



EXECUTIVE SUMMARY for 2015

IARTR – THE ITALIAN ASSISTED REPRODUCTIVE TECHNOLOGY REGISTER

**MONITORING THE ACTIVITY AND
OUTCOMES OF ITALIAN ART
CENTERS IN 2015.**

MONITORING THE ACTIVITY AND OUTCOMES OF ITALIAN ART CENTERS IN 2015

AUTHORS

**G. Scaravelli, V. Vigilano, R. De Luca, S. Bolli, R. Spoletini,
S. Fiaccavento, L. Speziale**

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

INDEX

SUMMARY OF OUTPUTS GENERATED FROM IARTR, 2015	5
THE ITALIAN ASSISTED REPRODUCTION TECHNOLOGY REGISTER (IARTR)	6
HOW DOES IARTR WORK?	7
THE IARTR WEB-SITE.....	8
1. ACCESS AND UTILIZATION OF ART SERVICES IN ITALY, 2015	9
1.1.ACCESS TO ART SERVICE	10
1.2.UTILIZATION OF ART SERVICES	12
2. EFFICACY OF ART 2015 AND.....	15
TIME TRENDS 2005-2015	15
2.1. ART, NON-DONOR CYCLES.....	16
2.1.1. <i>What are the steps for an ART treatment using fresh cycles?</i>	16
2.1.2. <i>What are the percentages of initiated cycles, retrievals and transfers that result in pregnancies for fresh cycles?</i>	17
2.1.3. <i>What is the percentage of thawing cycles and transfers that result in pregnancies for FER and FOR techniques?</i>	18
2.1.4. <i>What is the “Cumulative Pregnancy Rate”?</i>	19
2.1.5. <i>What is the gender distribution of infertility factors among ART users?</i>	20
2.1.6. <i>Is the use of ART increasing?</i>	21
2.1.7. <i>Did the use of different ART procedures change over time?</i>	22
2.1.8. <i>Did the use of FER procedures differ in Italy compared to other European countries over time?</i>	23
2.1.9. <i>Has the age of ART female patients changed over time?</i>	24
2.1.10. <i>Has the number of embryos transferred changed in fresh cycles?</i>	26
2.1.11. <i>Did pregnancy rates per transfer changed over time among different ART procedures ?</i>	27
2.1.12. <i>Did cumulative pregnancy rates per initiated cycle changed over time?</i>	28
2.1.13. <i>Did pregnancy rates per retrieval change over time among different female age groups?</i>	29
2.1.14. <i>Does the risk of pregnancy loss differ among women of different age groups?</i>	30
2.2. ART DONOR CYCLES.	31
2.2.1. <i>Which gametes were used in ART donor cycles in 2015?</i>	31

2.2.2. What is the age of recipient female patients in ART donor cycles in 2015?	32
2.2.3. What is the percentage of initiated cycles and transfer that result in pregnancies in ART donor cycles in 2015?.....	33
3. INDICATORS OF ART SAFETY.....	34
3.1.1. Did the percentages of singletons, twins and triplets- or- more deliveries for fresh cycles change over time?	35
3.1.2. Did the percentages of preterm live babies change over time?	36
3.1.3. Did the percentage of underweight live babies change over time?.....	37
4. IUI PROCEDURES	38
4.1.ACCESS TO IUI SERVICE.....	39
4.2. EFFICACY AND SAFETY OF IUI AND TRENDS	41
4.2.1. Is the use of IUI-H increasing?.....	41
4.2.2. Do percentages of IUI-H cycles resulting in pregnancy, differ among women of different age groups?.....	42
4.2.3. Did the percentages of singletons, twins and triplets- or- more deliveries change over time for intrauterine insemination cycles?	43
4.3. IUI DONOR CYCLES.....	44
4.3.1. What is the outcome in IUI donor cycles in 2015?	44
APPENDIX. SUMMARY TABLE OF ACTIVITY AND OUTCOMES OF ART PROCEDURES, YEARS 2010 – 2015.....	45
SUMMARY TABLE OF ACTIVITY AND OUTCOMES OF ALL PROCEDURES, 2010 – 2015.....	46
SUMMARY TABLE OF ACTIVITY AND OUTCOMES OF PROCEDURES WITH GAMETE/EMBRYO DONATION, 2014-2015	48

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

Summary of outputs generated from IARTR, 2015

	Non-donor Procedures				Gametes/embryo donation		
	IVF	ICSI	FER	FOR	Semen Donation	Egg Donation	Cryopreserved Embryos
N° of patients	45,689		10,557	1,418	494	1,220	369
N° Initiated cycles	7,985	47,344	12,903	1,529	559	1,308	420
N° Aspirations	7,107	43,107	-	-			
N° Transfers	5,765	32,210	11,849	1,221	437	1,206	409
<i>with 1 embryo</i>	1,551	9,372	6,957	381	121	276	165
<i>with 2 embryos</i>	2,866	15,477	4,193	638	233	708	230
<i>with 3 embryos</i>	1,200	6,785	653	197	83	222	14
<i>with 4 o + embryos</i>	148	576	46	5	-	-	-
N° Pregnancies	1,638	8,443	3,379	254	164	381	132
Pregnancy per Initiated cycles/thawings (%)	20.5	17.8	26.2	16.6	29.3	29.1	31.4
Pregnancy per Transfer (%)	28.4	26.2	28.5	20.8	37.5	31.6	32.3
Pregnancies lost to follow-up (%)	9.4	13.8	5.6	5.9	9.8	22.0	4.5
N° Pregancy losses	360	1,903	787	69	30	67	33
Pregnancy loss (%)	24.3	26.2	24.7	28.9	20.3	22.6	33.3
N° Deliveries	1,124	5,374	2,403	170	118	230	93
Twin deliveries (%)	17.5	17.2	8.7	12.4	20,3	21,7	17,2
Triplets or more deliveries (%)	0.6	0.9	0.2	0.6	-	0,9	-
N° Live born babies	1,332	6,363	2,609	193	142	281	109

THE ITALIAN ASSISTED REPRODUCTION TECHNOLOGY REGISTER (IARTR)

The Assisted Reproductive Technology 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 2005 (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.

The 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 and addresses, type of service offered (public, private or private covered by the National Health service), the different techniques performed, activity, availability, efficacy and safety of techniques application;

PROMOTE research and study on couple infertility causes, long-term evaluation of well-being of the children born after ART procedures; research on gametes characteristics new cryopreservation protocols; monitoring time trends in ART applications in order to compare different attitudes with other countries.

The Register prepares an annual epidemiological/statistical report on the ART centres' activity for the Minister of Health in order to illustrate to the Parliament the situation in the 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 39 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 data collection it is organized in two different times frames:

- The first phase of the collection is related to the activity conducted and the results obtained in 2015 and it was carried out from May to June 2016;
- The second phase of the collection is related to the outcomes of pregnancies obtained from ART treatments started in 2015 and it was carried out October to December 2016.

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 perform, 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 reasons, news on reproductive and infertility issues, and a steady overview on Italian and European legislation on the 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 140.000 users, with a daily average of about 380 hits, and is the second most visited site in the National Institute of Health Portal

1. ACCESS AND UTILIZATION OF ART SERVICES IN ITALY, 2015

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 Northern Italy (79 centers, 39.1% of the total) and in the Southern area (76 centers, 37.6% of the total), irrespective of the amount of their activity.

Figure 1: Regional distribution of the ART active centers, 2015. Total = 202 centers

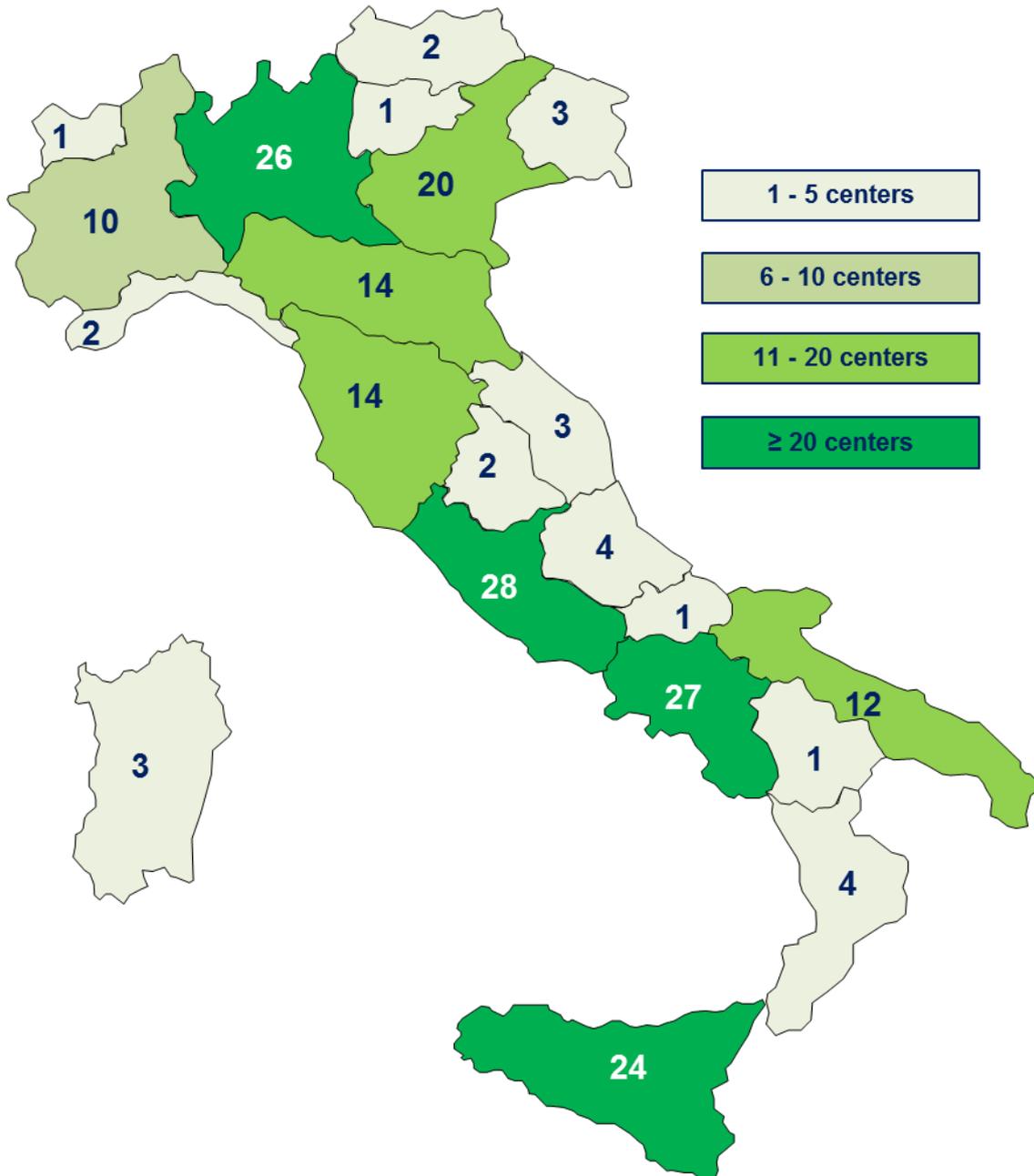


Table 1 shows the geographical distribution of ART centers according to the type of services offered. Overall, the number of centers active in 2015 was 202, 93 of which (46%) operating within the National Health Service (public and private), and 109 (54%) which provided only private service. The majority of ART centers providing public service was concentrated in the North of Italy, i.e. in the North West 76.9%, while in the Centre and in the South there were mainly private facilities (55.3% and 69.7%, respectively).

Table 1: ART centers distribution by region and type of service, 2015.

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	13	50.0	10	38.5	3	11.5
Liguria	2	2	100	0	-	0	-
North-West	39	19	48.7	11	28.2	9	23.1
A.P. Bolzano	2	1	50.0	0	-	1	50.0
A.P. 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	14	6	42.9	0	-	8	57.1
North-East	40	18	45.0	1	2.5	21	52.5
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	28	6	21.4	2	7.1	20	71.4
Central	47	13	27.7	8	17.0	26	55.3
Abruzzo	4	2	50.0	0	-	2	50.0
Molise	1	0	-	0	-	1	100
Campania	27	7	25.9	0	-	20	74.1
Puglia	12	3	25.0	0	-	9	75.0
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	76	23	30.3	0	-	53	69.7
Italy	202	73	36.1	20	9.9	109	54.0

1.2.Utilization of ART services

In **Table 2** time-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 539 cycles (+ 84.7%) and of 3,658 cycles (+ 136.4%), respectively.

The latest European data available refers to the activity of year 2013 (article in press). The number of started cycles per million inhabitants (calculated only for the 18 countries that have reported data of 100% of the centers) was 1,175 cycles vs. 1,070 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 (2005-2015) and in Europe (2005-2013).

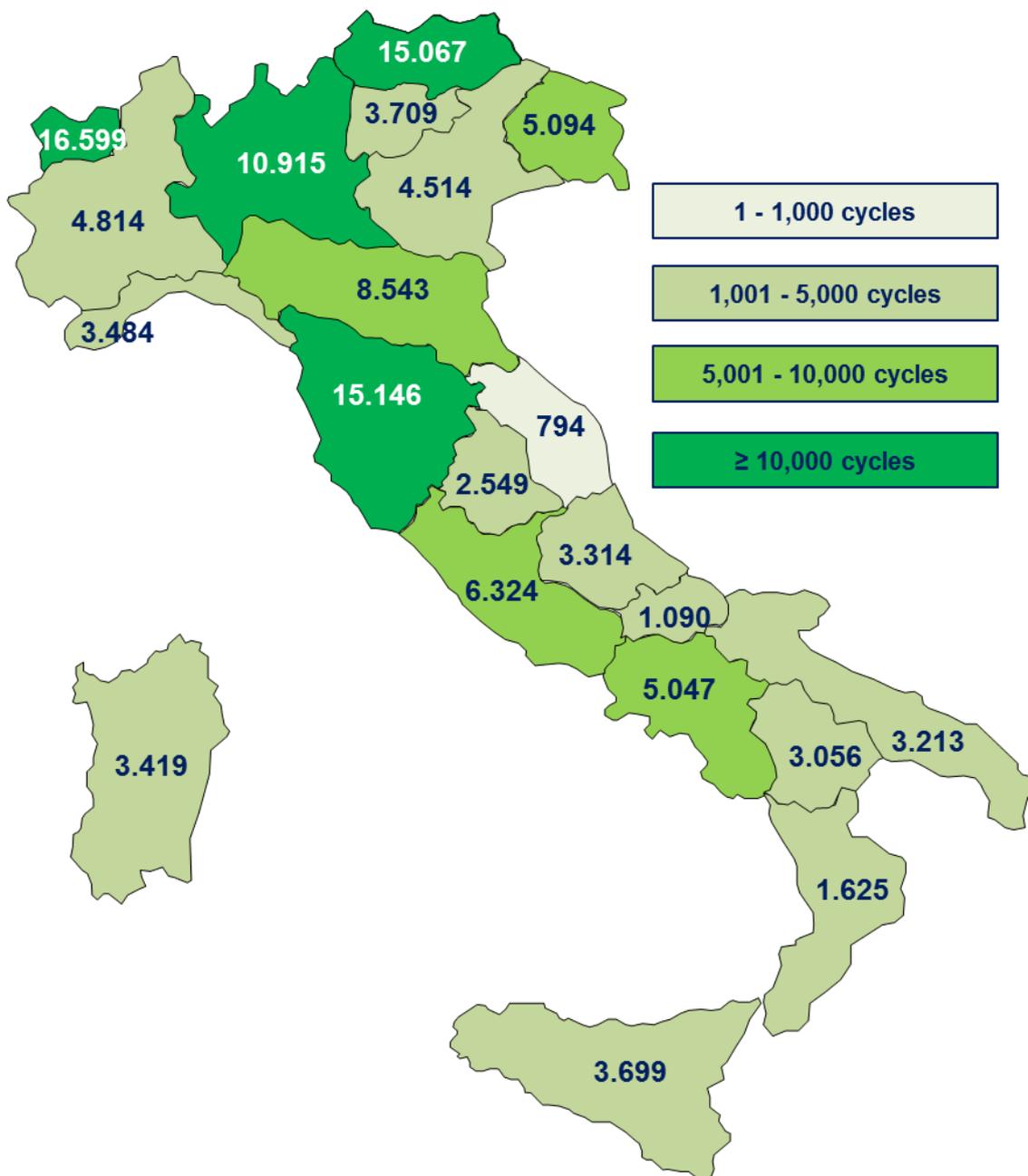
Years	ART Cycles/million population		ART cycles/million women (15 - 45 years)	
	Italy	Europe ^a	Italy	Europe ^a
2005	636	1,115	2,683	4,008
2006	692	850	3,328	3,503
2007	736	886	3,569	4,320
2008	800	947	3,905	4,661
2009	865	1,067	4,265	5,455
2010	973	1,221	4,863	6,258
2011	1,063	1,269	5,392	6,556
2012	1,078	1,252	5,562	6,519
2013	1,070	1,175	5,601	6,210
2014	1,102	-	5,855	-
2015	1,175	-	6,341	-

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. There is a great difference in the number of cycles performed among regions ranging from 16,599 cycles offered in Valle d'Aosta to 794 cycles provided in Marche (in small regions it depends on the small number of women living there). In general, only 6 regions in Northern and Central area have numbers above the national average (6,341 cycles), while all the southern regions 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)*, 2015.

