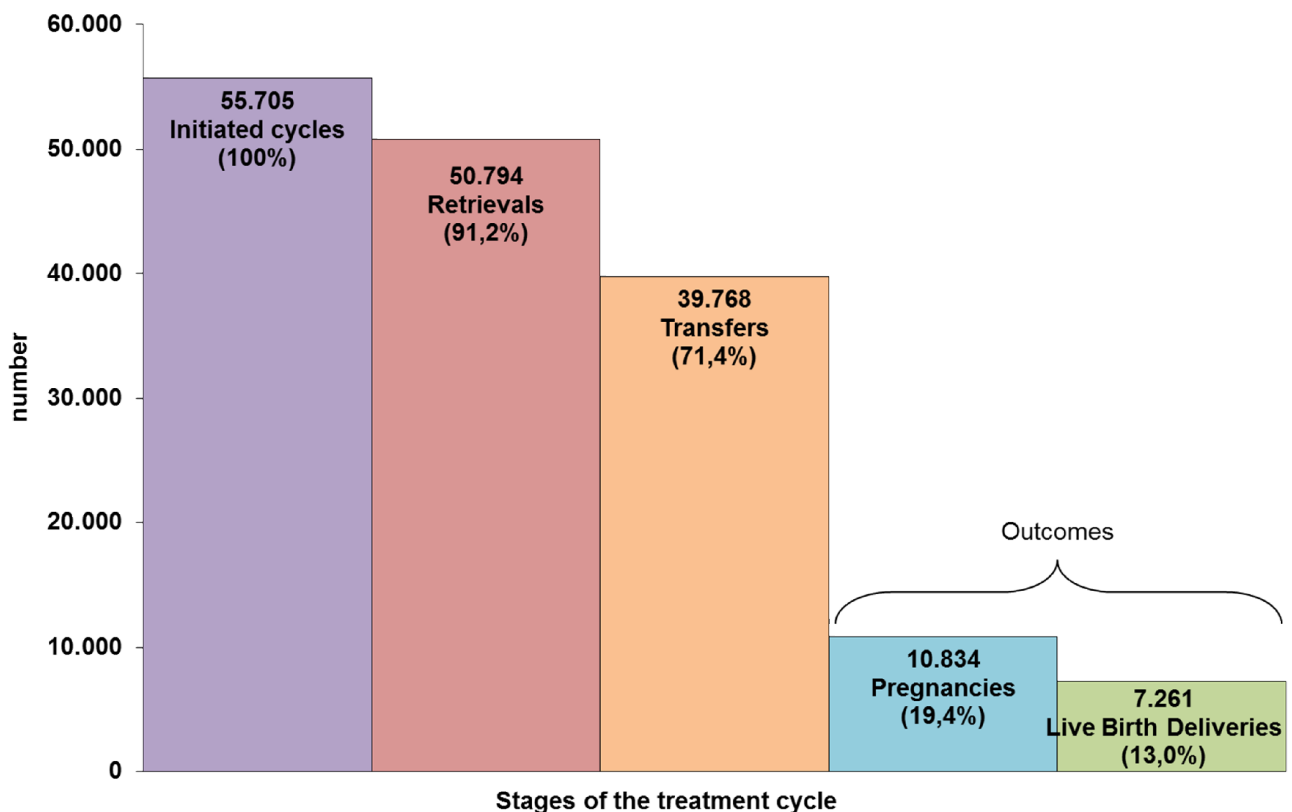
An ART cycle using fresh gametes:

- Is started when a woman begins taking fertility drugs to stimulate the ovaries to produce eggs or having her ovaries monitored for follicle production, if no drugs are given. **(initiated cycle)**
- It continues, if the egg follicles are produced, by a surgical procedure to retrieve the eggs contained in the ovaries **(retrieval)**
- After eggs collection, the sperm fertilize eggs in a dish with In Vitro Fertilization or with ICSI. **(fertilization)**
- If fertilization results, the embryo developed is transferred to the woman's womb **(transfer)**
- The embryo implant into the woman's womb **(implantation)**
- If implantation is successful, a clinical pregnancy occurs **(clinical pregnancy)**
- If the pregnancy progresses, a live birth delivery occurs, when at least one live born baby results from a delivery **(live birth delivery)**. A birth of twins, triplets or more are counted as one live birth

In **Figure 4** outcomes resulting from various steps of fresh cycles performed in 2014 are shown.

Of 55,705 fresh cycles, 91.2% resulted in an egg retrievals, 71.4% in an embryo transfers, 19.4% in a pregnancy and 13% in a live birth delivery.

Figure 4: Outcomes of ART using Fresh cycles by stage of the treatment cycle, 2014.



2.2.2. What are the percentages of initiated cycles, retrievals and transfers that result in pregnancies for fresh cycles?

When an ART treatment or procedure is applied using either not cryopreserved oocytes or embryos, it can be defined “**fresh cycle**”, that includes:

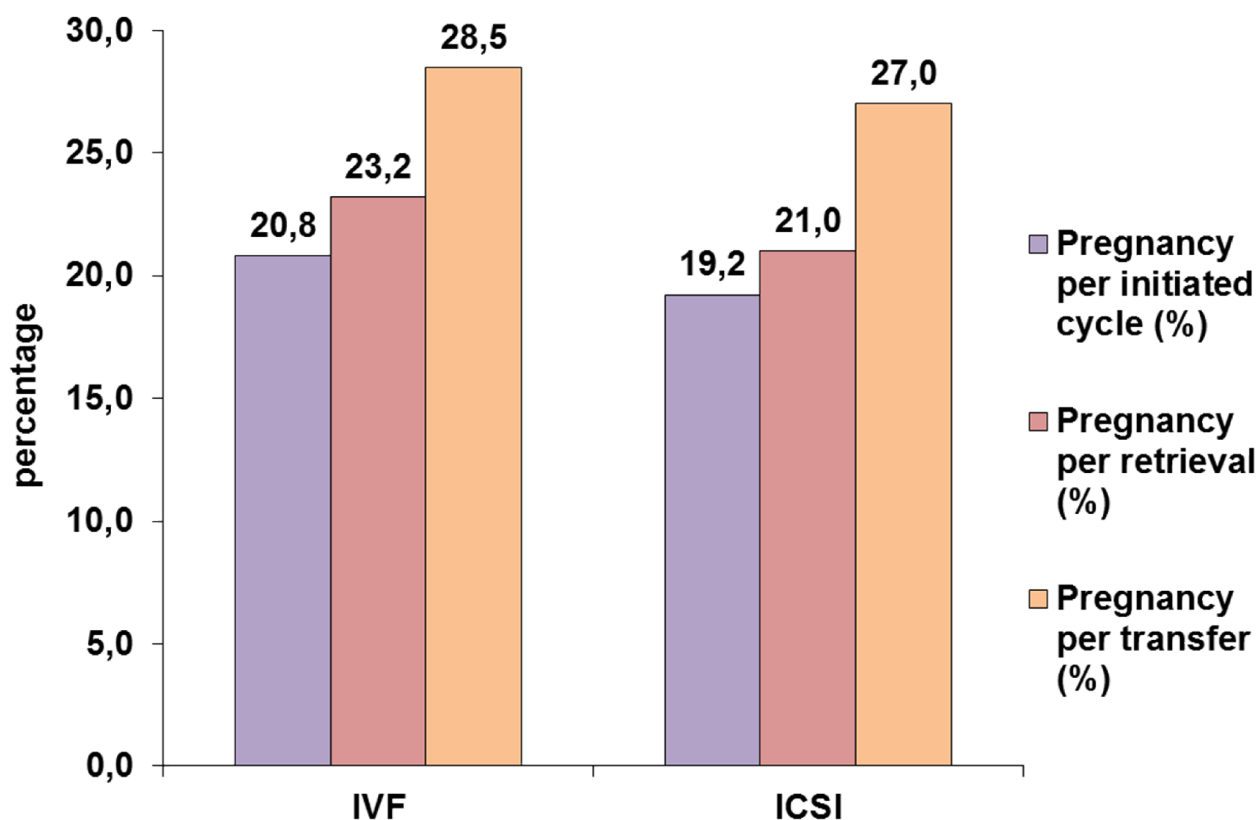
- **In vitro fertilization (IVF):** an ART procedure that involves extracorporeal fertilization;
- **IntraCytoplasmic Sperm Injection (ICSI):** a procedure in which a single spermatozoon is injected into the oocyte cytoplasm.

(source: ICMART and WHO revised glossary on ART terminology, 2009)

Pregnancy rates per initiated cycle, per retrieval and per transfer are shown in **Figure 5** (IVF and ICSI 2014). Overall, the rates after IVF were significantly higher than following ICSI.

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

Figure 5: Pregnancy rates per initiated cycle, per retrieval and per transfer using IVF or ICSI procedures, 2014.



2.2.3. What is the percentage of thawing cycles and transfers that result in pregnancies for FER and FOR techniques?

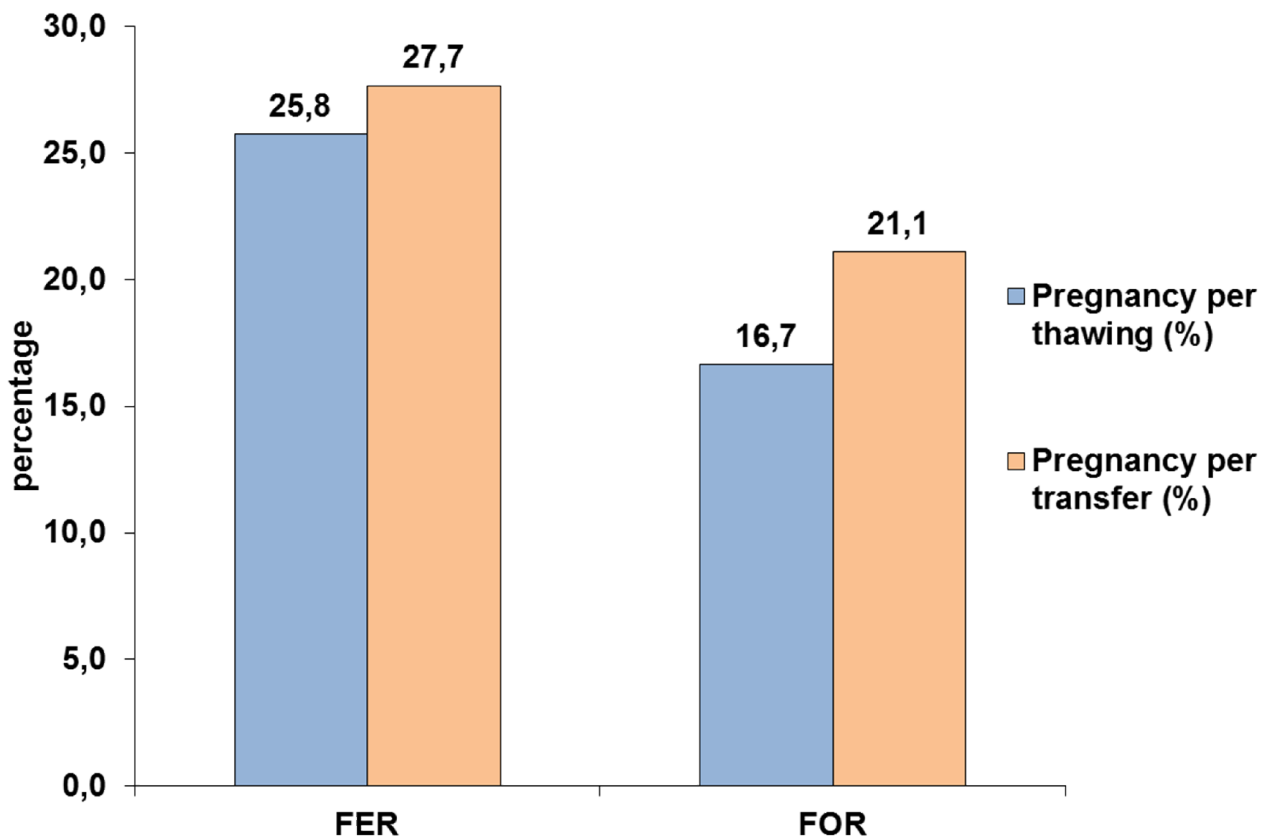
An ART treatment in which are used cryopreserved oocytes or embryos, it can be defined “frozen/thawing cycle”, that includes:

- **Frozen/thawed Embryo Replacement (FER):** ART procedure in which cycle monitoring is carried out with the intention of transferring a frozen/thawed embryo or embryos;
- **Frozen/thawed Oocyte Replacement (FOR):** ART procedure in which cycle is carried out with the intention of fertilizing thawed oocytes and performing embryo transfer.

