



EXECUTIVE SUMMARY for 2016

IARTR – THE ITALIAN ASSISTED REPRODUCTIVE TECHNOLOGY REGISTER

**MONITORING THE ACTIVITY AND
OUTCOMES OF ITALIAN ART
CENTERS IN 2016.**

MONITORING THE ACTIVITY AND OUTCOMES OF ITALIAN ART CENTERS IN 2016

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*

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Summary of outputs generated from IARTR, 2016

	Non-donor Procedures				Gametes/embryo donation		
	IVF	ICSI	FET	FO	Sperm Donation	Oocyte Donation	Embryo donation
N° of patients	44965		10557	1418	825	2674	1434
N° Initiated cycles	7584	46322	14990	1460	897	2901	1735
N° Aspirations	6857	41899	-	-	-	-	-
N° Transfers	5444	30594	14328	1187	722	2650	1709
<i>with 1 embryo</i>	1635	9250	8779	336	202	789	751
<i>with 2 embryos</i>	2836	15286	4938	679	412	1659	931
<i>with 3 embryos</i>	893	5575	589	172	108	202	27
<i>with 4 o + embryos</i>	80	483	22	0	-	-	-
N° Pregnancies	1479	7847	4128	238	280	882	551
Pregnancy per Initiated cycles/thawings (%)	19,5	16,9	27,5	16,3	31,2	30,4	31,8
Pregnancy per Transfer (%)	27,2	25,6	28,8	20,1	38,8	33,3	32,2
Pregnancies lost to follow-up (%)	6,3	12,2	6,7	4,6	16,4	17,8	6,4
N° Pregnancy losses	348	1734	963	73	50	164	115
Pregnancy loss (%)	25,1	25,2	25,0	32,2	21,4	22,6	22,3
N° Deliveries	1038	5158	2890	154	184	561	401
Twin deliveries (%)	15,0	15,7	7,4	13,6	20,1	15,2	16,7
Triplets or more deliveries (%)	0,3	0,5	0,2	0,6	1,1	0,5	0,2
N° Live born babies	1193	5979	3104	177	224	647	467

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 was audited in 2018 by Prof. Jacques de Mouzon, secretary of the ART World Register ICMART.

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, psychology 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 time frames:

- The first phase of the collection is related to the activity conducted and the results obtained in 2016 and it was carried out from May to June 2017;
- The second phase of the collection is related to the outcomes of pregnancies obtained from ART treatments started in 2016 and it was carried out from October to December 2017.

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, 2016

1.1. Access to ART service

In **Figure 1** the regional distribution of the 200 ART authorized centers in 2016 is represented, but only 183 are performed at least 1 ART cycle.

The largest number of ART centers is concentrated in Northern Italy (81 centers, 40,5% of the total) and in the Southern area (71 centers, 35,5% of the total), irrespective of the amount of their activity.

Figure 1: Regional distribution of the ART authorized centers and in brackets the number of centers per 100000 women of reproductive age (15-45 years), 2016.