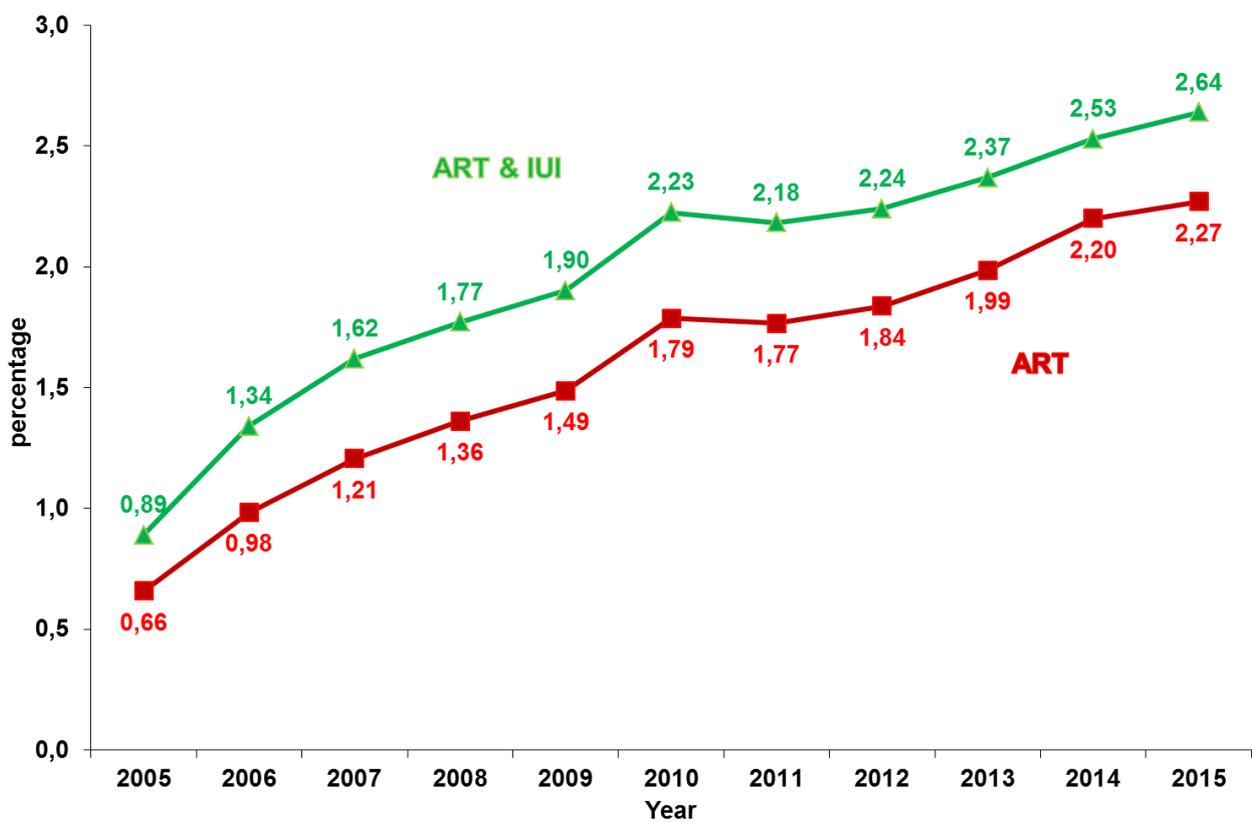


*Average resident population in 2015: Source ISTAT.

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 2015 the percentage of infants born with ART procedures increased 3 times.

Since its establishment, IARTR collected data on 116,771 infants, of which 94,070 from ART and 22,701 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 11.1% in 2015.

Figure 3: Time-trends of the percentage of babies born live after ART and after ART & IUI in relation to the annual national number of children born in Italy, 2005-2015.



2.EFFICACY OF ART 2015 AND TIME TRENDS 2005-2015

2.1. ART, non-donor cycles.

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

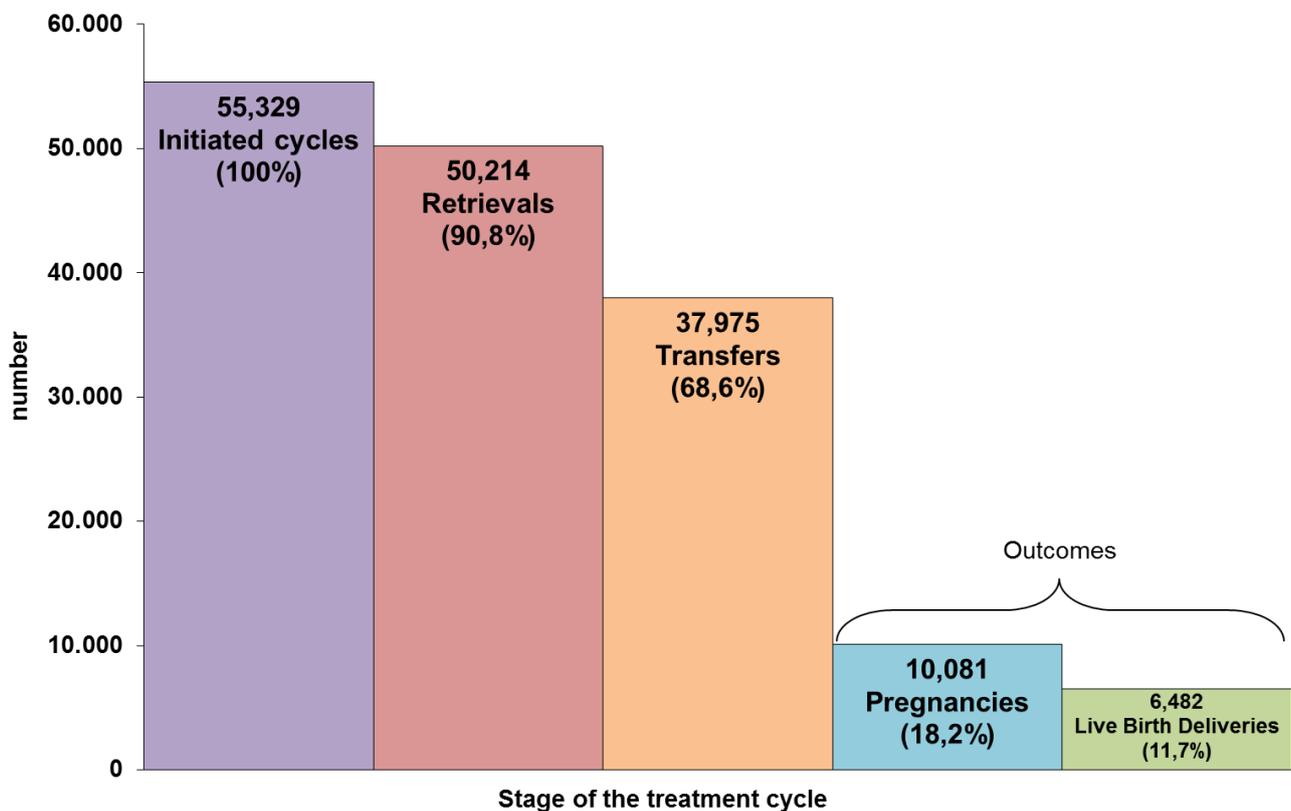
An ART cycle using fresh gametes:

- 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 2015 are shown.

Of 55,329 fresh cycles, 90.8% resulted in an egg retrievals, 68.6% in an embryo transfers, 18.2% in a pregnancy and 11,7% in a live birth delivery.

Figure 4: Outcomes of ART using fresh cycles by stage of the treatment cycle, 2015.



2.1.2. 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:

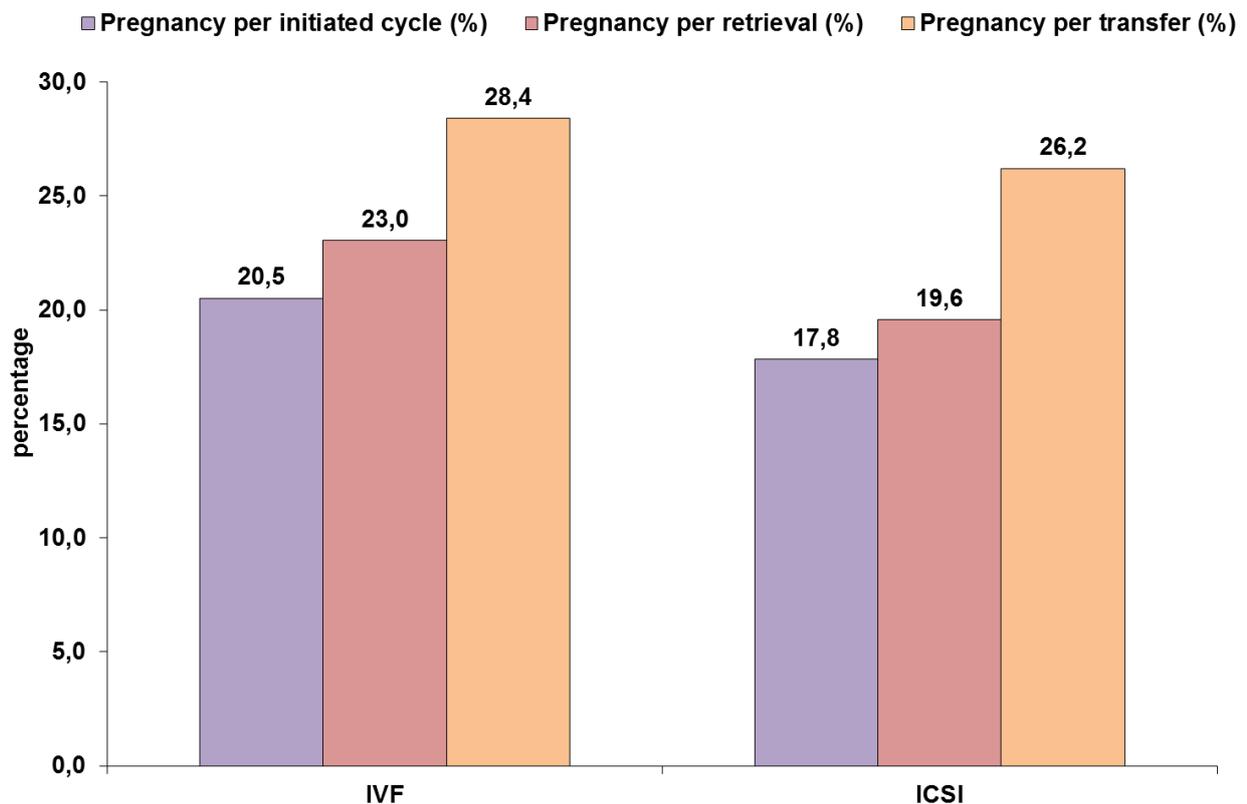
- **In vitro fertilization (IVF):** an ART procedure that involves extracorporeal fertilization;
- **Intra Cytoplasmic Sperm Injection (ICSI):** a procedure in which a single spermatozoon is injected into the oocyte cytoplasm.

(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 2015). 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, 2015.



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

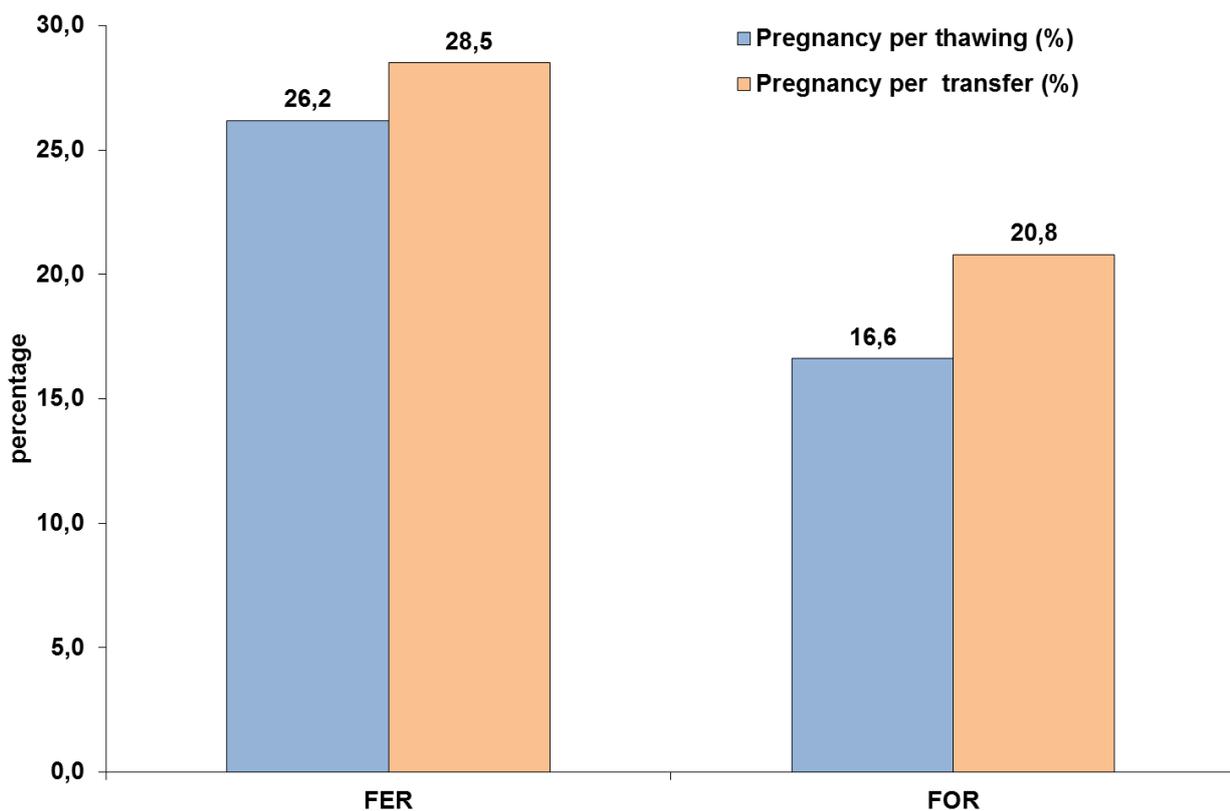
An ART treatment in which are used cryopreserved oocytes or embryos, it can be defined “frozen/thawing cycle”, that includes:

- **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, 2015.