(source: ICMART and WHO revised glossary on ART terminology, 2009)

In **Figure 6** the pregnancy rate per thawing and per transfer using FER or FOR are shown. FER rates were significantly higher than FOR ones.

Figure 6: Pregnancy Rates per thawing cycle and per transfer using FER and FOR procedures, 2014.

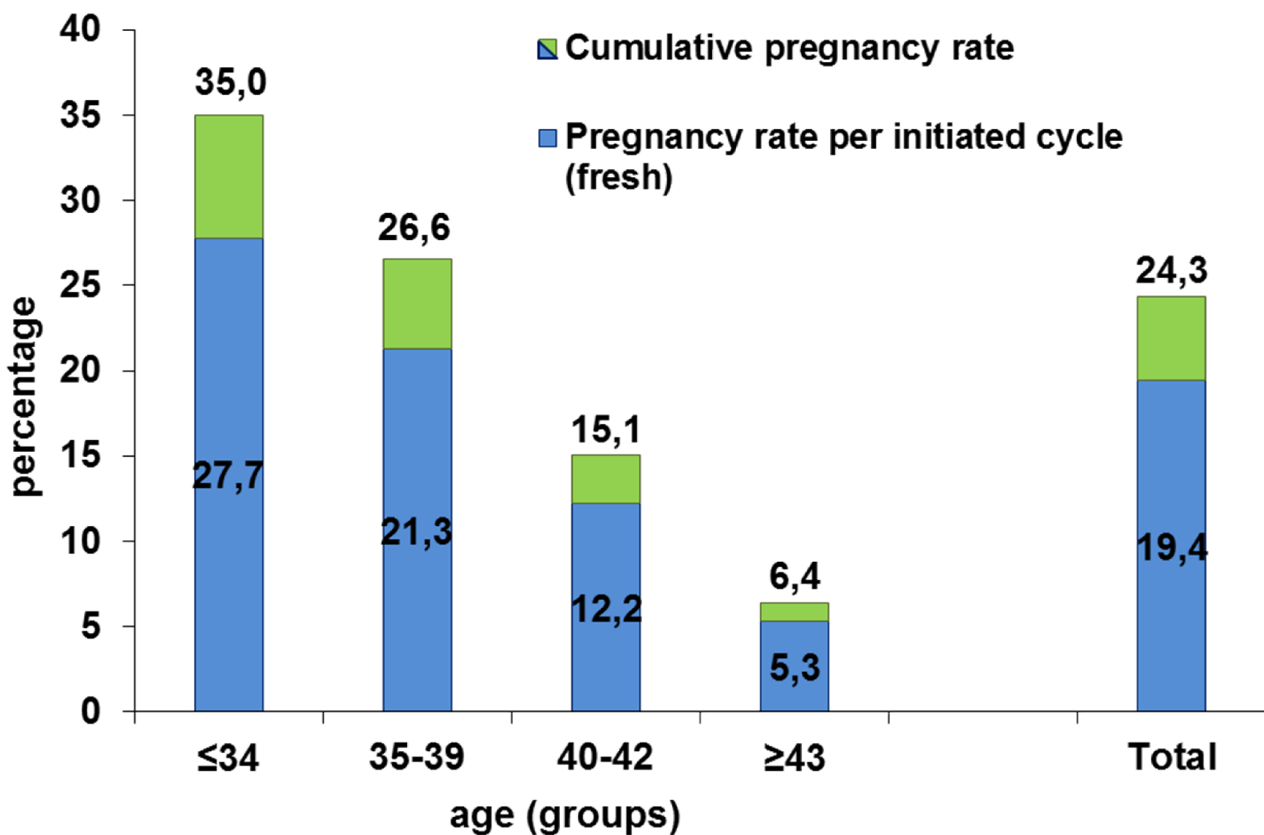


2.2.4. What is the Cumulative Pregnancy Rate?

The cumulative pregnancy rate is the overall chance of obtain a pregnancy from all fresh and frozen embryo transfers from one retrieval of eggs. To calculate the cumulative pregnancy rate (CPR), individual instead of summary 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 estimated added value of embryo and oocyte cryopreservation.

In **Figure 7** 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 25%.

Figure 7: Pregnancy rate per initiated cycle for fresh and Cumulative Pregnancy Rate per initiated cycle, by female patients age groups, 2014.



2.2.5. What is the gender distribution of infertility factors among ART users?

Figure 8 shows major causes of infertility among patients who had ART using fresh cycles in 2014. Diagnoses range from one infertility factor in the patient or partner to multiple infertility factors in either one or both members of the couple

- Female factor:

- **Tubal factor** - fallopian tubes are blocked or damaged, could prevent sperm from getting to the egg and eggs from getting to the uterus
- **Ovulatory dysfunction** - ovaries are not producing eggs normally. The ovaries develop many small cysts instead of ripening and maturing one egg in 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.

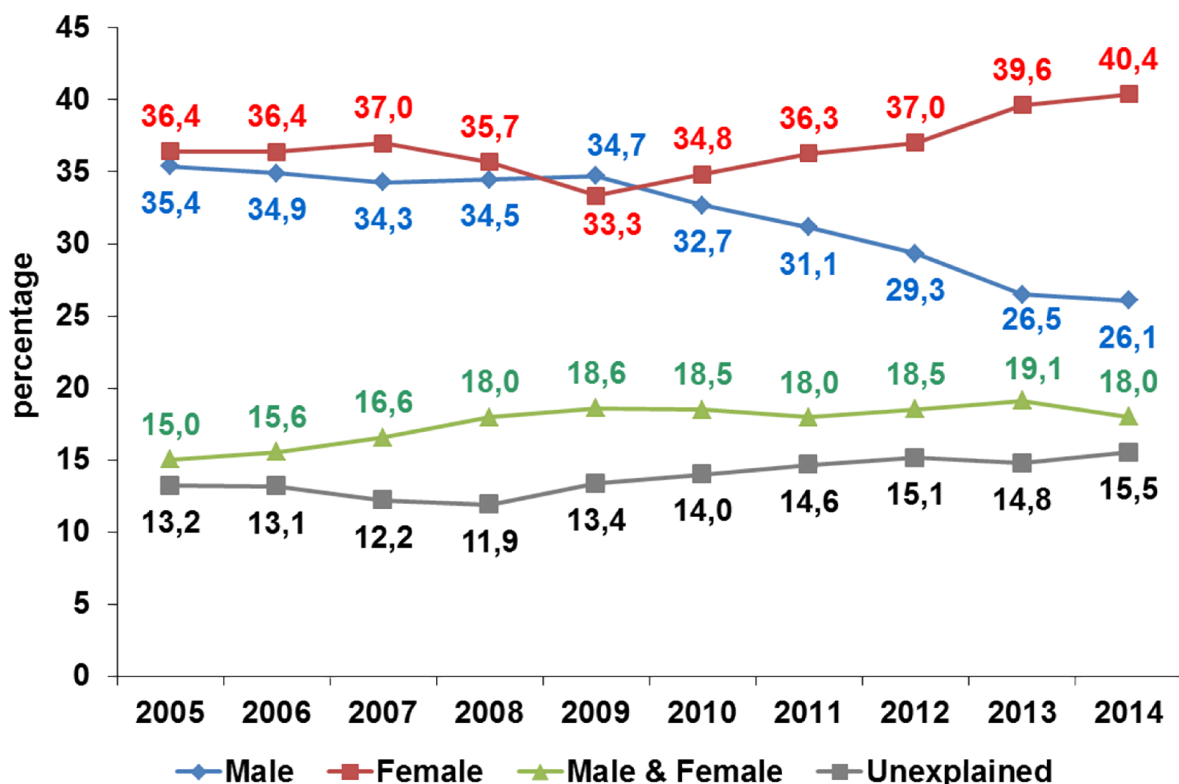
- **Male factor** - Low or no sperm counts, poor sperm motility (the ability to move), and abnormally-shaped sperm can all cause infertility.

- **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 8: Trends of gender distributions of infertility causes among patients who had ART using fresh cycle, 2014. Total couples treated: 45,985



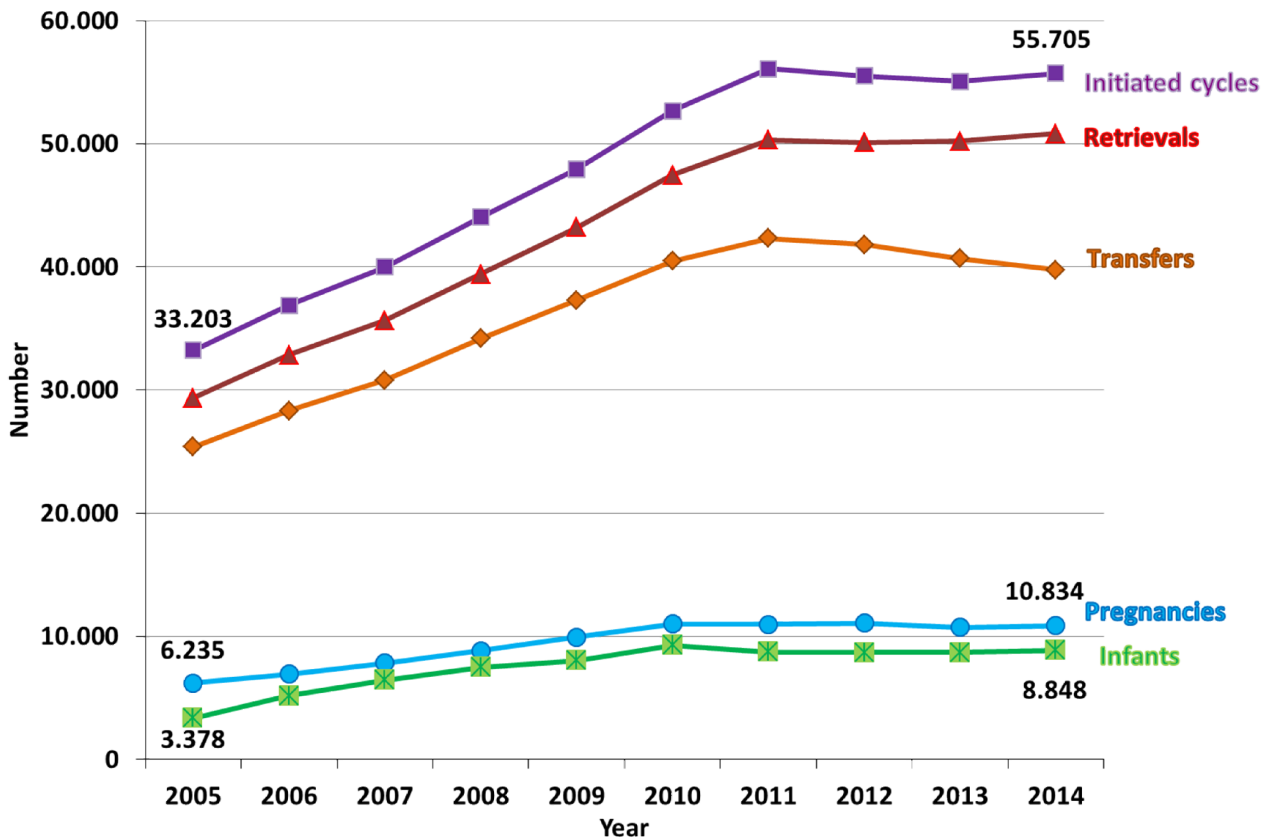
2.2.6. Is the use of ART increasing?

Figure 9 shows the number of cycle, retrievals, transfers performed, pregnancies obtained and infants born using fresh cycles from 2005 to 2014.

The numbers of initiated cycles and pregnancies increased by 68% and 74%, respectively, over time. In details, from 33,203 cycles and 6,235 pregnancies in 2005 to 55,705 cycles and 10,834 pregnancies in 2014.

The number of infants born after fresh ART cycles in 2014 was 161.9% higher than in 2005. However, data on infants must be considered with some caution because of pregnancy lost to follow-up that varied from 40% in 2005 to 10.7% in 2014.

Figure 9: Trends of initiated cycles, retrievals, transfers, pregnancies and deliveries obtained from fresh cycles, 2005–2014.



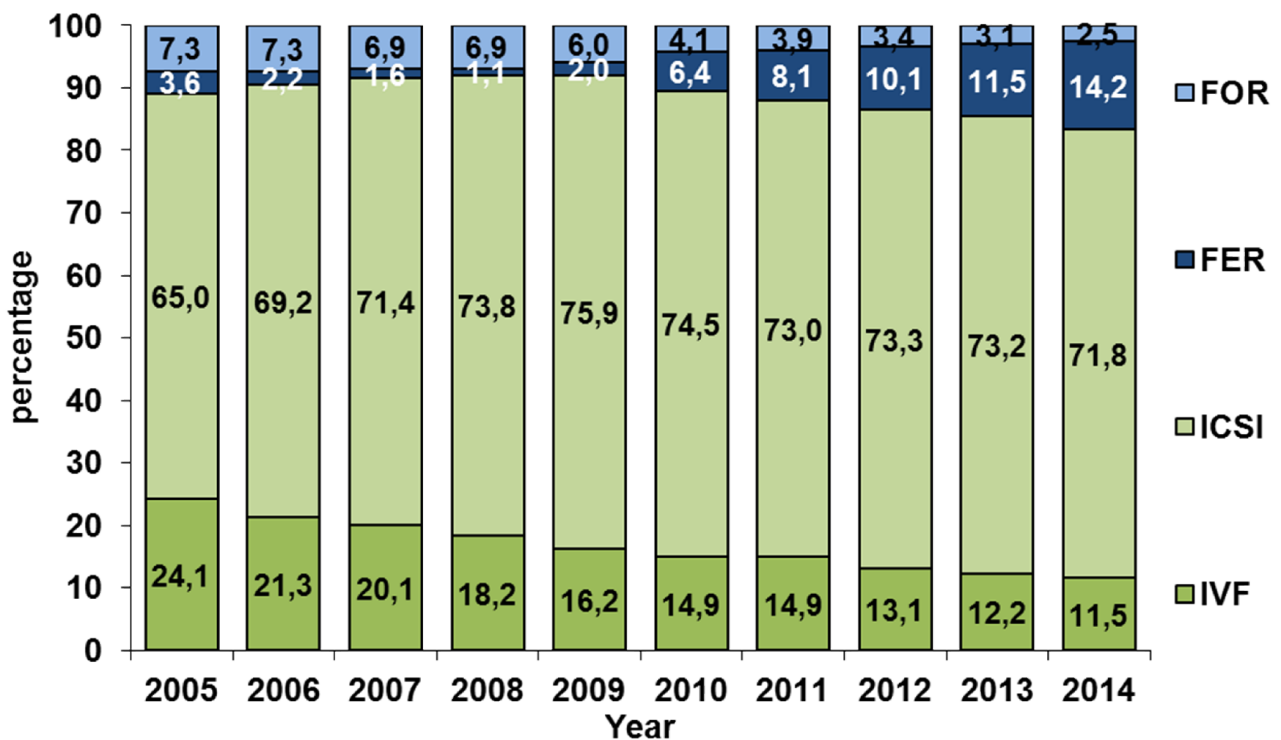
2.2.7. Did the use of different ART procedures change over time?

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

Figure 10 shows percentage of initiated cycles with fresh cycles (performed using ICSI and IVF procedures), thawing with FER and FOR from 2005 through.

The number of ICSI cycles increased from 24,209 in 2005 to 48,010 in 2014, while IVF cycles decreased from 8,994 to 7,695. Also FER thawing increased from 1,338 to 9,501, while FOR procedures decreased from 2,711 to 1,639.

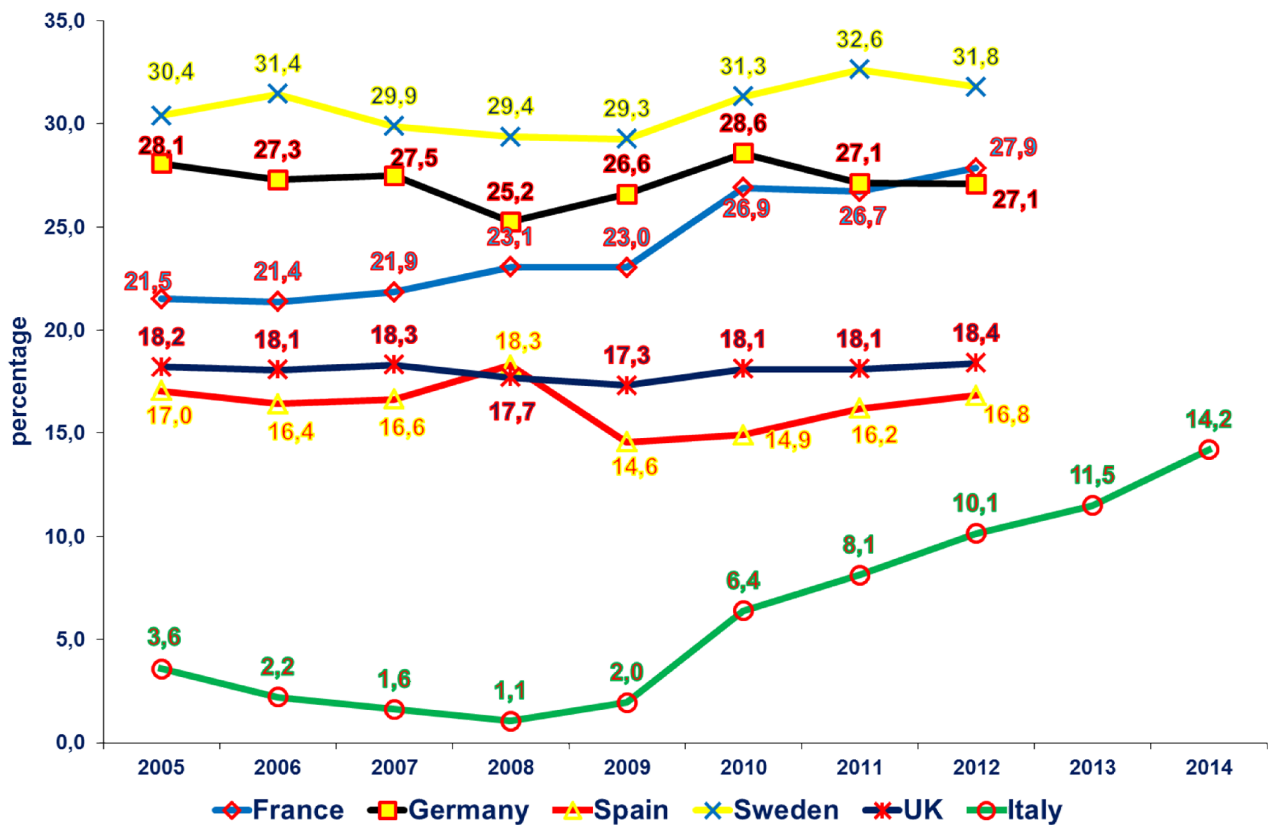
Figure 10: Trends of ART procedures, 2005-2014.



2.2.8. Did the use of FER procedures differ in Italy compared to other European countries over time?

In 2004 the Italian Parliament approved a law (40/2004) regulating ART in which embryo cryopreservation was banned. 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 and resumed steadily after 2009. As it shown in **Figure 11** percentage of FER cycles performed increased from 3.6% in 2005 to 14.2% in 2014. In comparison with some of the largest European countries, Italy showed the lowest number of FER cycles performed

Figure 11: Trends of percentages of FER thawing on total ART initiated cycles in Europe, 2005-2014.

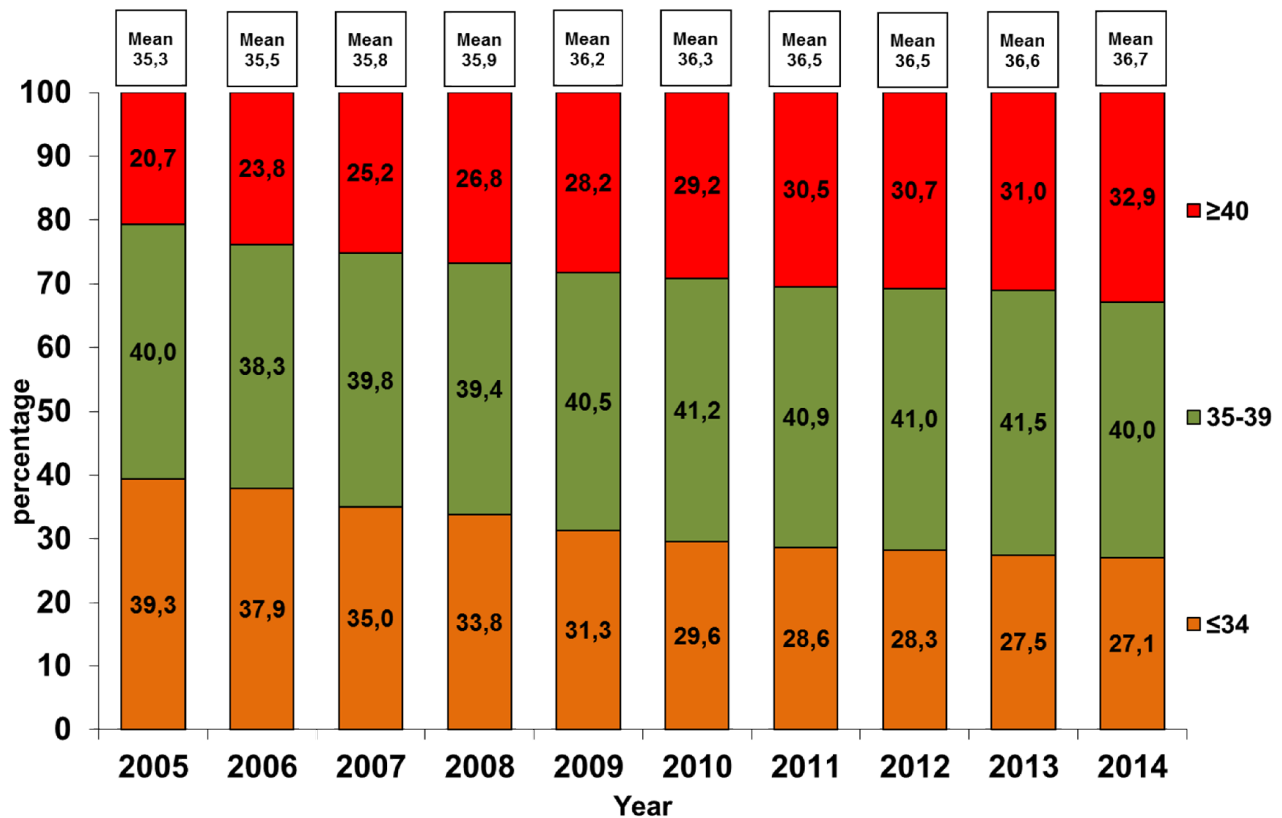


2.2.9. Has the age of ART female patients changed over time?

Figure 12 shows the distribution of fresh cycles by women age groups, from 2005 to 2014.