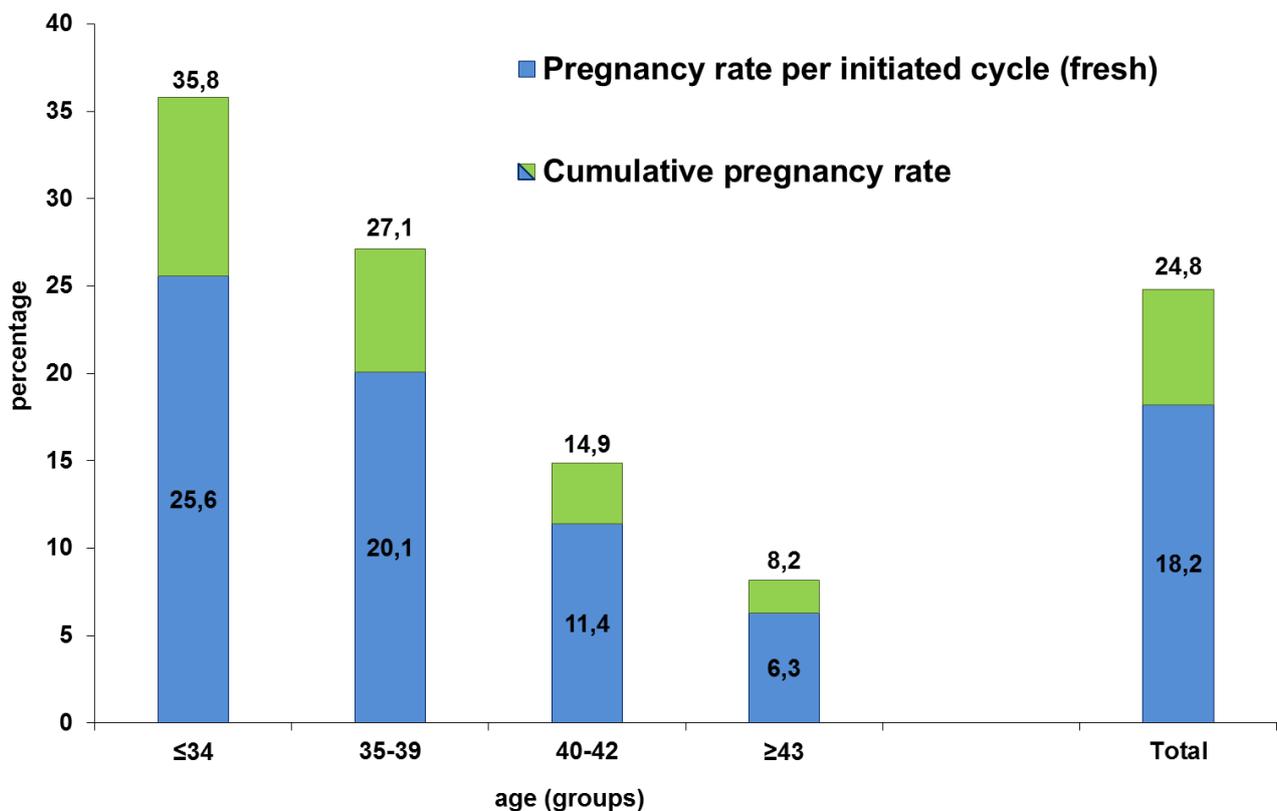


2.1.4. What is the “Cumulative Pregnancy Rate”?

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 these 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 36%.

Figure 7: Pregnancy rates per initiated cycle for fresh and Cumulative pregnancy rates per initiated cycle, by female patients age groups, 2015.



2.1.5. 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 2015. 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.

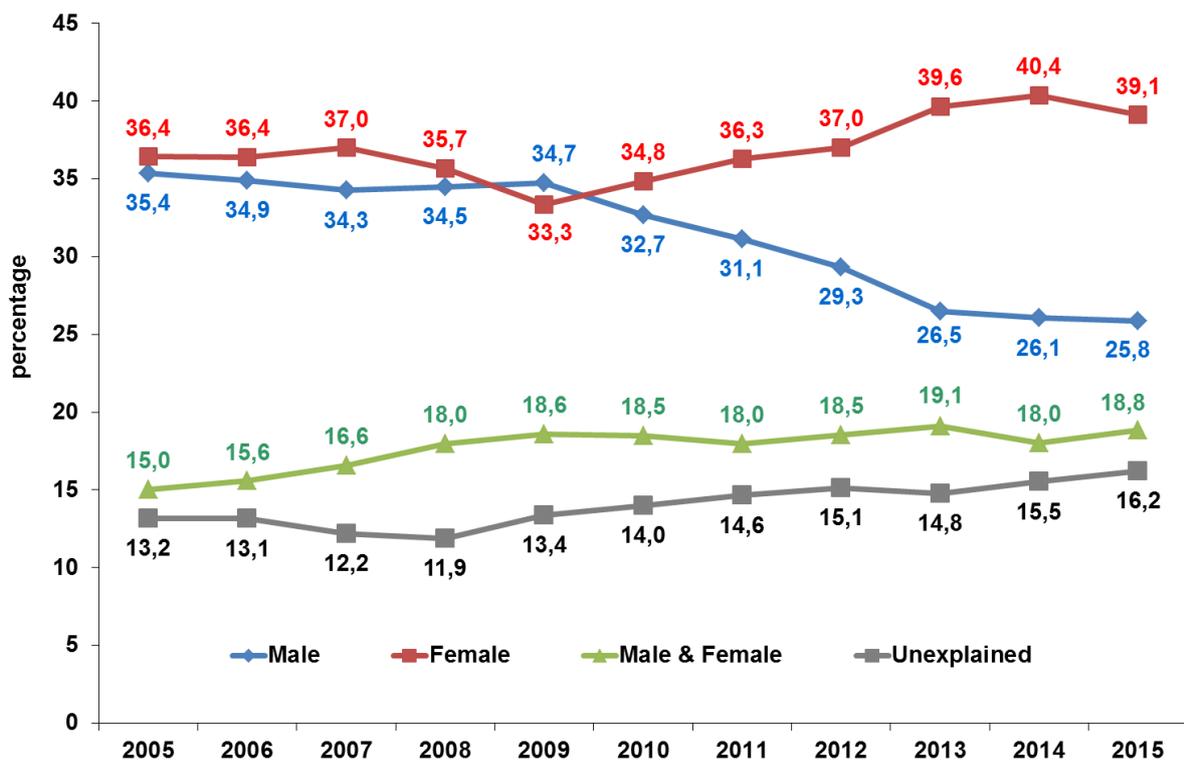
- **Male factor** - Low or no sperm counts, poor sperm motility, and abnormally-shaped sperm can all cause infertility.

- **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: Time-trends of gender distributions of infertility causes among patients who had ART using fresh cycle, 2015. Total couples treated: 45,689



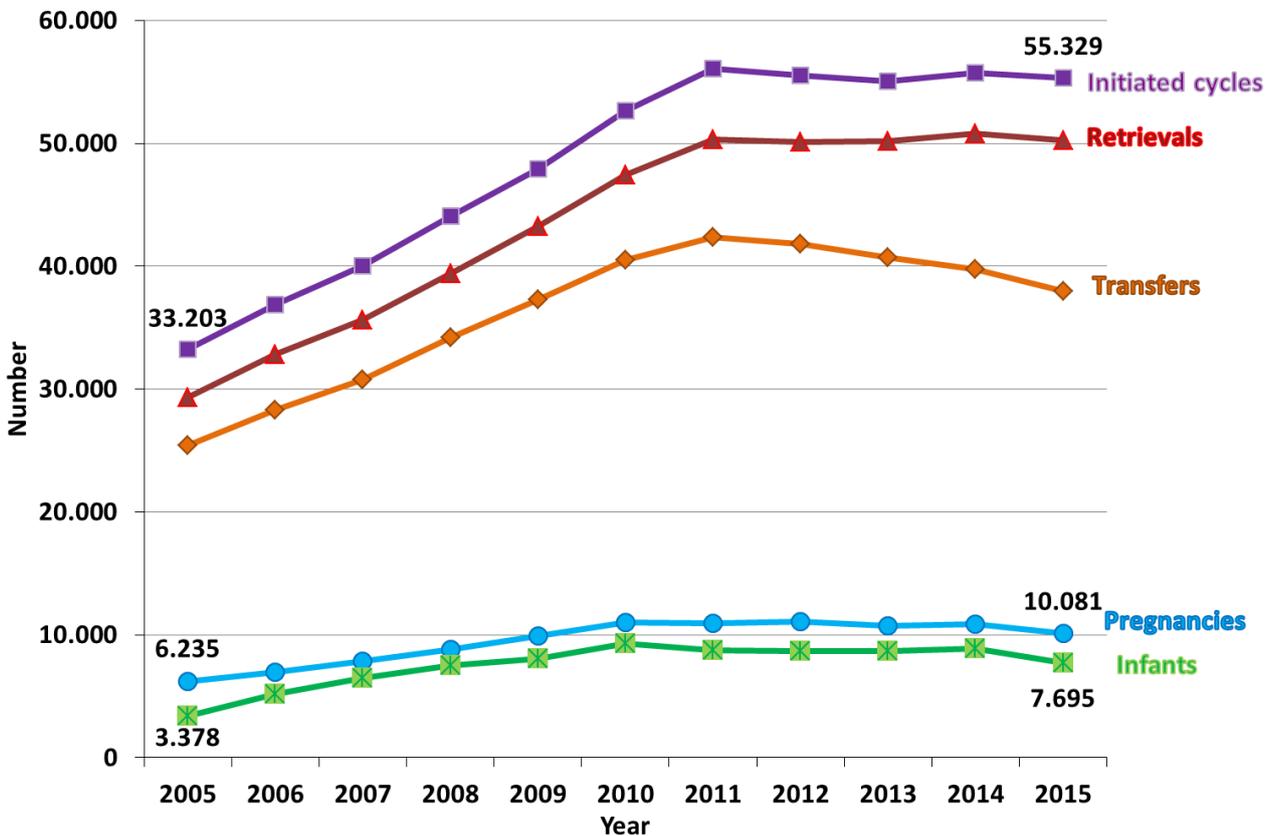
2.1.6. Is the use of ART increasing?

Figure 9 shows the number of cycle, retrievals, transfers performed, pregnancies obtained and infants born using fresh cycles from 2005 to 2015.

The numbers of initiated cycles and pregnancies obtained increased by 67% and 62%, respectively, over time. In details, from 33,203 cycles and 6,235 pregnancies in 2005 to 55,329 cycles and 10,081 pregnancies in 2015.

The number of infants born after fresh ART cycles in 2015 was 128% 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 11.1% in 2014.

Figure 9: Time-trends of initiated cycles, retrievals, transfers, pregnancies and deliveries obtained from fresh cycles, 2005–2015.



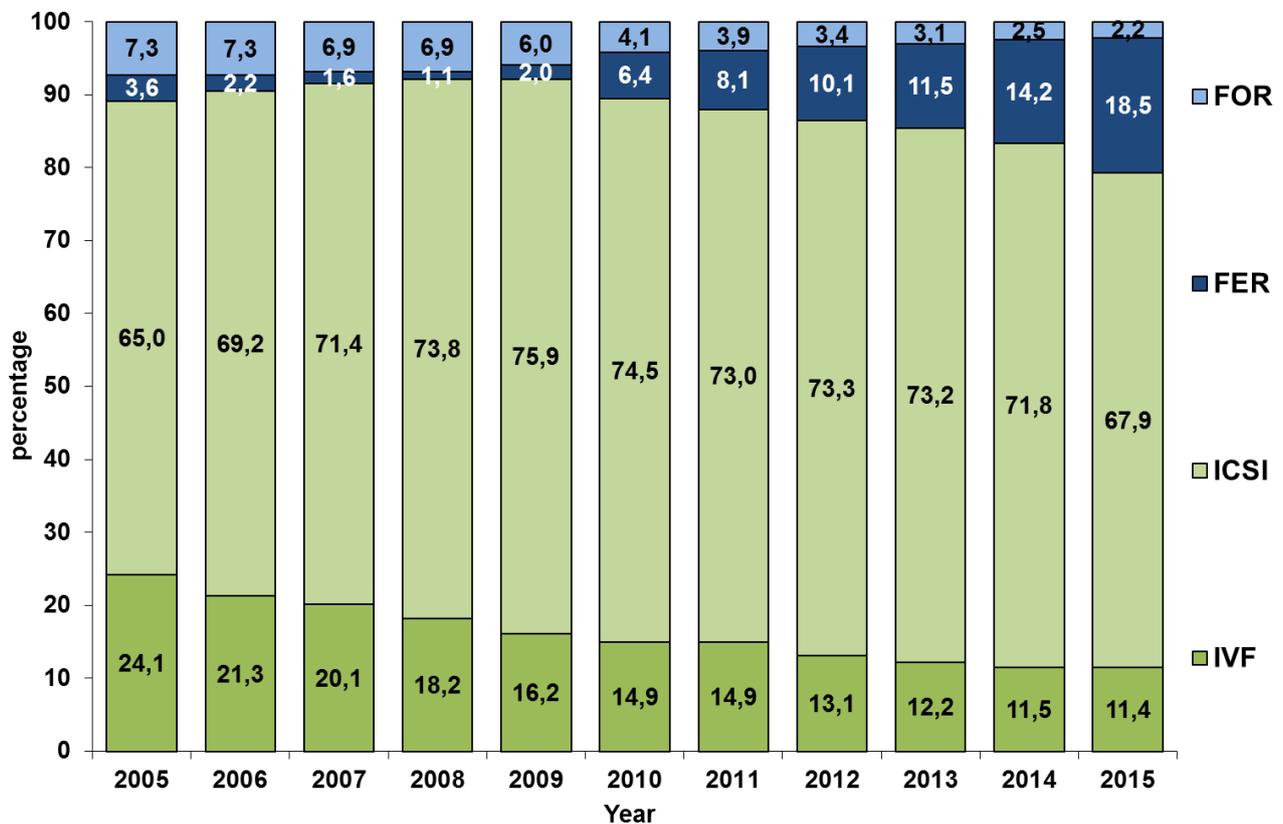
2.1.7. Did the use of different ART procedures change over time?

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), and thawing with FER and FOR from 2005 through 2015.

The number of ICSI cycles increased from 24,209 in 2005 to 47,344 in 2015, while IVF cycles decreased from 8,994 to 7,985. Also FER thawing increased from 1,338 to 12,903, while FOR procedures decreased from 2,711 to 1,529.

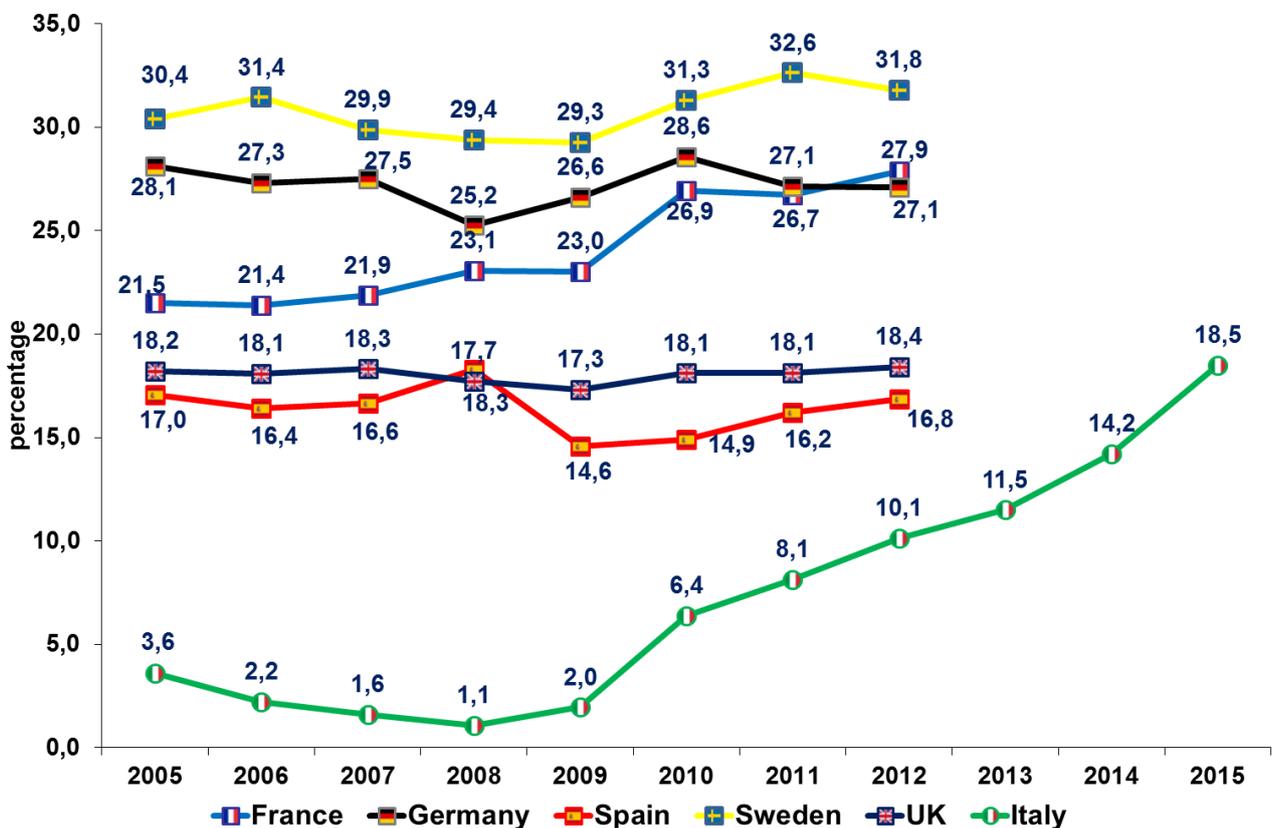
Figure 10: Time-trends of ART procedures, 2005-2015.



2.1.8. 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 18.5% in 2015. In comparison with some of the largest European countries, Italy showed the lowest number of FER cycles performed

Figure 11: Time-trends of percentages of FER thawing on total ART initiated cycles in Europe, 2005-2015.

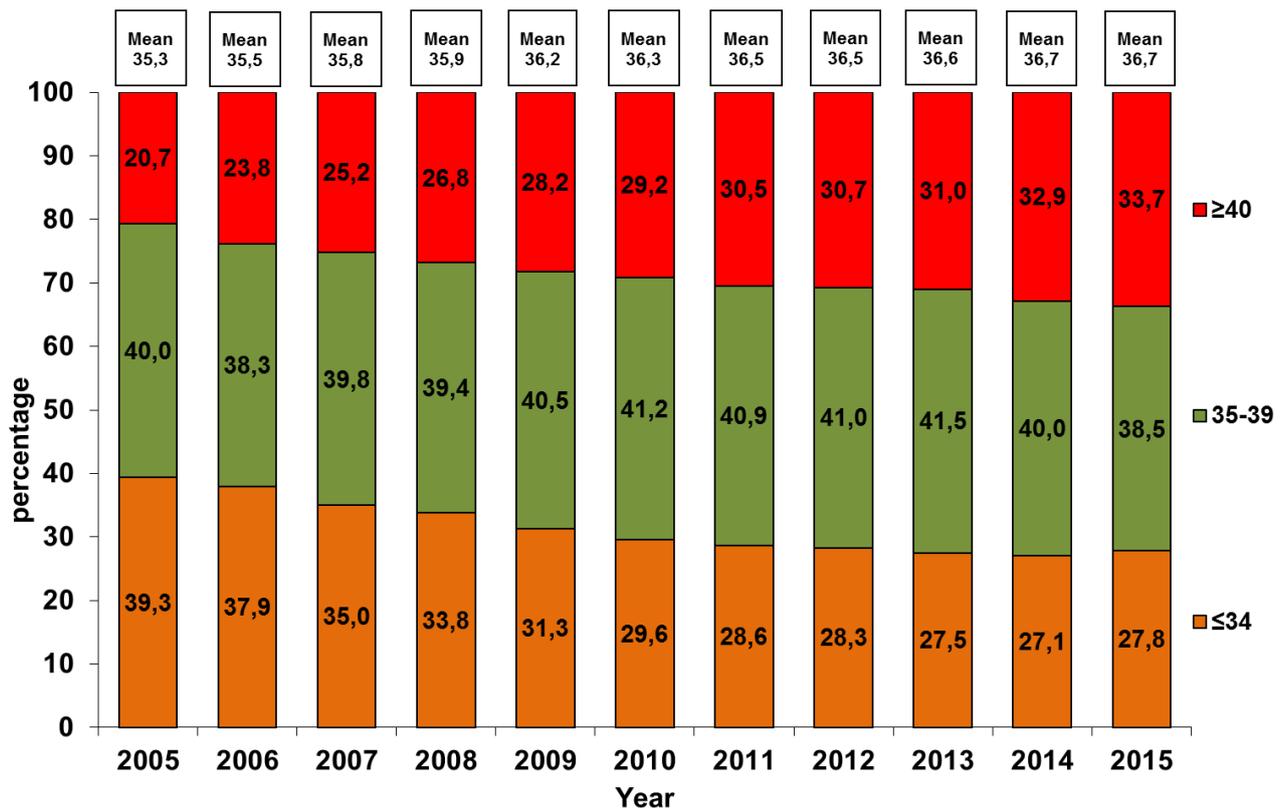


2.1.9. Has the age of ART female patients changed over time?

Figure 12 shows the distribution of fresh cycles by women age groups, from 2005 to 2015.

For women older than 40 the percentage of fresh cycles performed increased from 20.7% in 2005 to 33.7% in 2015, whilst the percentage of fresh cycles performed in women ≤ 34 years old decreased from 39.3% in 2005 to 27.8% in 2015. Overall, the mean age of women who had fresh cycles increase from 35.3 to 36.7 years over time.

Figure 12: Time-trends of fresh initiated cycles distributions by age classes of female patients, 2005-2015.



Figures 13 and 14 (on the next page) show the distributions of the initiated cycles (thawing) with embryo (FER) and oocyte (FOR) frozen/thawing techniques according to the age groups of the patients at the time of freezing, from 2009 (when IARTR start of collecting this data) to 2015. For cycles started with FER (Figure 13) is observed a slight decrease in the mean age of patients from 35.4 in 2014 to 35.2 years in 2015. Patients with less than 35 years increased (+ 2.2%), while the percentage of patients between 35 and 39 years (-0.7%) and those in patients over 40 years (-1.5%) decreased. Regarding the cycles started with FOR (Figure 14), there is an increase of patients over 40 years (+ 1.2%) compared to 2014. The percentage of patients between 35 and 39 years (-0.8%) and those with less than 35 years (-0.3%) slightly decreased. The average age grew slightly to 35.2 years.

Figure 13: Time-trends of FER thawing cycles distributions by age classes of female patients, 2009-2015.

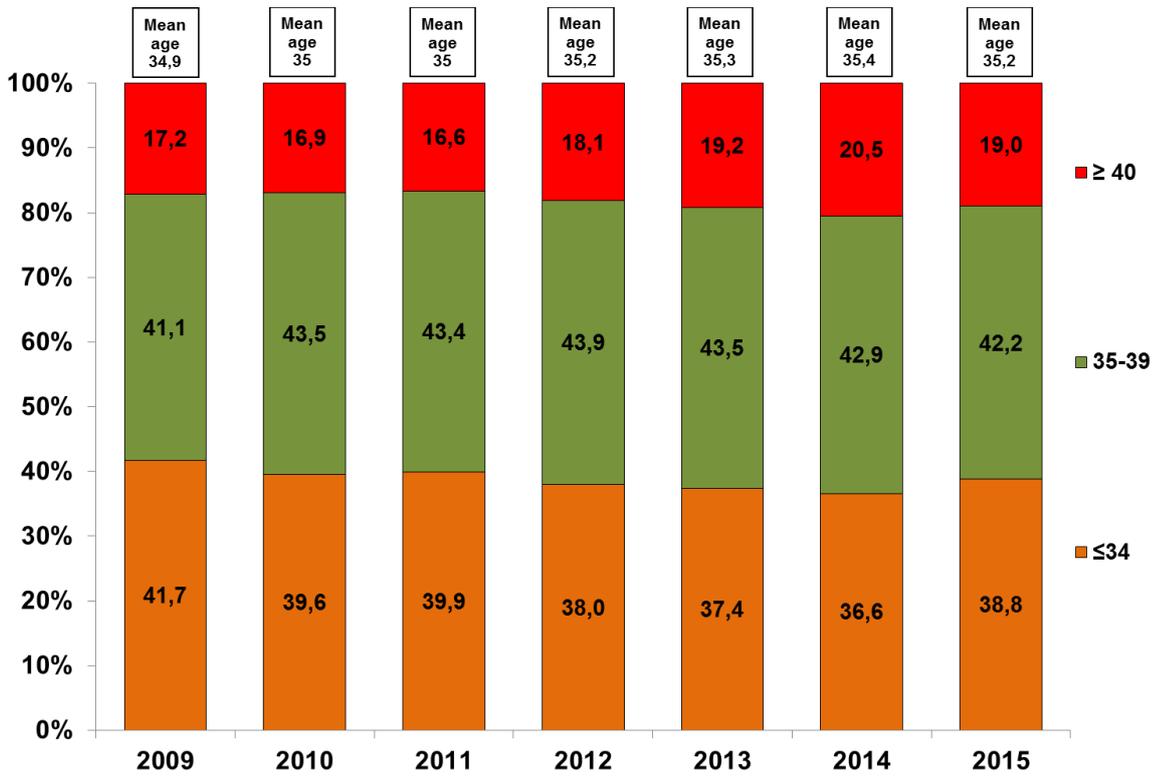
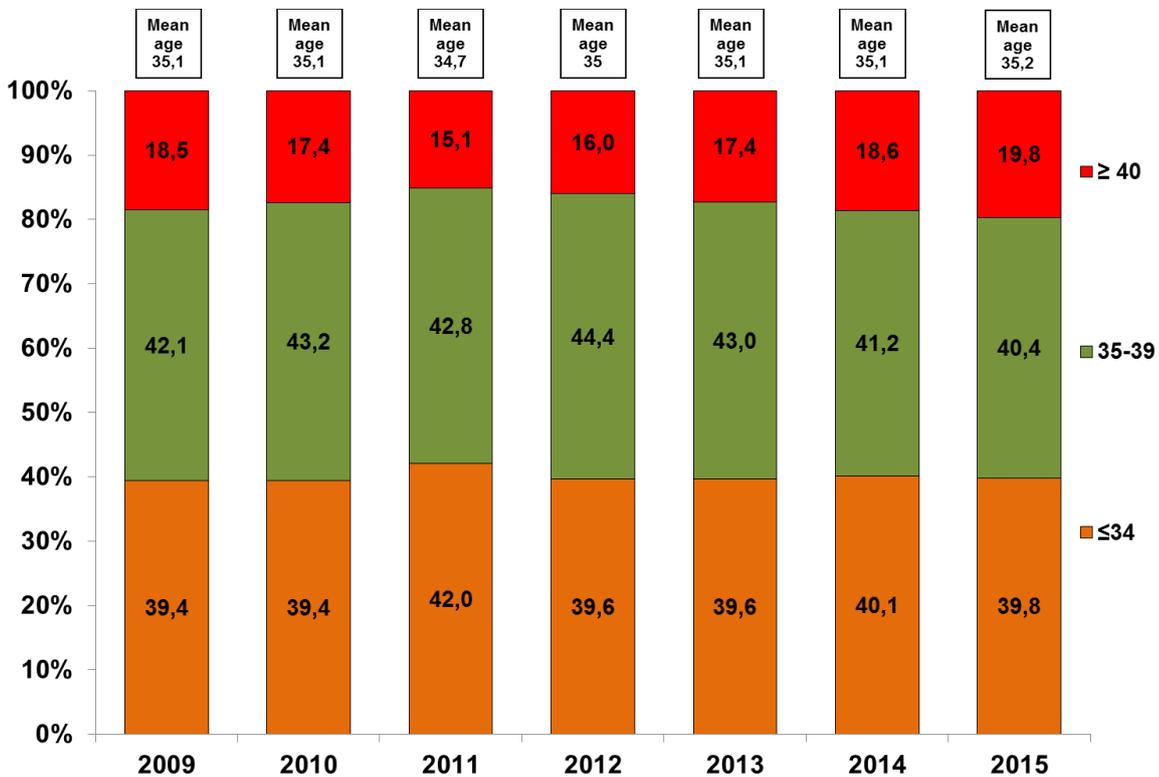


Figure 14: Time-trends of FOR thawing cycles distributions by age classes of female patients, 2009-2015.

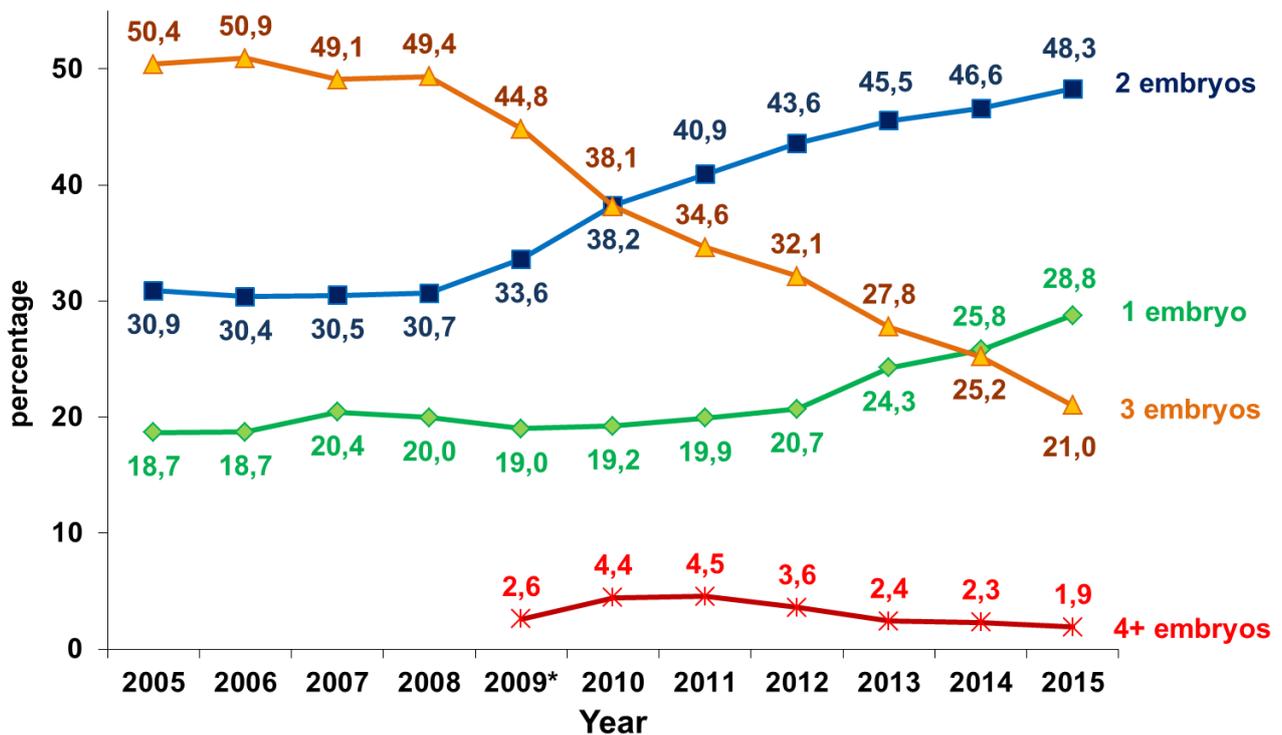


2.1.10. Has the number of embryos transferred changed in fresh cycles?

Figure 15 shows trends with the number of embryos transferred in fresh cycles.