For women older than 40 the percentage of fresh cycles performed increased from 20.7% in 2005 to 32.9. Whilst the percentage of fresh cycles performed in women ≤ 34 years old decreased from 39.3% in 2005 to 27.1% in 2014. Overall, the mean age of women who had fresh cycles increase from 35.3 to 36.7 years over time

Figure 12: Trends of fresh initiated cycles distributions by age classes of female patients, 2005-2014.

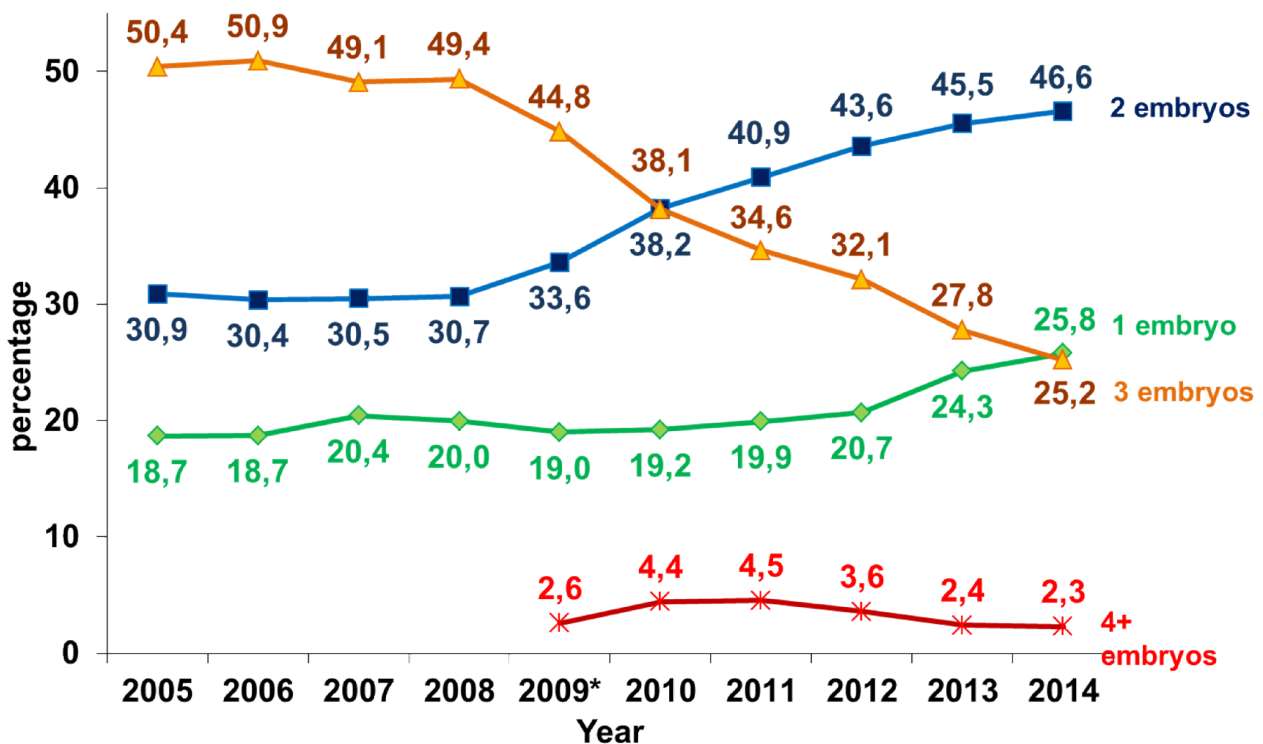


2.2.10. Has the number of embryos transferred changed in fresh cycles?

Figure 13 shows trends with the number of embryos transferred in fresh cycles.

From 2005 to 2014 the transfer with one and two embryos increased from 18.7% and 30.9% to 25.8% and 46.6%, respectively. On the other hand transfers with 3 embryos dramatically decreased from 50.4%, first to 38.1% in 2010 to reach the 25.2% in 2014. As it shown in the figure, this trend begin from the end of 2009 when law 40/2004 was changed, and the limit to transfer maximum three embryos removed. Values of transfers with four or more embryos were quite stable during time, from 2.6% in 2009 to 2.3% in 2014. The average number of embryos transferred decreased from 2.3 embryos per transfer in 2005 to 2 in 2014.

Figure 13: Trends of transfer by number of embryos transferred, 2005-2014.



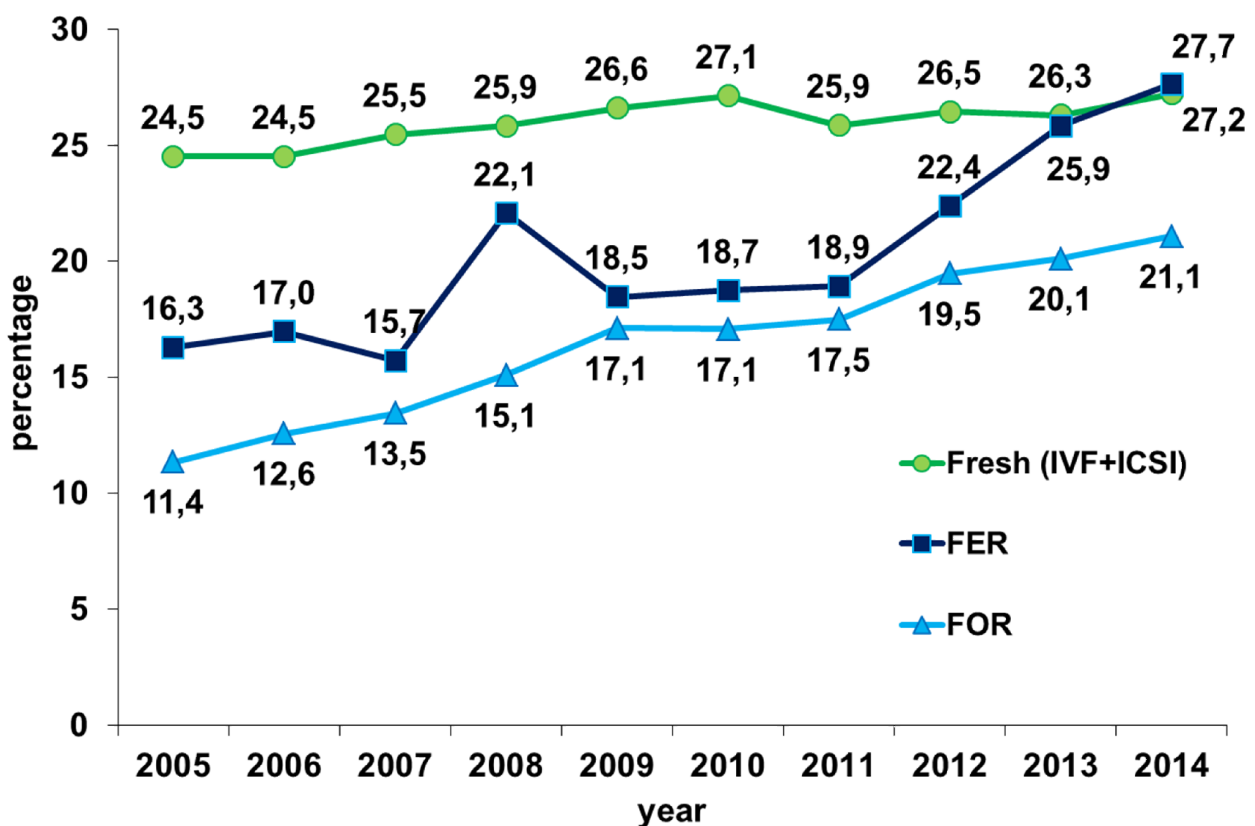
*year of the Costitutional Court sentence 151/2009.

2.2.11. Did pregnancy rates per transfer changed over time among different ART procedures ?

Figure 14 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 pregnancy rates increasing from 24.5% in 2005 to 27.2% in 2014, those with frozen embryos increased from 16.3% to 27.7%, and those with frozen oocytes from 11.4% to 21.1%.

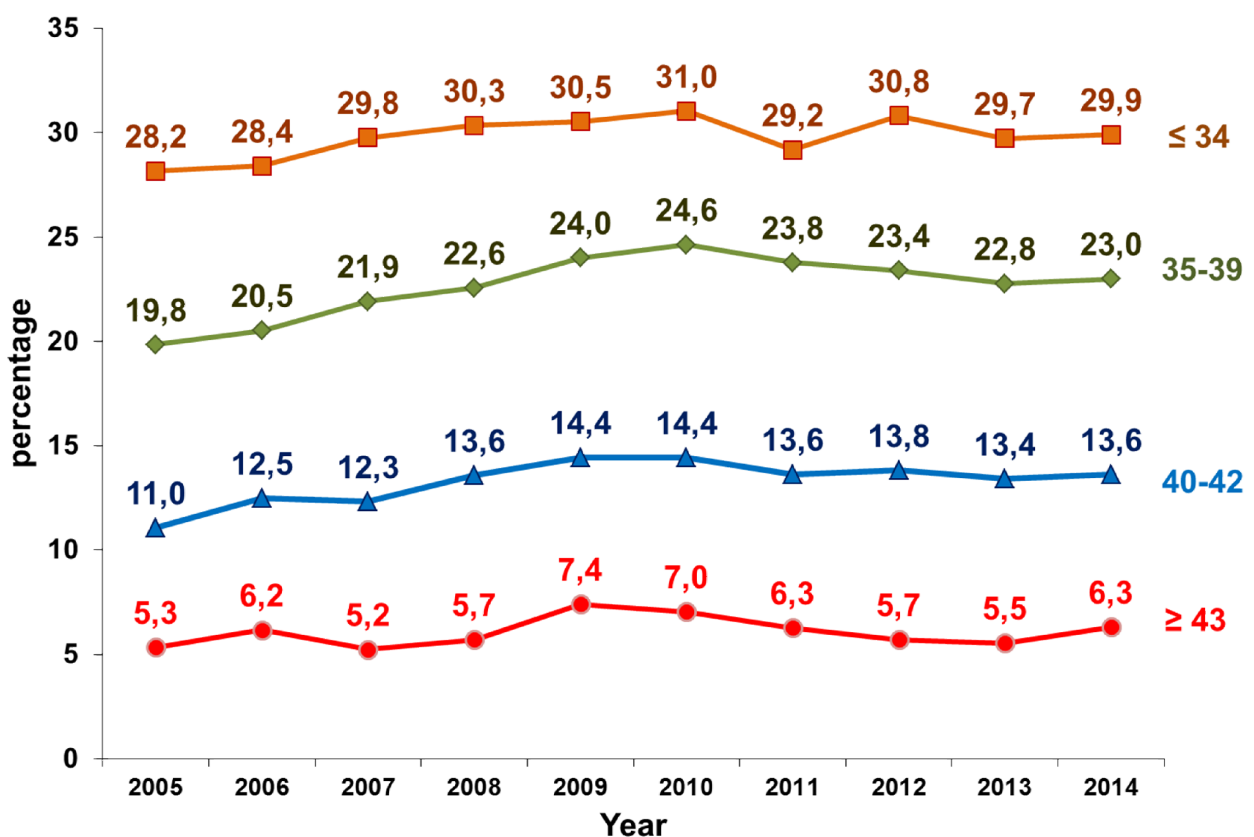
Figure 14: Trends of pregnancy rate per transfer for fresh, thawed embryos (FER) and thawed/warmed oocytes cycles (FOR), 2005-2014.