From 2005 to 2015 the transfer with one and two embryos increased from 18.7% and 30.9% to 28.8% and 48.3%, respectively. On the other hand transfers with 3 embryos dramatically decreased from 50.4%, first to 38.1% in 2010 to reach the 21% in 2015. 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 all the embryos created for a maximum of three removed. Values of transfers with four or more embryos were quite stable during time, from 2.6% in 2009 to 1.9% in 2015. The average number of embryos transferred decreased from 2.3 embryos per transfer in 2005 to less than 2 in 2015.

Figure 15: Time-trends of transfer by number of embryos transferred, 2005-2015.



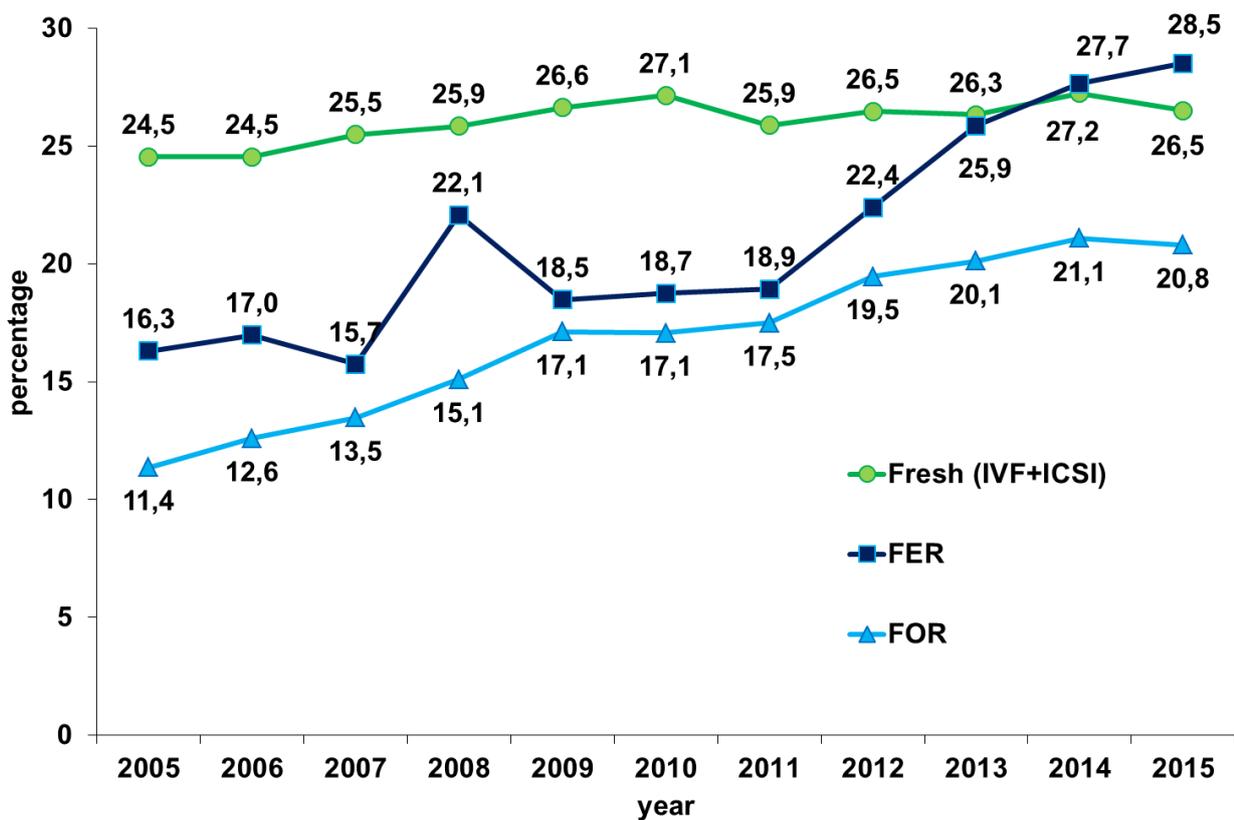
*year of the Constitutional Court sentence 151/2009.

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

Figure 16 shows pregnancy rates per transfer in order to compare cycles with fresh oocytes vs. those using frozen embryos (FER) or frozen oocytes (FOR).

Overall, FER cycles showed the best pregnancy rates increasing highly from 16.3% in 2005 to 28.5% in 2015, those with fresh oocytes slightly increased from 24.3% to 26.5%, and those with frozen oocytes from 11.4% to 20.8%.

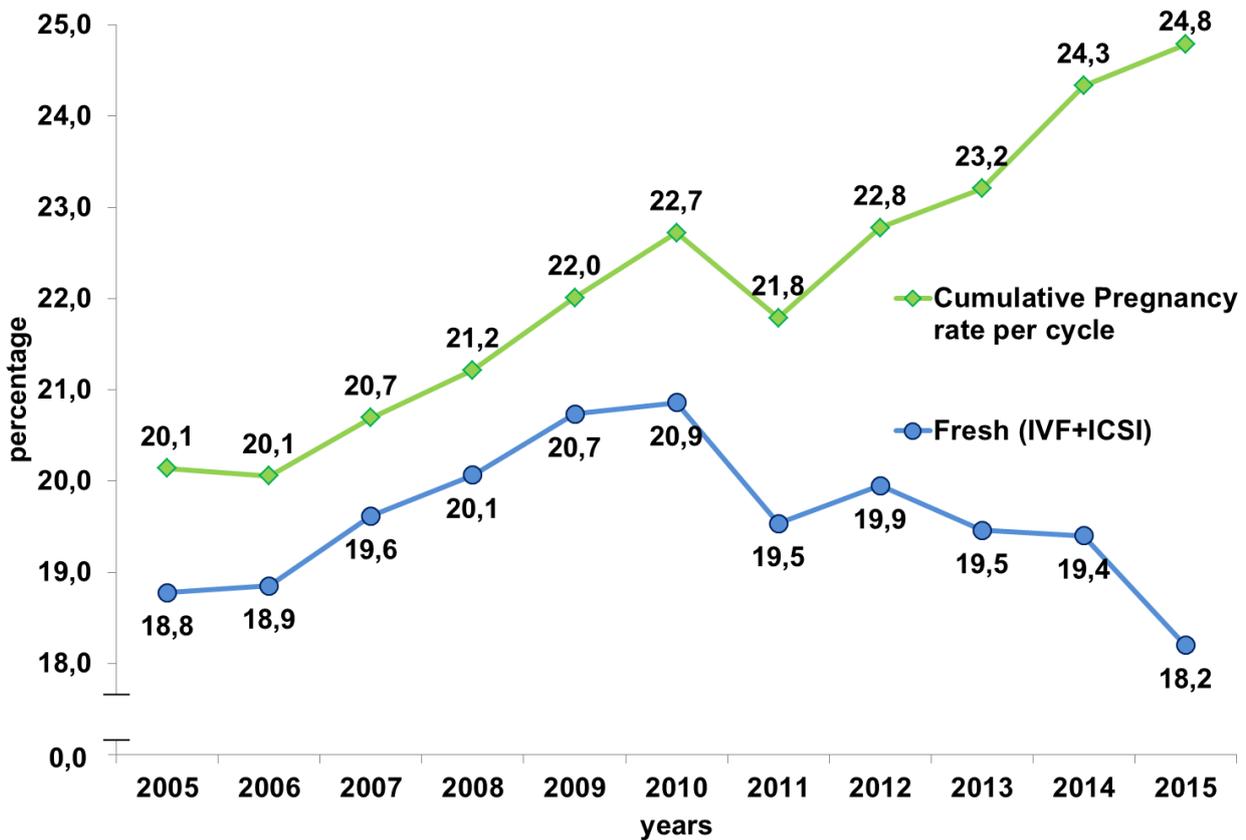
Figure 16: Time-trends of pregnancy rate per transfer for fresh, thawed embryos (FER) and thawed/warmed oocytes cycles (FOR), 2005-2015.



2.1.12. Did cumulative pregnancy rates per initiated cycle changed over time?

Figure 17 compares the percentage of pregnancies obtained on fresh initiated cycles with the Cumulative Pregnancy Rate over time. As described in chapter 2.2.4, CPR is presented as the sum of pregnancies obtained from fresh cycles and with frozen/thawing cycles (FER and FOR) as nominator and the number of initiated cycles with fresh techniques of the same year as denominator. CPR gives an estimate of the likelihood of obtain a pregnancy for a woman undergoing an ART cycle, also having the opportunity to perform oocyte and/or embryo thawing cycles. Moreover, the comparison of pregnancy rate from fresh cycles vs. CPR may show the estimated added value of embryo and oocyte cryopreservation. As the Figure 14B show this value is constantly growing from +7.2% in 2005 to a 36.2% in 2015

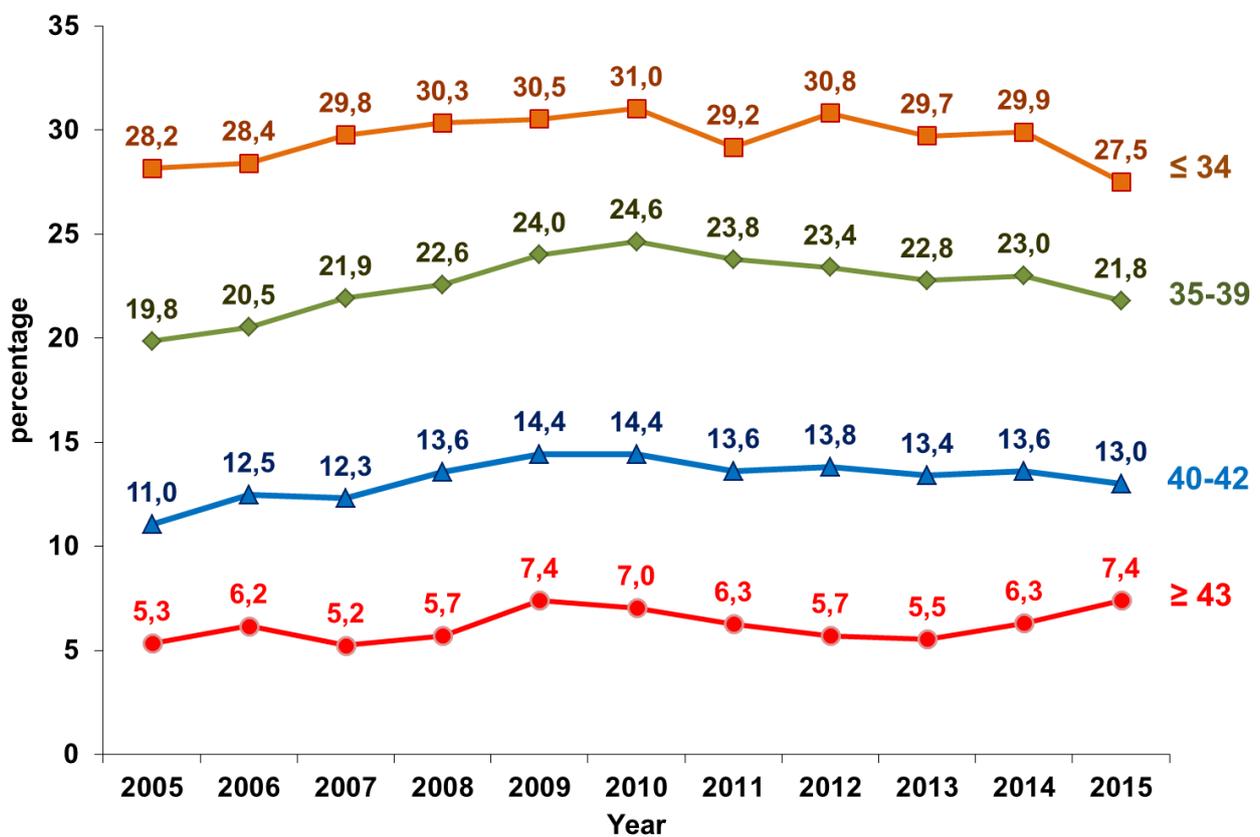
Figure 17: Time-trends of pregnancy rate per initiated cycle for fresh and cumulative pregnancy rate per initiated cycle, 2005-2015.



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

Figure 18 shows pregnancy rates per retrieval according to women age groups, after fresh cycles. From 2005 to 2015 pregnancy rates per retrieval decreased from 28.2% to 27.5% for women aged less than 34, while they increased from 19.8% to 21.8% for women aged 35-39, from 11.0% to 13.0% for women aged over 40-42 and from 5.3% to 7.4% in women aged more than 42 years.

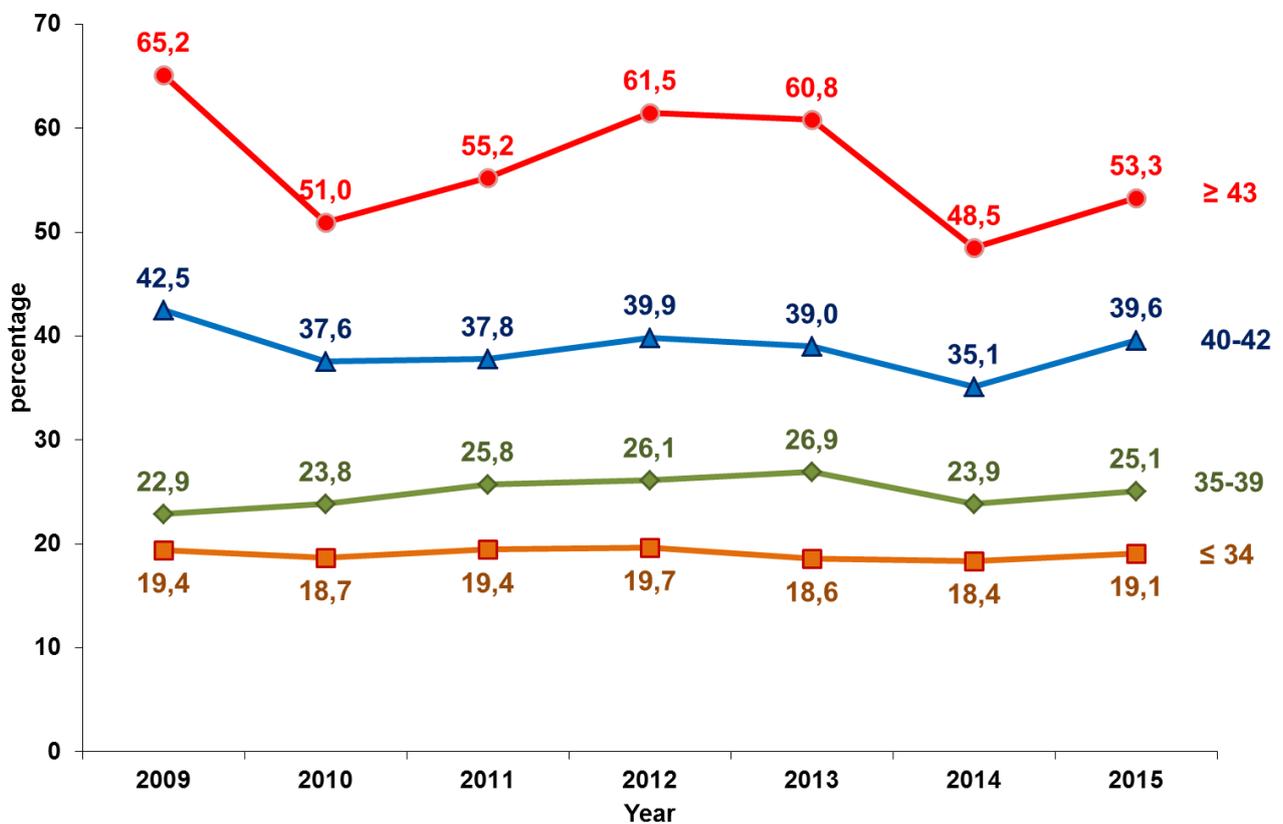
Figure 18: Time-trends of pregnancy rates per retrievals with fresh cycles by age groups of female patients, 2005-2015.



2.1.14. 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 19** rates in older age groups were much higher. Rates decreased over time from 65.2% to 53.5% for women older than 43 years old and from 42.5% to 39.6% for women aged 40-42. Rates for the age classes younger than 40 were quite stable from 2009 to 2014.

Figure 19: Time-trends of percentages of total pregnancy loss using ART cycles by female age groups, 2009-2015.



2.2. ART donor cycles.

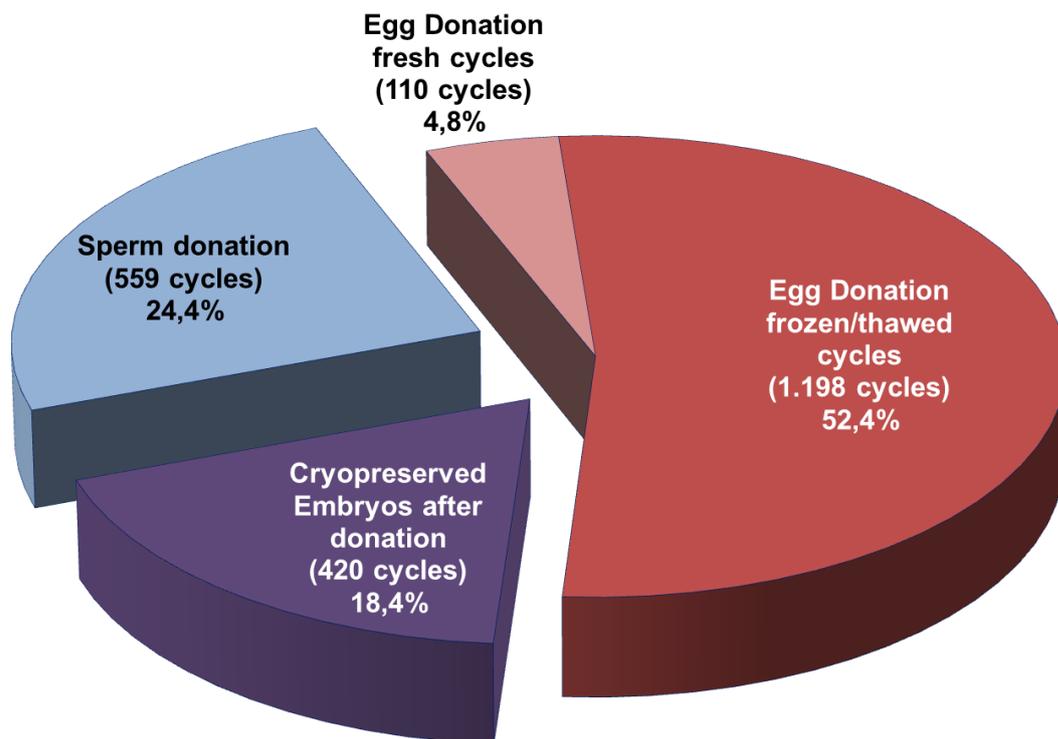
In April 2014 Italian Constitutional Court removed the prohibition, set out in the law, regarding the practice of ART techniques using donor gametes, now permitted under specific conditions.

For more detailed data on activity and outcomes regarding ART donor cycles, please check on Summary table for 2015 (on page 42).

2.2.1. Which gametes were used in ART donor cycles in 2015?

Figure 20 shows the distribution of types of ART cycles using donor gametes applied in Italy in 2015. In about 57% of ART donor cycles, fresh or frozen eggs were used. In almost 24% of cycles there was a sperm donation. More than 18% of cycles were performed using cryopreserved embryos obtained from donation of a gamete.

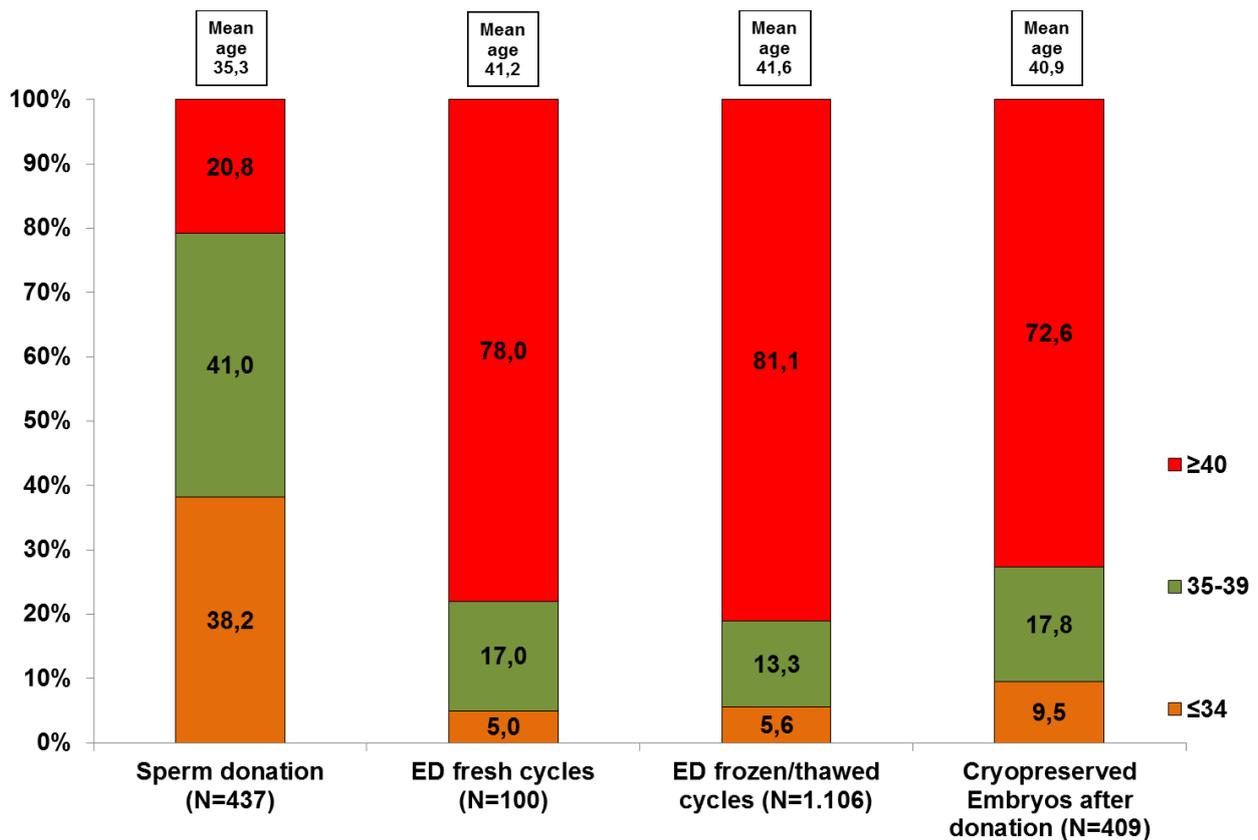
Figure 20: Distribution of all ART cycles using donor gametes or cryopreserved embryos after donation, 2015. Total cycles = 2.287.



2.2.2. What is the age of recipient female patients in ART donor cycles in 2015?

Figure 21 shows the distribution of transfers performed according to the recipient female age group at the start of a cycle performed with a gamete donation. The different distribution by age depending on the different types of gametes and embryos used reflects the indication of the treatment of the technique itself.

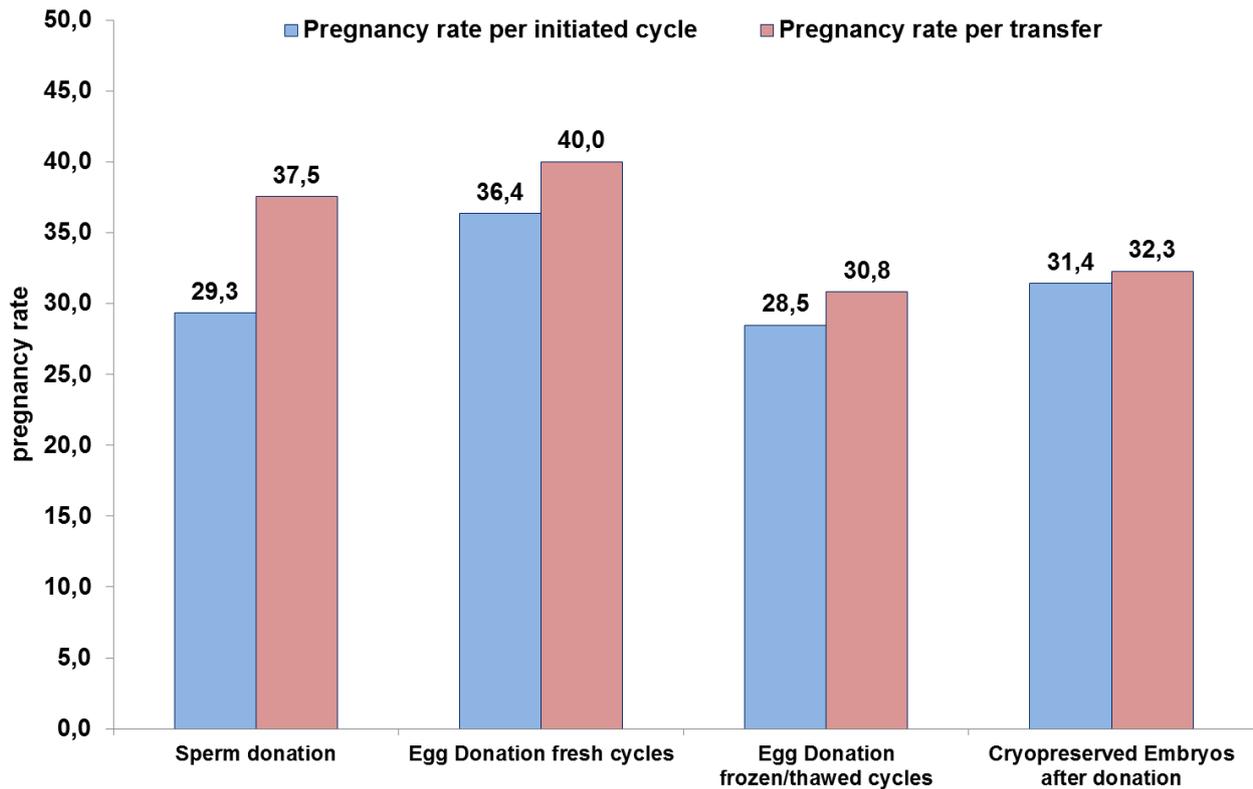
Figure 21: Distribution of transfers cycles using donor gametes or cryopreserved embryos after donation by recipient female age groups, 2015.



2.2.3. What is the percentage of initiated cycles and transfer that result in pregnancies in ART donor cycles in 2015?

In Figure 22 the pregnancy rate per initiated cycle and per transfer in ART donor techniques are shown. Highest rates are obtained in ART donor cycles with the utilization of fresh egg.

Figure 22: Distribution of pregnancy rate per initiated cycle and per transfer using donor gametes or cryopreserved embryos after donation, 2015.



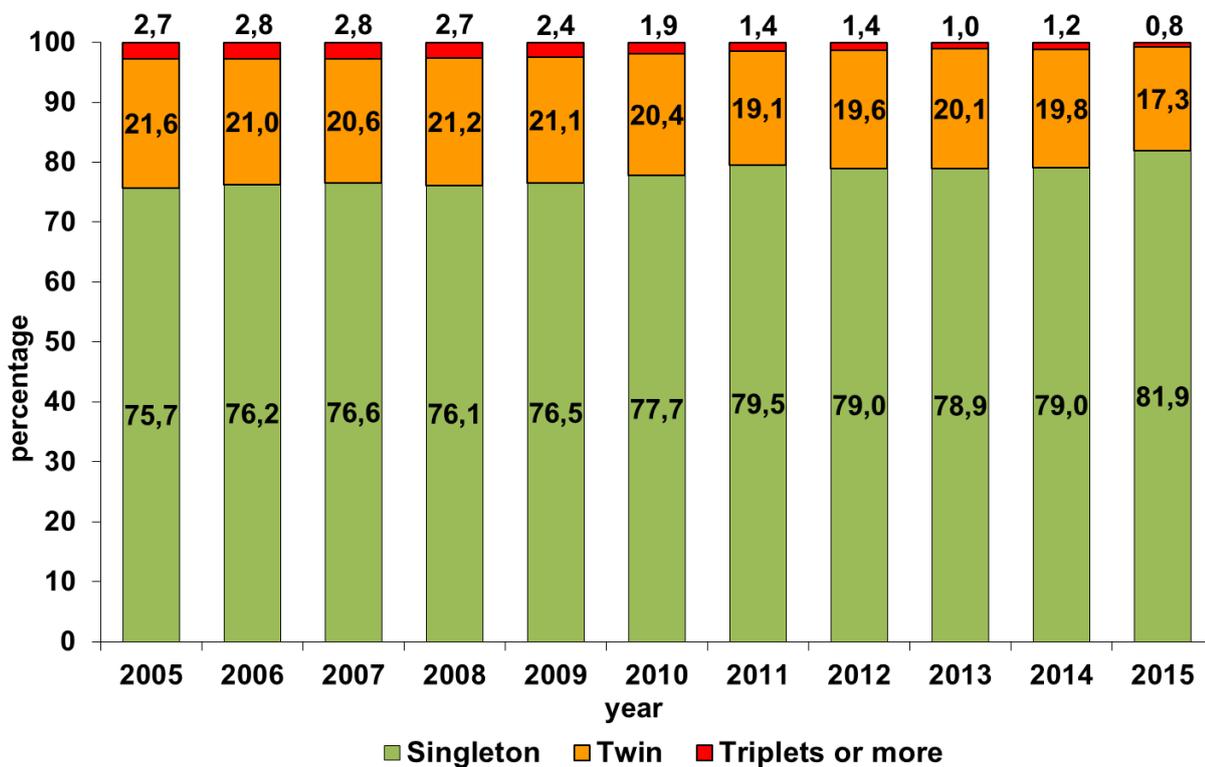
3.INDICATORS OF ART SAFETY

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

Figure 23 shows trends for singleton and triplet deliveries in fresh cycles.

From 2005 to 2015 twin delivery rates decreased from 21.6% to 17.3% while numbers of triplets and more deliveries decreased from 2.7% to 0.8%, similar to the 0.6% 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 23: Time-trends of multiplicity of deliveries from fresh cycles, 2005-2015.