2.2.12. Did pregnancy rates per retrieval change over time among different female age groups?

Figure 15 shows pregnancy rates per retrieval according to women age groups, after fresh cycles. From 2005 to 2014 pregnancy rates per retrieval increased from 28.2% to 29.9% for women aged less than 34, from 19.8% to 23% for women aged 35-39 and from 11.4% to 13.4% for women aged over 40-42. Percentages are fairly stable in women aged more than 42 years.

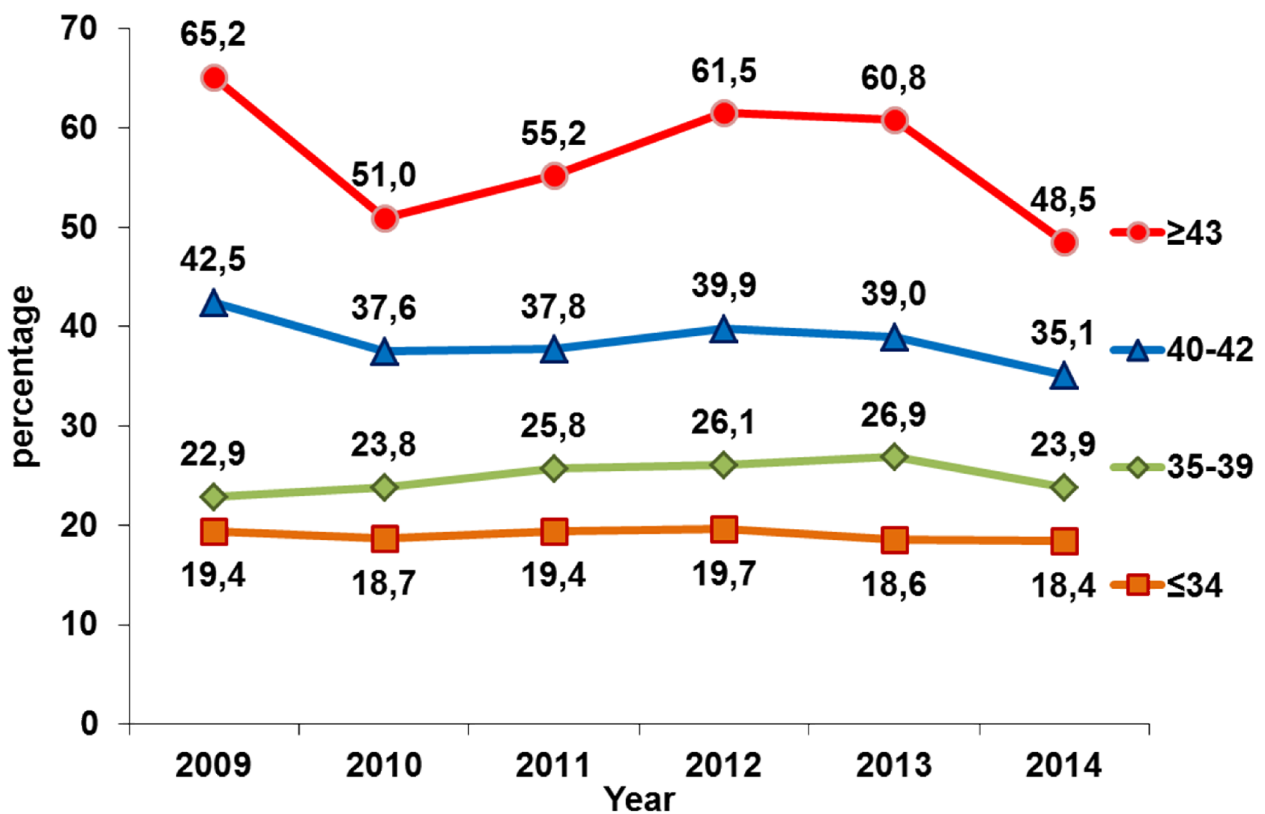
Figure 15: Trends of pregnancy rates per retrievals with fresh cycles by age groups of female patients, 2005-2014.



2.2.13. Does the risk of pregnancy loss differ among women of different age groups?

Increasing female age also increases the risk of negative pregnancy outcomes (spontaneous or therapeutic abortions and ectopic pregnancies). As it is shown in **Figure 16** rates in older age groups were much higher. Rates decreased over time from 65.2% to 48.5% for women older than 43 years old and from 42.5% to 35.1% for women aged 40-42. Rates for the age classes younger than 40 were quite stable from 2009 to 2014.

Figure 16: Trends of percentages of total pregnancy loss using ART cycles by female age groups, 2009-2014.



2.2. ART donor cycles.

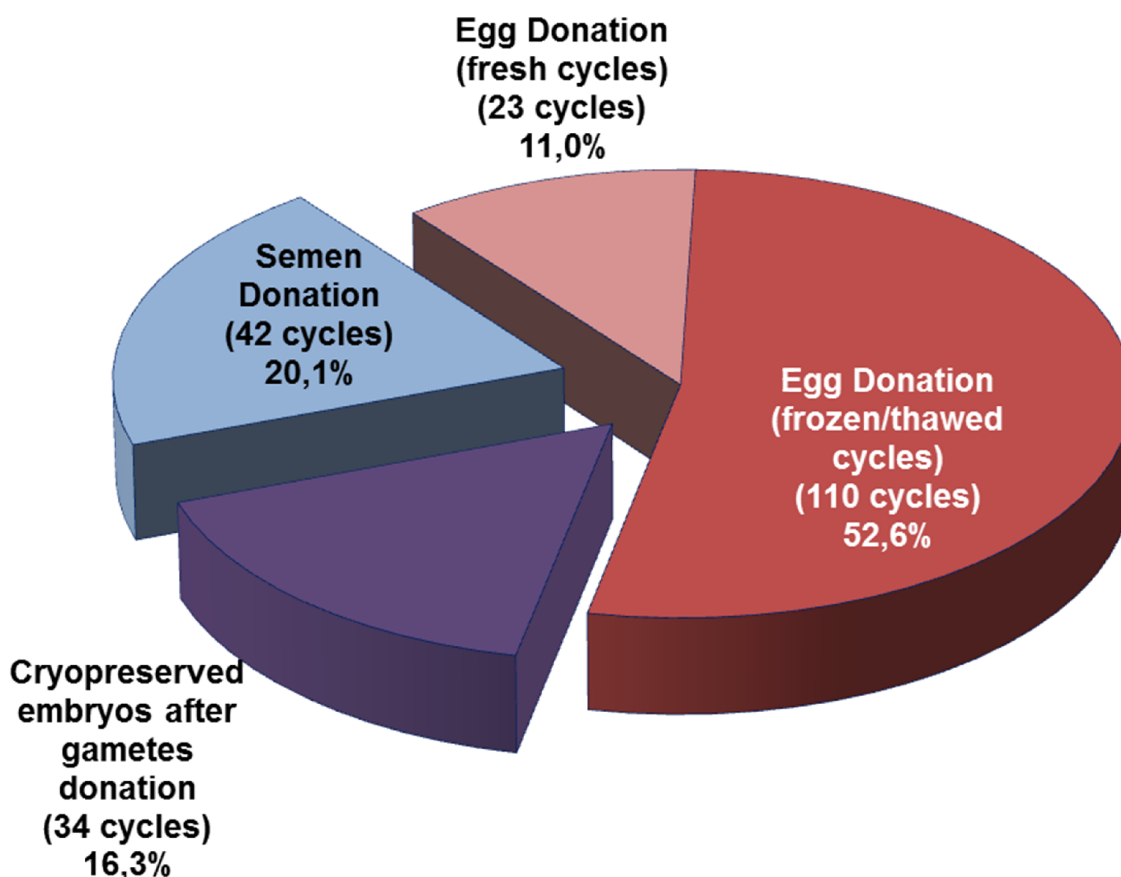
In April 2014 Italian Constitutional Court removed the prohibition, set out in the law, regarding the practice of ART techniques using donor gametes, now permitted under specific conditions.

For this reasons the activity of ART using donor gametes in 2014 is still low (representing just few months of the year) and does not allowed for accurate epidemiological evaluations. So, please check on Summary table for 2014 (on page 42), for more detailed data on activity and outcomes regarding ART donor cycles.

2.2.1. Which gametes were used in ART donor cycles in 2014?

Figure 17 shows the distribution of types of ART cycles using donor gametes applied in Italy in 2014. In about 63% of ART donor cycles, fresh or frozen eggs were used. In almost 20% of cycles there was a semen donation. More than 16% of cycles were performed using cryopreserved embryos obtained from donation of a gamete.

Figure 17: Distribution of all ART cycles using donor gametes or cryopreserved embryos after donation, 2014. Total cycles = 209.



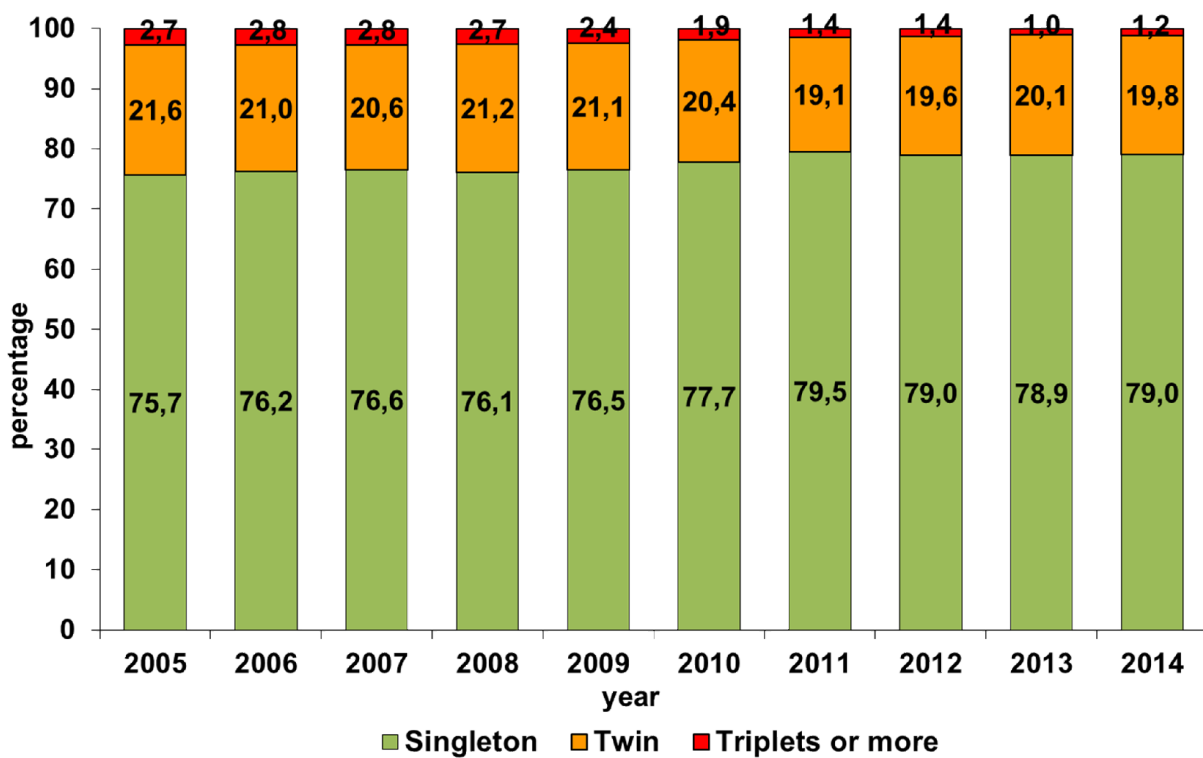
3.INDICATORS OF ART SAFETY

3.1.1. Did the percentages of singletons, twins and triplets- or- more deliveries for fresh cycles change over time?

Figure 19 shows trends for singleton and triplet deliveries in fresh cycles.

From 2005 to 2014 twin delivery rates decreased from 21.6% to 19.8% while numbers of triplets and more deliveries decreased from 2.7% to 1.2%, twice the average value in Europe, as reported in 2012 EIM data. We must remember that from 2004 till 2009 the Law obliged to transfer at once, all the embryos created for a maximum of 3.

Figure 19: Trends of multiplicity of deliveries from fresh cycles, 2005-2014.

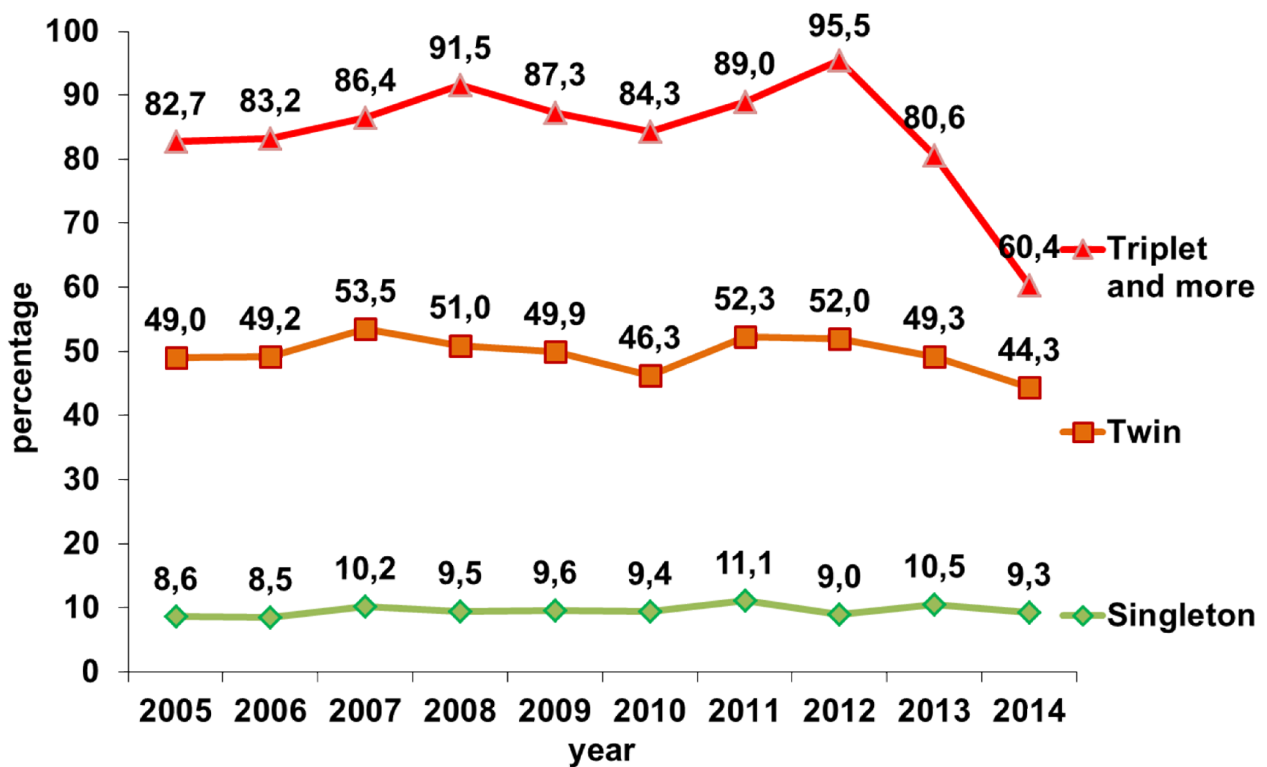


3.1.2. Did the percentages of preterm live babies change over time?

Figure 20 shows trends of ART preterm live born babies that are highly correlated with the multiplicity of deliveries.

The percentage of preterm live babies in singleton deliveries are quite stable during all the period. Otherwise in twins and triplets deliveries there is a variability from year to year, but overall the trend is downwards for both: from 49% in 2005 to 44.3% in 2014 for twins and from 82.7% in 2005 to 60.4% in 2014 for triplets or more.

Figure 20. Trends of percentage of preterm ART live born babies (<37 week of gestation) by multiplicity of deliveries, 2005-2014.

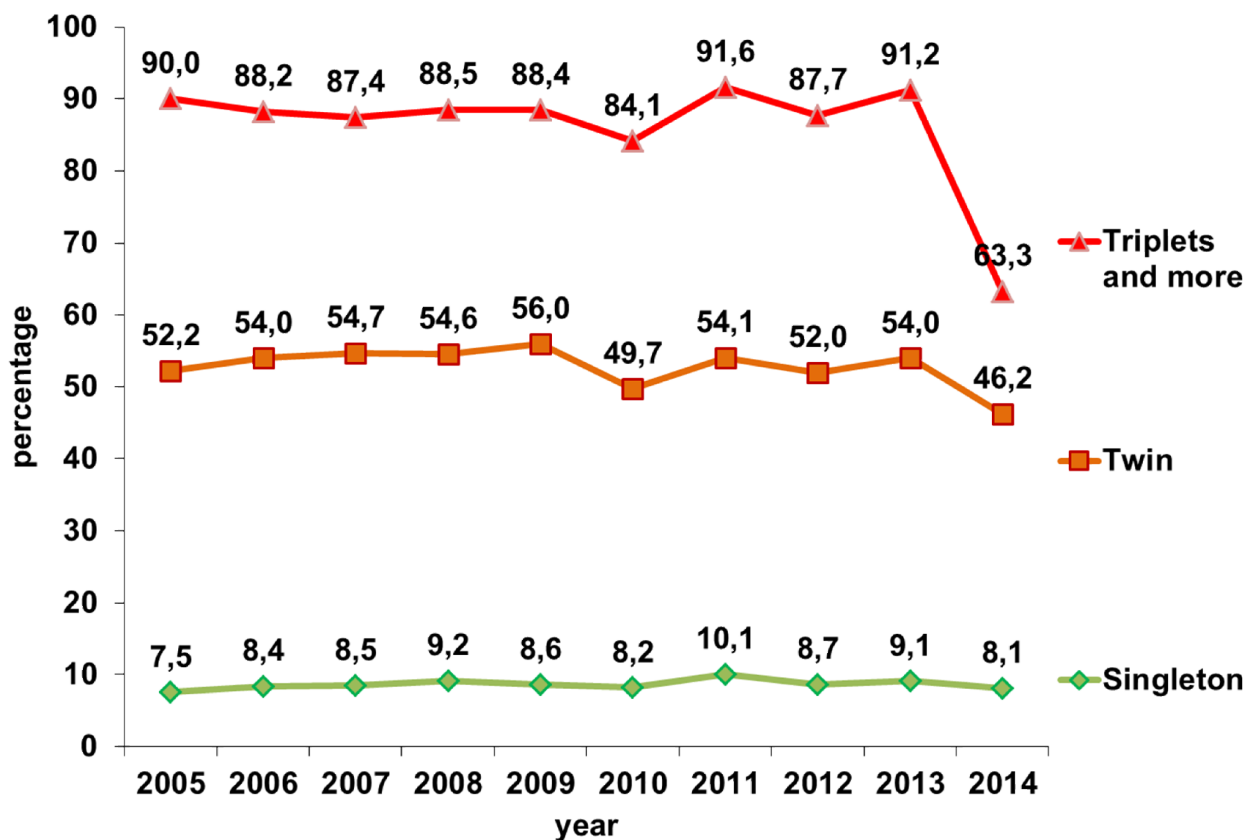


3.1.2. Did the percentage of underweight live babies change over time?

Figure 21 shows the trends of ART live born babies underweight that are highly correlated with the multiplicity of deliveries as already described in respect to prematurity.

In babies born underweight, the percentage in singleton deliveries are quite stable during all the period. Overall the trend is downwards for both twins and triplets and more deliveries, from 52.2% in 2005 to 46.2% in 2014 and from 90% in 2005 to 63.3% in 2014 respectively.

Figure 21. Trends of percentage of ART live born babies underweight (<2,500 gr) by multiplicity of deliveries, 2005-2014.