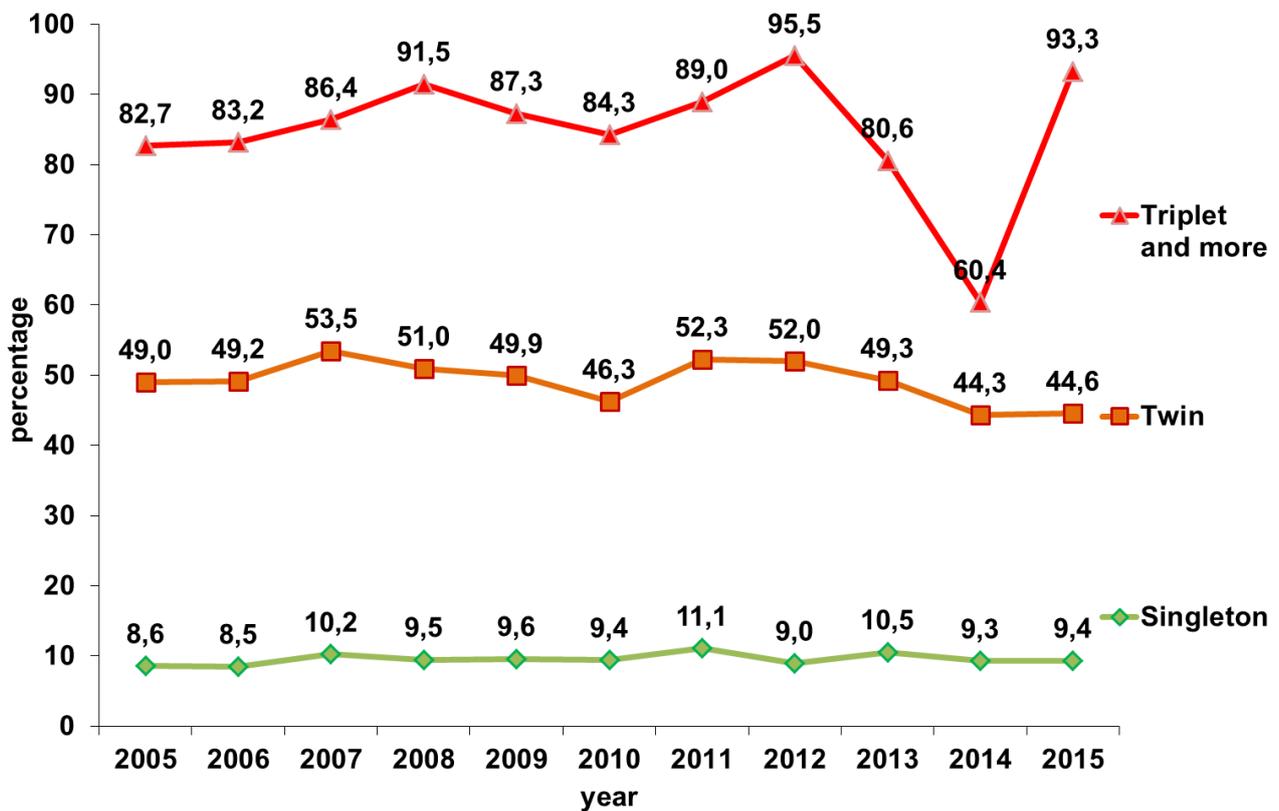


3.1.2. Did the percentages of preterm live babies change over time?

Figure 24 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 twins, from 49% in 2005 to 44.6% in 2015 and upwards for triplets from 82.7% in 2005 to 93.3% in 2015.

Figure 24. Time-trends of percentage of preterm ART live born babies (<37 week of gestation) by multiplicity of deliveries, 2005-2015.

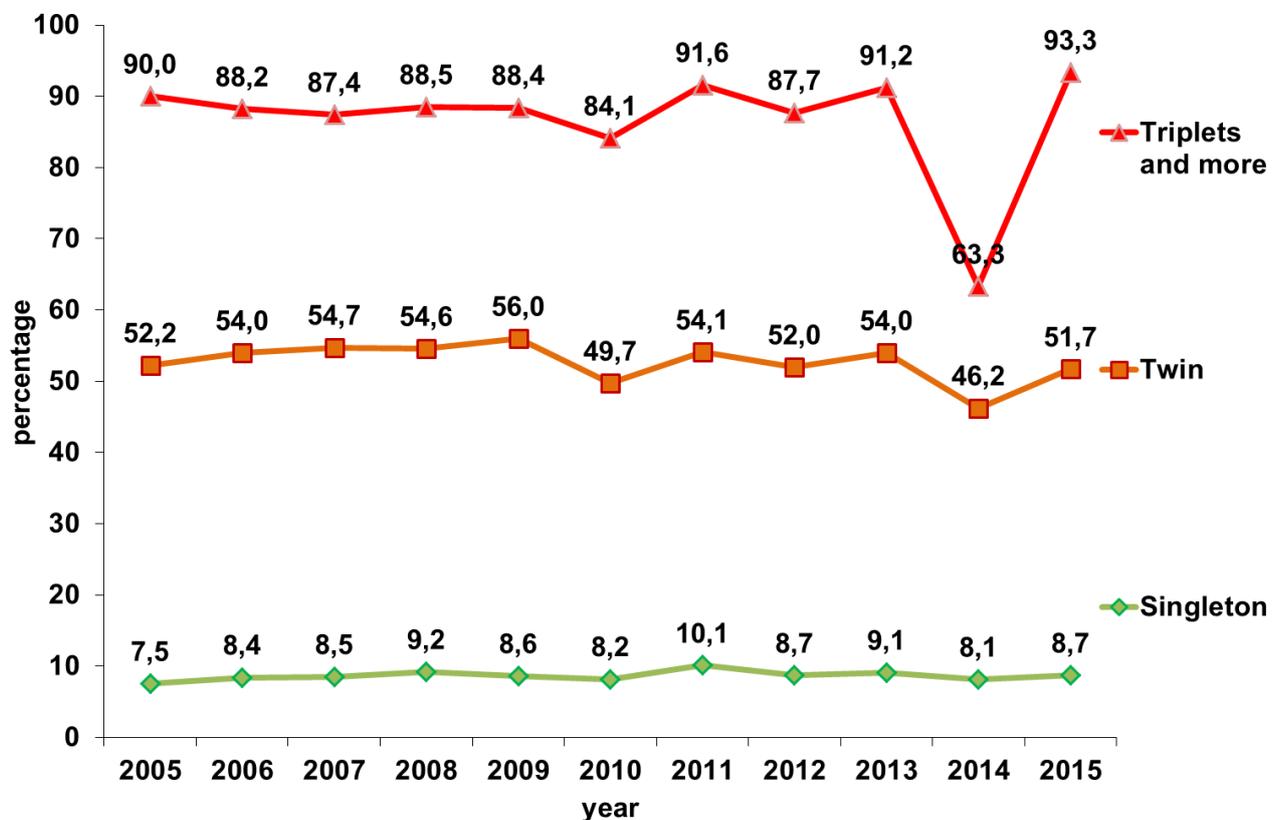


3.1.3. Did the percentage of underweight live babies change over time?

Figure 25 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 also quite stable for both twins and triplets and more deliveries, from 52.2% in 2005 to 51.7% in 2014 and from 90% in 2005 to 93.3% in 2015 respectively.

Figure 25. Time-trends of percentage of ART live born babies underweight (<2,500 gr) by multiplicity of deliveries, 2005-2015.



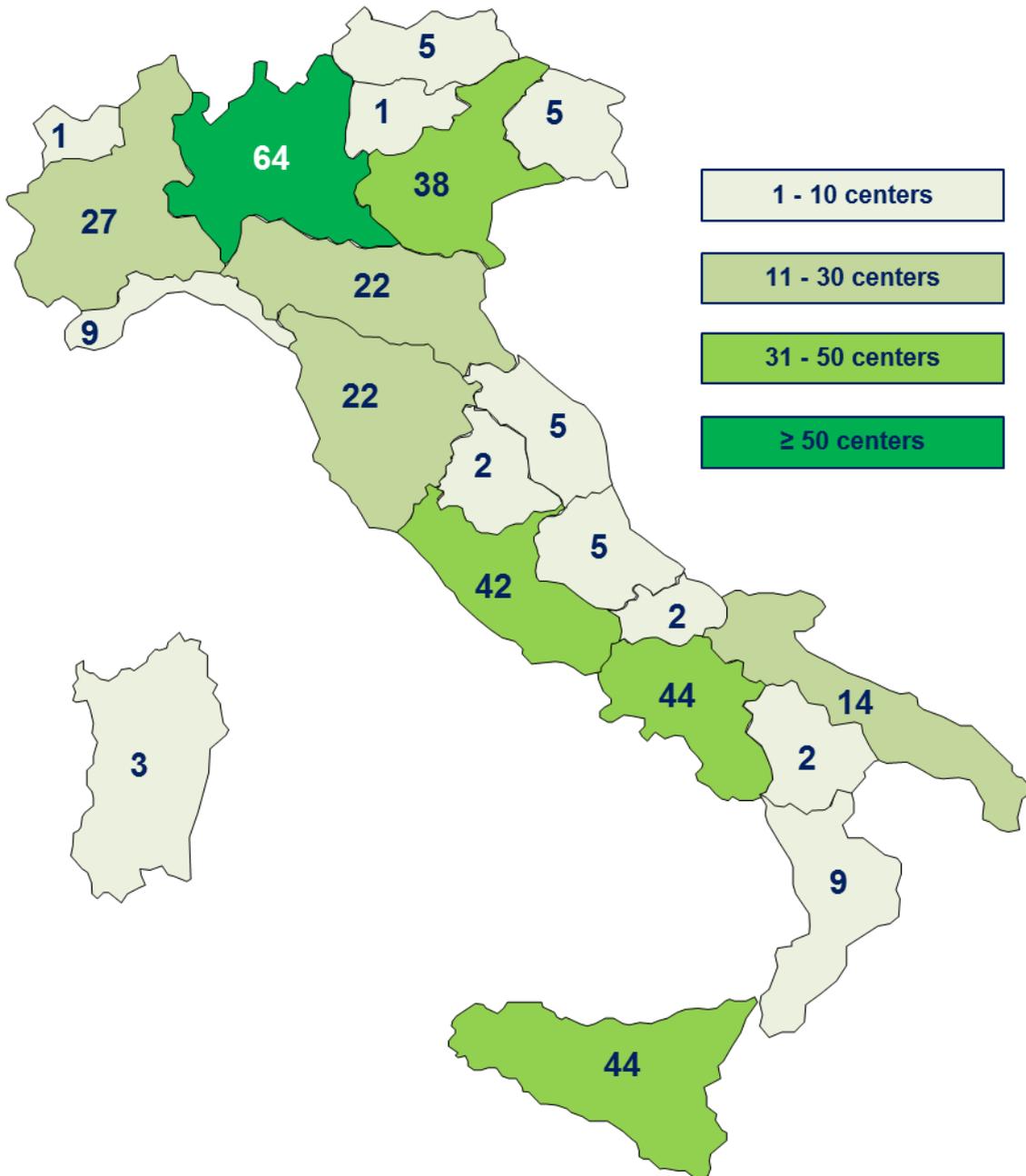
4.IUI PROCEDURES

4.1. Access to IUI service

In **Figure 26** the regional distribution of centers performing IUI are represented.

The largest number of the centers is concentrated in Northern Italy (172, 47% of the total) and then in the South (123 centers, 33.6% of the total), irrespective of the amount of activity they have carried out.

Figure 26: Regional distribution of IUI + ART active centers, 2015. Total = 366



As shown in **Table 3**, in 2015 there were 366 centers that have performed IUI of which only 138 operating within the National Health System (public and private 37.7%) and 228 providing private service (62.3%).

Most of public centers that performs IUI in Italy were in North: 68 out of 114 centers (59.6%).

Table 3: IUI centers distribution by region and type of service, 2015.

Region and Geographical Area	Total	Type of Service					
		Public		Private covered by NHS		Private	
		N	%	N	%	N	%
Piemonte	27	11	40,7	1	3,7	15	55,6
Valle d'Aosta	1	1	100	0	-	0	-
Lombardia	64	20	31,3	11	17,2	33	51,6
Liguria	9	4	44,4	0	-	5	55,6
Northwest	101	36	35,6	12	11,9	53	52,5
P.A. Bolzano	5	4	80,0	0	-	1	20,0
P.A. Trento	1	1	100	0	-	0	-
Veneto	38	14	36,8	2	5,3	22	57,9
Friuli Venezia Giulia	5	3	60,0	1	20,0	1	20,0
Emilia Romagna	22	10	45,5	0	-	12	54,5
Northeast	71	32	45,1	3	4,2	36	50,7
Toscana	22	7	31,8	6	27,3	9	40,9
Umbria	2	1	50,0	0	-	1	50,0
Marche	5	2	40,0	0	-	3	60,0
Lazio	42	7	16,7	3	7,1	32	76,2
Central	71	17	23,9	9	12,7	45	63,4
Abruzzo	5	3	60,0	0	-	2	40,0
Molise	2	0	-	0	-	2	100
Campania	44	9	20,5	0	-	35	79,5
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	44	8	18,2	0	-	36	81,8
Sardegna	3	3	100	0	-	0	-
South and Islands	123	29	23,6	0	-	94	76,4
Italy	366	114	31,1	24	6,6	228	62,3

4.2. Efficacy and safety of IUI and trends

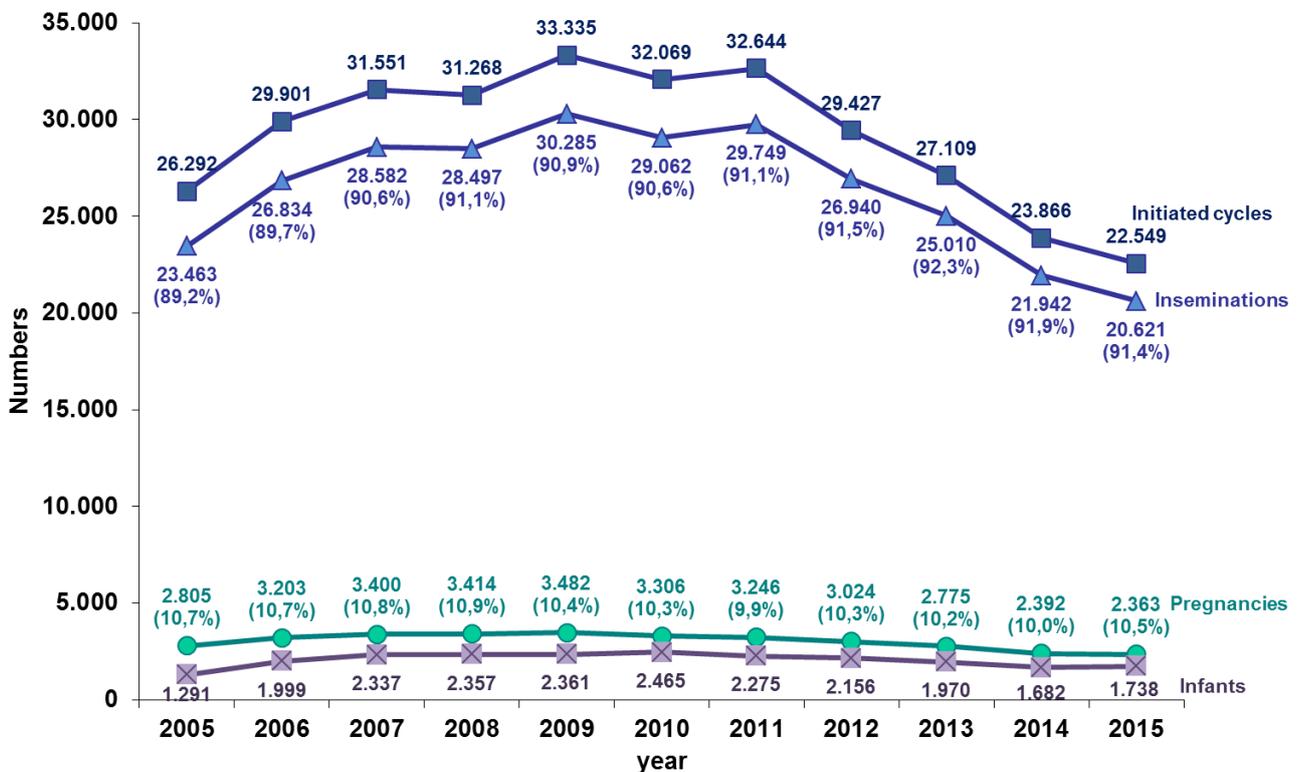
4.2.1. Is the use of IUI-H increasing?