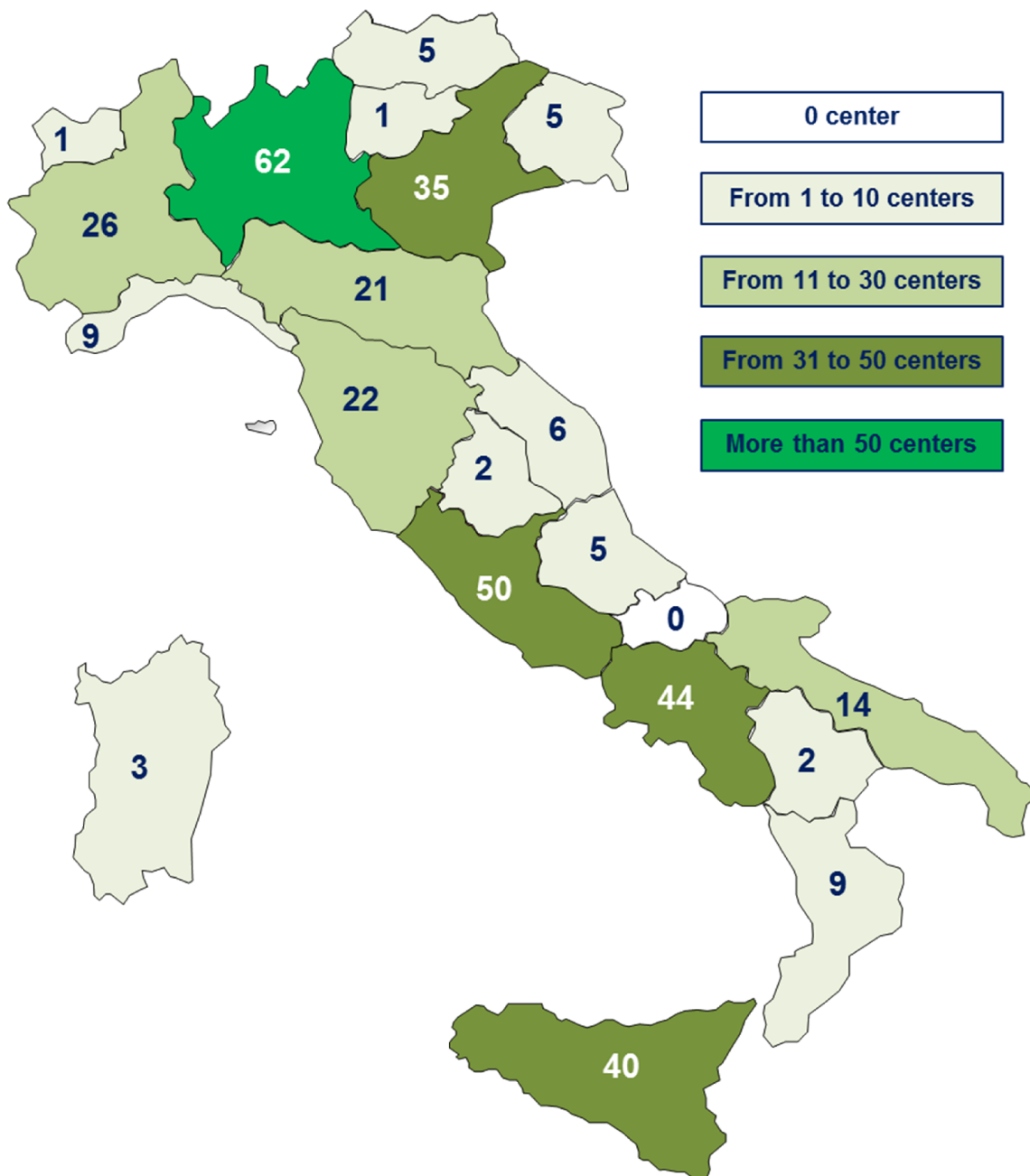
4. IUI PROCEDURES

4.1. Access to IUI service

In Figure 22 the regional distribution of IUI centers are represented.

The largest number of IUI centers is concentrated in Southern Italy (117, 32.3% of the total) and in the Northwest (98 centers, 27.1% of the total), irrespective of the amount of activity they have carried out.

Figure 22: Regional distribution of IUI + ART active centers, 2014. Total = 362



As shown in **Table 3**, in 2014 there were 362 centers that have performed IUI of which only 136 operating within the National Health System (public and private 37.6%) and 226 providing private service (62.4%).

Most of public centers that performs IUI in Italy were in North: 67 out of 114 centers (58.8%).

Table 3: IUI centers distribution by region and type of service, 2014.

Region and Geographical Area	Total	Type of Service					
		Public		Private covered by NHS		Private	
		N	%	N	%	N	%
Piemonte	26	11	42,3	1	3,8	14	53,8
Valle d'Aosta	1	1	100	0	-	0	-
Lombardia	62	20	32,3	10	16,1	32	51,6
Liguria	9	4	44,4	0	-	5	55,6
Northwest	98	36	36,7	11	11,2	51	52,0
P.A. Bolzano	5	4	80,0	0	-	1	20,0
P.A. Trento	1	1	100	0	-	0	-
Veneto	35	13	37,1	1	2,9	21	60,0
Friuli Venezia Giulia	5	3	60,0	1	20,0	1	20,0
Emilia Romagna	21	10	47,6	0	-	11	52,4
Northeast	67	31	46,3	2	3,0	34	50,7
Toscana	22	7	31,8	6	27,3	9	40,9
Umbria	2	1	50,0	0	-	1	50,0
Marche	6	2	33,3	0	-	4	66,7
Lazio	50	7	14,0	3	6,0	40	80,0
Central	80	17	21,3	9	11,3	54	67,5
Abruzzo	5	3	60,0	0	-	2	40,0
Molise	0	-	-	-	-	-	-
Campania	44	10	22,7	0	-	34	77,3
Puglia	14	3	21,4	0	-	11	78,6
Basilicata	2	2	100	0	-	0	-
Calabria	9	1	11,1	0	-	8	88,9
Sicilia	40	8	20,0	0	-	32	80,0
Sardegna	3	3	100	0	-	0	-
South and Islands	117	30	25,6	0	-	87	74,4
Italy	362	114	31,5	22	6,1	226	62,4

4.2. Efficacy and safety of IUI and trends

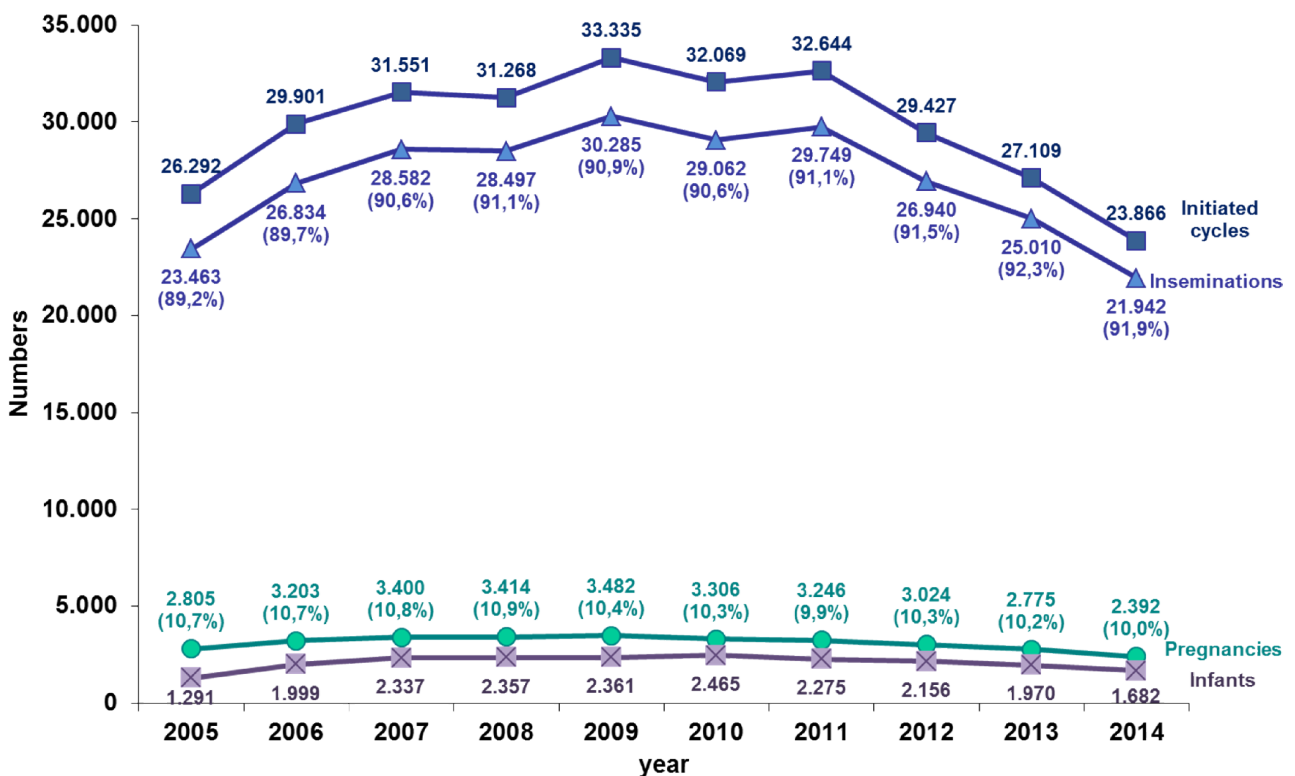
4.2.1. Is the use of IUI-H increasing?

Intrauterine insemination (IUI) is a medical procedure in which a sperm sample is deposited directly into the women's uterus to achieve a fertilization and then a pregnancy. It can be performed using husband semen (IUI-Homologous) or with the semen of an anonymous donor (IUI-Donor).

As described for ART techniques using donor gametes (on page 27) the IUI-D procedures was permitted only after the sentence of the Italian Constitutional Court in April 2014. So the activity of IUI-D in 2014 is low (only 37 initiated cycles) and does not allowed for accurate epidemiological evaluations. So please check on Summary table for 2014 (on page 42) for more detailed data.

In **Figure 23** the use of IUI-H from 2005 to 2014 is represented. Number of IUI-H cycles decreased from 26,292 to 23,866 after having reached his maximum of 33,335 cycles in 2009. There were no changes in pregnancy rate from 10.7% in 2005 to 10% in 2014. Average women age increase of 0.58 year during time.

Figure 23: Trends of outcomes of IUI-H cycles, 2005-2014.

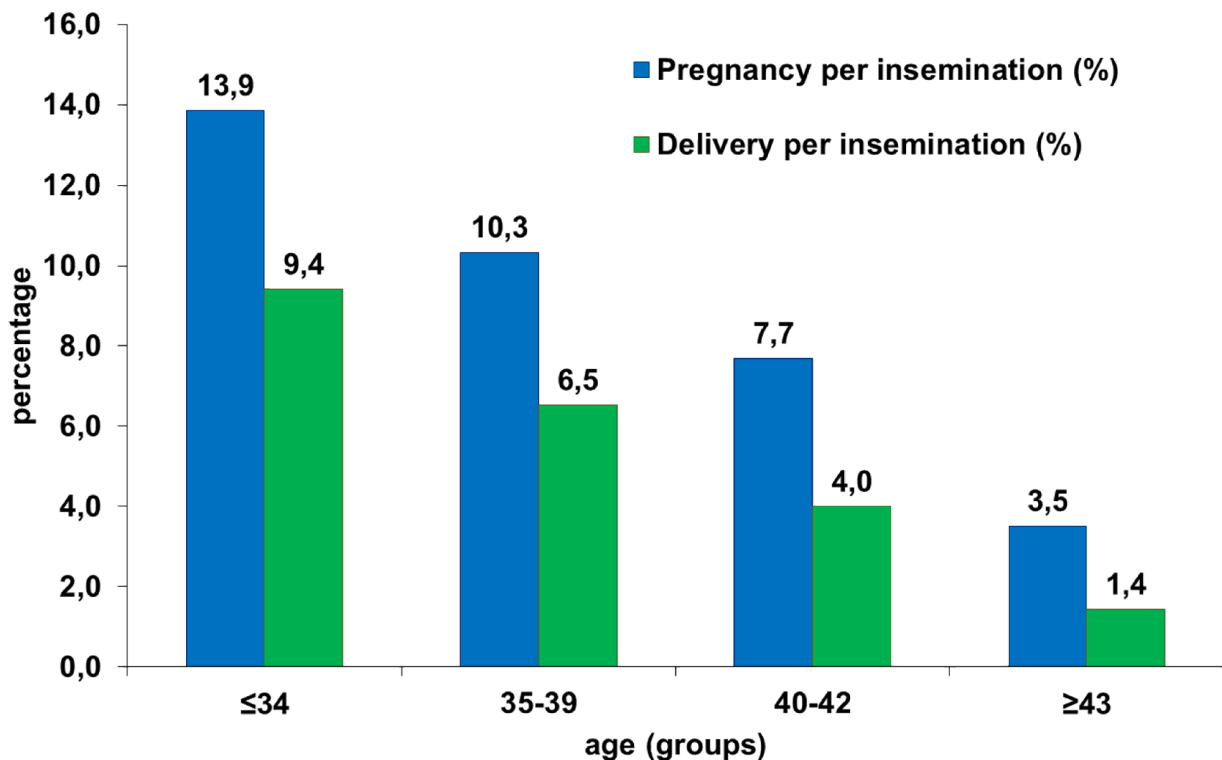


4.2.2. Do percentages of IUI-H cycles resulting in pregnancies, differ among women of different age groups?

Figure 24 shows percentages of initiated cycles and insemination for IUI-H that resulted in pregnancies among women of different age groups.

The probability to obtain a pregnancy and to reach a delivery in an IUI-H treatment is highly related to the age of women. Numbers in older women are very small: in over 43 it is 3.5% for pregnancy and 1.4% for delivery.

Figure 24: Pregnancy rates and delivery rates per insemination for H-IUI cycles by age groups of female patients, 2014.

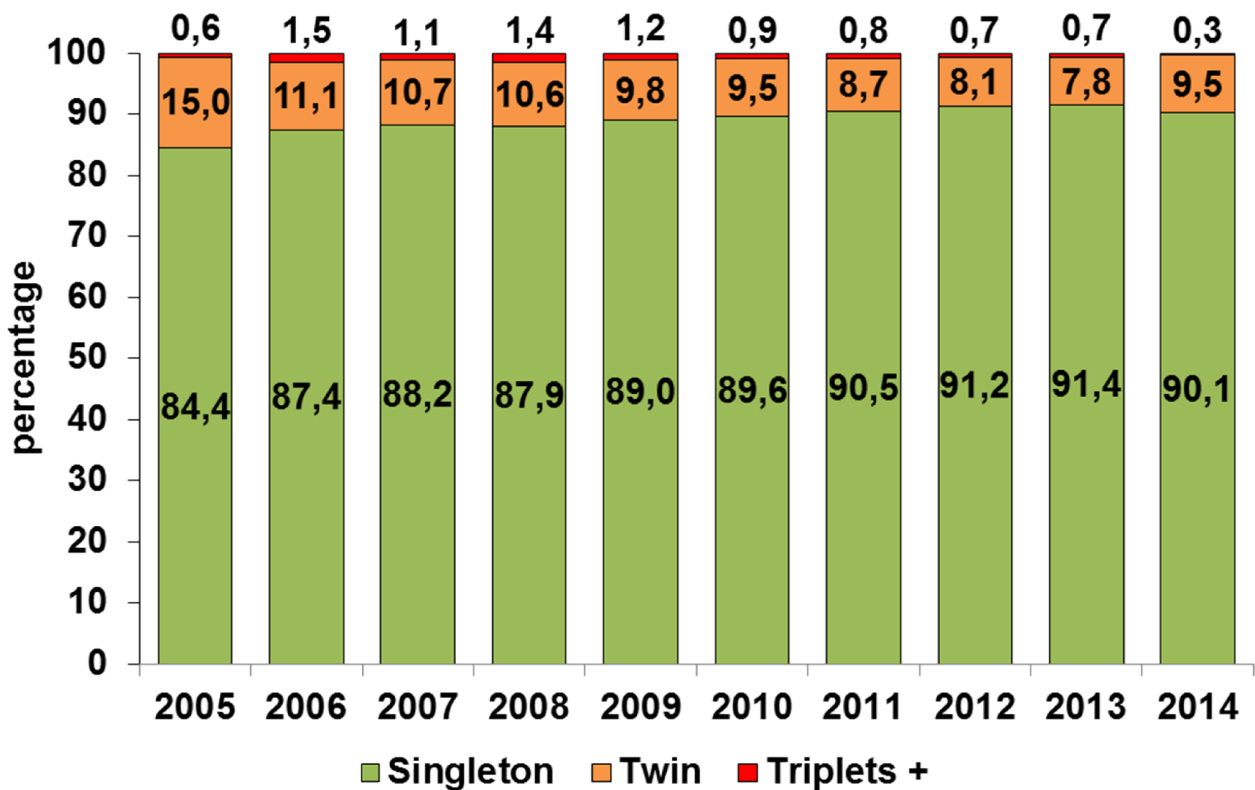


4.2.3. Did the percentages of singletons, twins and triplets- or- more deliveries change over time for intrauterine insemination cycles?

Figure 25 shows time trends for multiplicity of deliveries in H-IUI cycles.

From 2005 to 2014 twin deliveries rates decreased from 15% to 9.5% while percentage of triplets and more deliveries are quite stable. In 2014, 9 deliveries out of 10 were singleton.

Figure 25: Trends of multiplicity of deliveries from H-IUI cycles, 2005-2014.



APPENDIX. SUMMARY TABLE OF ACTIVITY
AND OUTCOMES OF ART PROCEDURES,
YEARS 2005 – 2014

Summary table of activity and outcomes of non-donor procedures, 2005 – 2014

	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
N° Clinics	316	329	342	354	350	357	354	355	369	362
% of clinics reporting data to ISS	91.2	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
<u>ALL PROCEDURES Nondonor (H-IUI + ART)</u>										
N° Patients	46,519	52,206	55,437	59,174	63,840	69,797	73,570	72,543	71,741	70,589
N° Initiated cycles	63,585	70,695	75,280	79,125	85,385	90,944	96,427	93,634	91,556	90,711
N° Pregnancies	9,499	10,608	11,685	12,767	14,033	15,274	15,467	15,670	15,550	15,947
% Pregnancies lost to follow-up	43.2	23.6	15.4	15.2	16.7	11.4	13.4	14.0	11.4	11.8
N° Monitored pregnancies	5,392	8,108	9,884	10,825	11,691	13,537	13,395	13,484	13,770	14,070
N° Deliveries	4,033	6,148	7,513	8,319	8,896	10,387	10,065	10,101	10,305	10,732
N° Live born	4,940	7,507	9,137	10,212	10,819	12,506	11,933	11,974	12,187	12,658
<u>ART non-donor ACTIVITY (FRESH + THAWING CYCLES)</u>										
N° clinics reporting data (with at least 1 patients treated)	169	184	181	185	180	174	179	182	178	175
N° Patients	30,749	33,775	36,465	40,142	43,525	50,090	53,558	54,458	54,523	55,654
N° Initiated cycles	37,293	40,794	43,729	47,857	52,050	58,875	63,783	64,207	64,447	66,845
N° Pregnancies	6,694	7,405	8,285	9,353	10,551	11,968	12,221	12,646	12,775	13,555
% Pregnancies lost to follow-up	41.3	21.5	13.3	12.6	14.8	10.2	12.2	13.2	10.3	10.7
N° Monitored pregnancies	3,928	5,812	7,181	8,173	8,992	10,744	10,736	10,978	11,461	12,109
N° Deliveries	2,919	4,384	5,437	6,245	6,782	8,167	8,003	8,127	8,495	9,203
N° Live born	3,649	5,508	6,800	7,855	8,458	10,041	9,658	9,818	10,217	10,976
<u>INDICATORS OF THE AVAILABILITY OF SERVICES</u>										
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	5,860
ART Initiated cycles per 1 million inhabitants	636	692	736	800	865	973	1,050	1,078	1,070	1,103

Summary table of activity and outcomes of non-donor procedures, 2005 – 2014

	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
<u>ONLY FRESH non-donor CYCLES</u>										
N° clinics reporting data (with at least 1 patients treated)	169	184	181	185	180	174	179	182	178	175
N° Patients	27,254	30,274	33,169	36,782	39,775	44,365	46,491	46,491	46,433	45,985
N° Initiated cycles	33,244	36,912	40,026	44,065	47,929	52,676	56,092	55,505	55,050	55,705
Average age calculated	35.25	35.50	35.77	35.93	36.17	36.34	36.48	36.50	36.55	36.68
N° Aspirations	29,380	32,860	35,666	39,462	43,257	47,461	50,290	50,096	50,174	50,794
N° Transfer	25,402	28,315	30,780	34,179	37,301	40,468	42,331	41,822	40,696	39,768
N° Pregnancies	6,243	6,962	7,854	8,847	9,940	10,988	10,959	11,077	10,712	10,834
% Pregnancies rate per cycles	18.8	18.9	19.6	20.1	20.7	20.9	19.5	20.0	19.5	19.4
% Pregnancies rate per aspirations	21.2	21.2	22.0	22.4	23.0	23.2	21.6	22.1	21.3	21.3
% Pregnancies rate per transfers	24.6	24.6	25.5	25.9	26.6	27.2	25.9	26.5	26.3	27.2
% Twin Pregnancies	18.5	18.5	18.7	20.1	20.0	20.2	18.8	18.9	19.4	19.5
% Triplet or more Pregnancies	3.4	3.5	3.6	3.4	2.7	2.3	1.8	1.8	1.6	1.4
% Pregnancies lost to follow-up	42.3	21.5	13.5	12.6	15.0	10.8	12.7	13.9	10.9	11.9
N° Monitored pregnancies	3,603	5,464	6,793	7,728	8,453	9,806	9,572	9,535	9,540	9,542
N° Deliveries	2,680	4,141	5,165	5,938	6,414	7,512	7,193	7,116	7,125	7,277
N° Live born	3,385	5,218	6,486	7,492	8,043	9,286	8,734	8,680	8,677	8,848
<u>ONLY THAWING non-donor CYCLES</u>										
N° Patients	3,495	3,501	3,296	3,360	3,750	5,725	7,067	7,967	8,090	9,669
N° Initiated cycles	4,049	3,882	3,703	3,792	4,121	6,199	7,691	8,702	9,397	11,140
N° Pregnancies	451	443	431	506	611	980	1,262	1,569	2,063	2,721
% Pregnancies lost to follow-up	27.9	21.4	10.0	12.1	11.8	4.3	7.8	8.0	6.9	5.7
N° Monitored pregnancies	325	348	388	445	539	938	1,164	1,443	1,921	2,567
N° Deliveries	239	243	272	307	368	655	810	1,011	1,370	1,926
N° Live born	264	290	314	363	415	755	924	1,138	1,540	2,128

	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
<u>IUI-H ACTIVITY</u>										
N° clinics reporting data (with at least 1 patient treated)	275	276	275	297	303	302	298	311	307	299
N° Patients	15,770	18,431	18,972	19,032	20,315	19,707	20,012	18,085	17,218	14,935
N° Initiated cycles	26,292	29,901	31,551	31,268	33,335	32,069	32,644	29,427	27,109	23,866
N° Pregnancies	2,805	3,203	3,400	3,414	3,482	3,306	3,246	3,024	2,775	2,392
% Pregnancy Rate per cycle	10.7	10.7	10.8	10.9	10.4	10.3	9.9	10.3	10.2	10.0
% Pregnancies lost to follow-up	47.8	28.3	20.5	22.3	22.5	15.5	18.1	17.1	16.8	18.0
N° Monitored pregnancies	1,464	2,296	2,703	2,652	2,699	2,793	2,659	2,506	2,309	1,961
N° Deliveries	1,114	1,764	2,076	2,074	2,114	2,220	2,062	1,974	1,810	1,529
N° Live born	1,291	1,999	2,337	2,357	2,361	2,465	2,275	2,156	1,970	1,682

Summary table of activity and outcomes of procedures with gamete/embryo donation, 2014

ART Donor cycles	
N° clinics reporting data (with at least 1 patients treated)	17
N° Patients	205
N° Initiated cycles	209
N° Pregnancies	87
N° Pregnancies lost to follow-up	26.4
N° Monitored Pregnancies	64
Deliveries	49
N° Live born	61
IUI Donor cycles	
N° clinics reporting data (with at least 1 patients treated)	13
N° Patients	32
N° Initiated cycles	37
N° Pregnancies	7
N° Pregnancies lost to follow-up	6
N° Monitored Pregnancies	1
Deliveries	1
N° Live born	1