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. For the activity of IUI-D in 2015, please check on Summary table for 2015 (on page 42) for more detailed data.

In **Figure 27** the use of IUI-H from 2005 to 2015 is represented. Number of IUI-H cycles decreased from 26,292 to 22,549 after having reached his maximum of 33,335 cycles in 2009. There were no changes in pregnancy rate from 10.7% in 2005 to 10.5% in 2015. Average women age increase of 0.5 year during time.

Figure 27: Time-trends of outcomes of IUI-H cycles, 2005-2015.

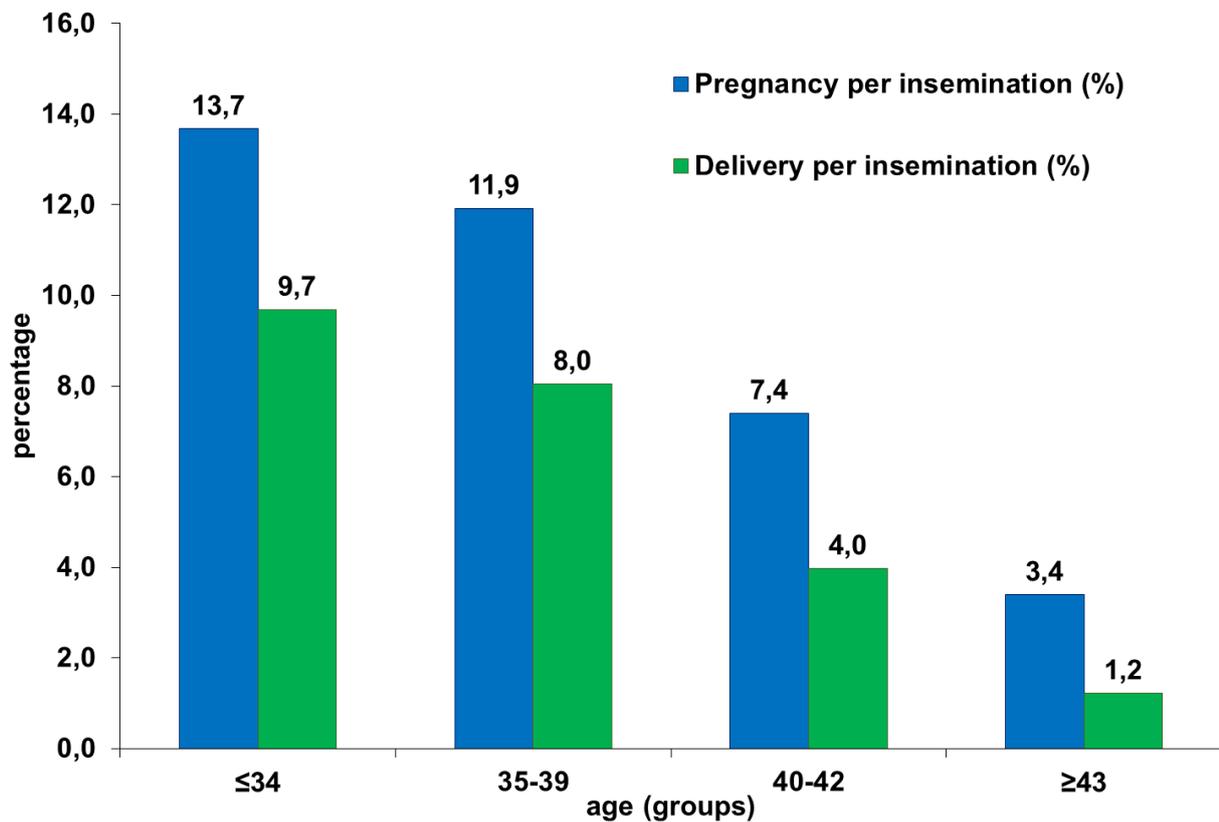


4.2.2. Do percentages of IUI-H cycles resulting in pregnancy, differ among women of different age groups?

Figure 28 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 3.4% for pregnancy and 1.2% for delivery.

Figure 28: Pregnancy rates and delivery rates per insemination for H-IUI cycles by age groups of female patients, 2015.

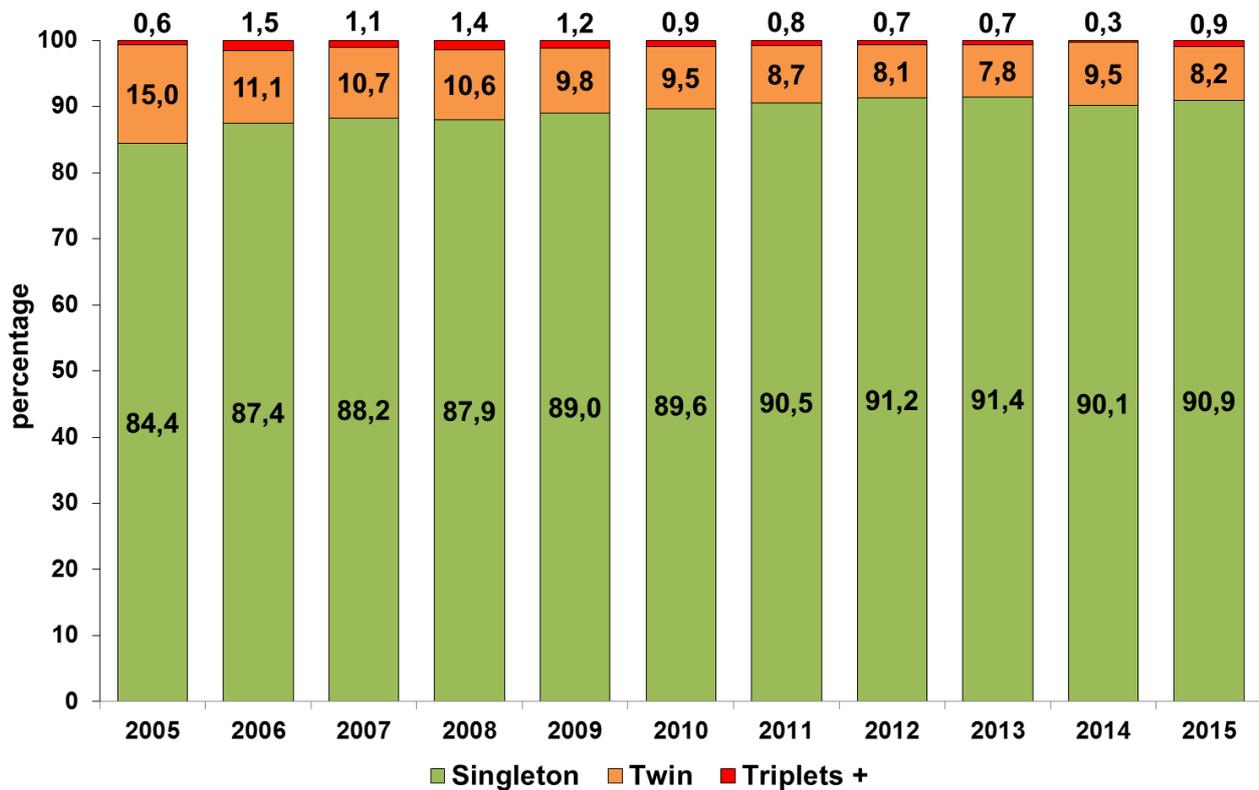


4.2.3. Did the percentages of singletons, twins and triplets- or- more deliveries change over time for intrauterine insemination cycles?

Figure 29 shows time trends for multiplicity of deliveries in H-IUI cycles.

From 2005 to 2015 twin deliveries rates decreased from 15% to 8.2% while percentage of triplets and more deliveries are quite stable. In 2015, 9 deliveries out of 10 were singleton.

Figure 29: Time-trends of multiplicity of deliveries from H-IUI cycles, 2005-2015.

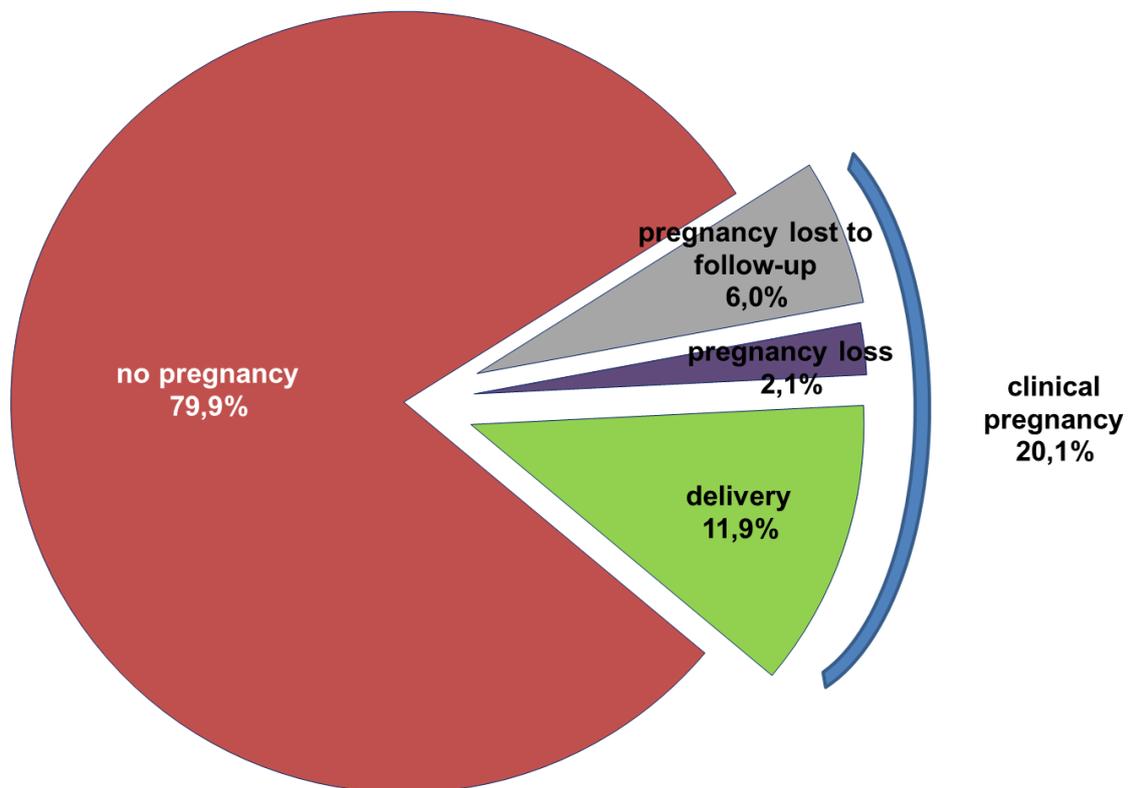


4.3. IUI donor cycles.

4.3.1. What is the outcome in IUI donor cycles in 2015?

In total, 20.1% of the 513 initiated cycles using donor sperm in IUI cycle started in 2015 resulted in a clinical pregnancy and 11.9% has resulted in a delivery. However most of these cycles (about 80%) did not produce a pregnancy while a small proportion (2.1%) resulted in a pregnancy loss (i.e. ectopic pregnancy or miscarriage or therapeutic abortion).

Figure 30: Outcome of D-IUI cycles, 2015 (513 initiated cycles)



APPENDIX. SUMMARY TABLE OF ACTIVITY
AND OUTCOMES OF ART PROCEDURES,
YEARS 2010 – 2015

Summary table of activity and outcomes of all procedures, 2010 – 2015

	2010	2011	2012	2013	2014*	2015*
N° Clinics	357	354	355	369	362	366
% of clinics reporting data to ISS	100	100	100	100	100	100
ALL PROCEDURES (H-IUI, D-IUI, ART-Non donor and ART-Donor)						
N° Patients	69,797	73,570	72,543	71,741	70,826	74,292
N° Initiated cycles	90,944	96,427	93,634	91,556	90,957	95,110
N° Live born	12,506	11,933	11,974	12,187	12,720	12,836
H-IUI and D-IUI activity						
N° Patients	19,707	20,012	18,085	17,218	14,967	14,545
N° Initiated cycles	32,069	32,644	29,427	27,109	23,903	23,062
N° Pregnancies	3,306	3,246	3,024	2,775	2,399	2,466
% Pregnancy Rate per cycle	10.3	9.9	10.3	10.2	10.0	10.7
% Pregnancies lost to follow-up	15.5	18.1	17.1	16.8	18.2	16.8
N° Deliveries	2,220	2,062	1,974	1,810	1,530	1,649
N° Live born	2,465	2,275	2,156	1,970	1,683	1,807
ART activity (Fresh-non donor, Thawing-non donor, donor)						
N° Patients	50,090	53,558	54,458	54,523	55,859	59,747
N° Initiated cycles	58,875	63,783	64,207	64,447	67,054	72,048
N° Pregnancies	11,968	12,221	12,646	12,775	13,642	14,391
Cumulative Pregnancy Rate per couple treated with fresh cycle	27.0	26.3	27.2	27.5	29.7	31.5
% Pregnancies lost to follow-up	10.2	12.2	13.2	10.3	10.8	11.3
N° Deliveries	8,167	8,003	8,127	8,495	9,252	9,512
N° Live born	10,041	9,658	9,818	10,217	11,037	11,029
INDICATORS OF THE AVAILABILITY OF SERVICES						
ART Initiated cycles per 1 million women aged 15 and 45	4,809	5,293	5,562	5,601	5,860	6,341
ART Initiated cycles per 1 million inhabitants	973	1,050	1,078	1,070	1,103	1,175

	2010	2011	2012	2013	2014*	2015*
ONLY FRESH CYCLES (Non Donor)						
N° Patients	44,365	46,491	46,491	46,433	45,985	45,689
N° Initiated cycles	52,676	56,092	55,505	55,050	55,705	55,329
Average age calculated	36.34	36.48	36.50	36.55	36.68	36.68
N° Pregnancies	10,988	10,959	11,077	10,712	10,834	10,081
% Pregnancies rate per cycles	20.9	19.5	20.0	19.5	19.4	18.2
% Pregnancies rate per aspirations	23.2	21.6	22.1	21.3	21.3	20.1
% Pregnancies rate per transfers	27.2	25.9	26.5	26.3	27.2	26.5
% Twin Pregnancies	20.2	18.8	18.9	19.4	19.5	17.0
% Triplet or more Pregnancies	2.3	1.8	1.8	1.6	1.4	0.9
% Pregnancies lost to follow-up	10.8	12.7	13.9	10.9	11.9	13.1
N° Deliveries	7,512	7,193	7,116	7,125	7,277	6,498
N° Live born	9,286	8,734	8,680	8,677	8,848	7,695
ONLY THAWING CYCLES (Non Donor)						
N° Patients	5,725	7,067	7,967	8,090	9,669	11,975
N° Initiated cycles	6,199	7,691	8,702	9,397	11,140	14,432
N° Pregnancies	980	1,262	1,569	2,063	2,721	3,633
% Pregnancies lost to follow-up	4.3	7.8	8.0	6.9	5.7	5.6
N° Deliveries	655	810	1,011	1,370	1,926	2,573
N° Live born	755	924	1,138	1,540	2,128	2,802

Summary table of activity and outcomes of procedures with gamete/embryo donation, 2014-2015

Donor activity		
	2014	2015
ART-Donor activity		
N° clinics reporting data (with at least 1 patients treated)	17	69
N° Patients	205	2,083
N° Initiated cycles	209	2,287
N° Pregnancies	87	677
% Pregnancies lost to follow-up	26.4	15.7
N° Deliveries	49	441
N° Live born	61	532
IUI-D activity (sperm donation)		
N° clinics reporting data (with at least 1 patients treated)	13	52
N° Patients	32	379
N° Initiated cycles	37	513
N° Pregnancies	7	103
% Pregnancies rate per cycles	18.9	20.1
N° lost to follow-up pregnancies	6	31
N° Deliveries	1	61
N° Live born	1	69