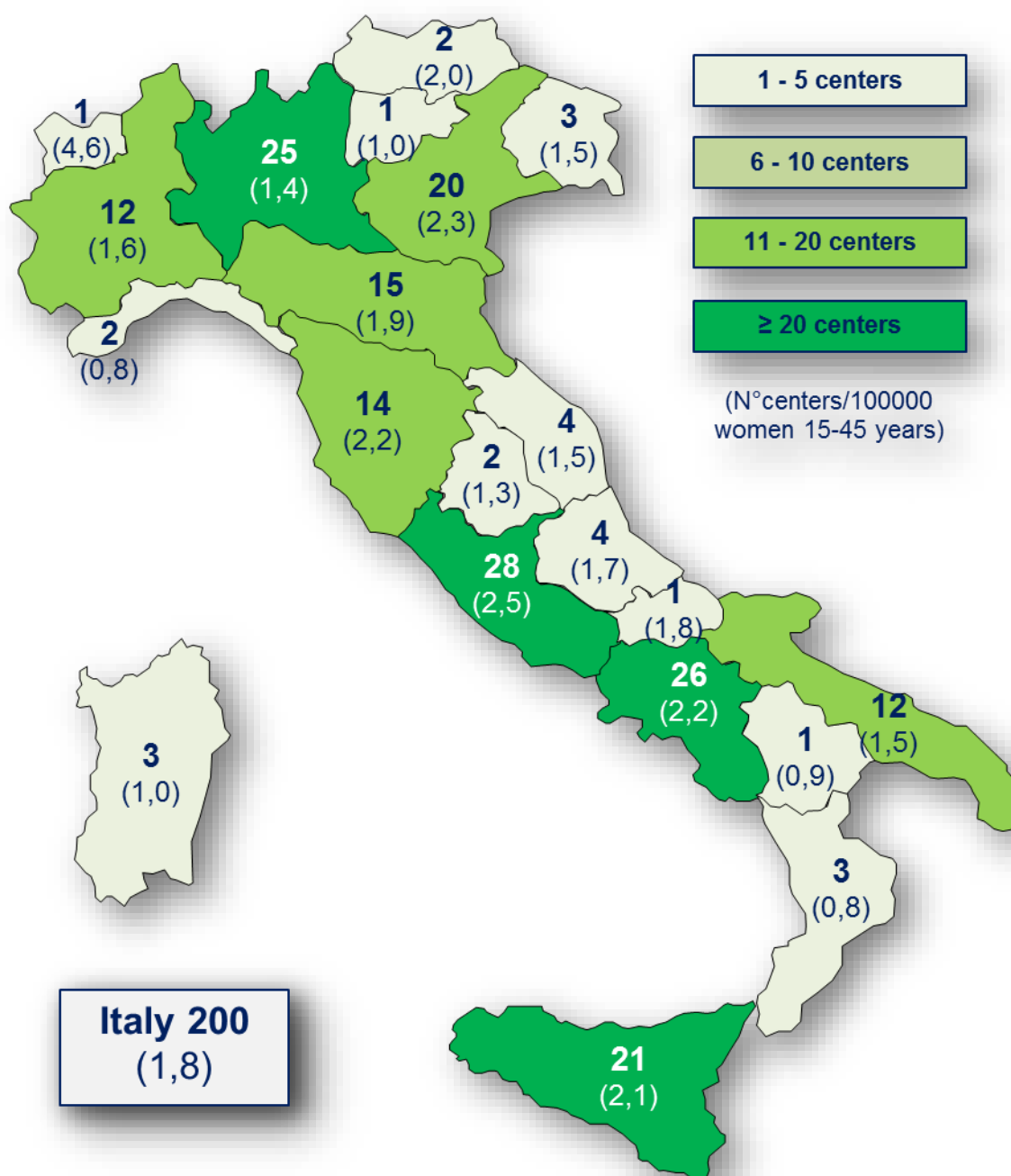


Table 1 shows the geographical distribution of ART centers according to the type of services offered. Overall, the number of centers active in 2016 was 200, 93 of which (46,5%) operating within the National Health Service (public and private), and 107 (53,5%) which provided only private service. The majority of ART centers providing public service was concentrated in the North of Italy, i.e. in the North West 80%, while in the Centre and in the South there were mainly private facilities (54,2% and 71,8%, respectively).

Table 1: ART authorized centers distribution by region and type of service, 2016.

Region and Geographical Area	ART centers	Art centers by type of Service					
		Public		Private covered by NHS		Private	
		N	%	N	%	N	%
Piemonte	12	5	41,7	1	8,3	6	50,0
Valle d'Aosta	1	1	100	0	0	0	0
Lombardia	25	13	52,0	10	40,0	2	8,0
Liguria	2	2	100	0	0	0	0
North-West	40	21	52,5	11	27,5	8	20,0
A.P. Bolzano	2	1	50,0	0	0	1	50,0
A.P. Trento	1	1	100	0	0	0	0
Veneto	20	8	40,0	0	0,0	12	60,0
Friuli Venezia Giulia	3	2	66,7	1	33,3	0	0
Emilia Romagna	15	6	40,0	0	0	9	60,0
North-East	41	18	43,9	1	2,4	22	53,7
Toscana	14	5	35,7	5	35,7	4	28,6
Umbria	2	1	50,0	0	0	1	50,0
Marche	4	3	75,0	0	0	1	25,0
Lazio	28	6	21,4	2	7,1	20	71,4
Central	48	15	31,3	7	14,6	26	54,2
Abruzzo	4	2	50,0	0	0	2	50,0
Molise	1	0	0	0	0	1	100
Campania	26	7	26,9	0	0	19	73,1
Puglia	12	3	25,0	0	0	9	75,0
Basilicata	1	1	100	0	0	0	0
Calabria	3	0	0	0	0	3	100
Sicilia	21	4	19,0	0	0	17	81,0
Sardegna	3	3	100	0	0	0	0
South and Islands	71	20	28,2	0	0	51	71,8
Italy	200	74	37,0	19	9,5	107	53,5

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 601 cycles (+ 94,4%) and of 4098 cycles (+ 152,8%), respectively. The latest European data available refers to the activity of year 2013¹.

The number of started cycles per million inhabitants (calculated only for the 17 countries that have reported data of 100% of the centers) was 1175 cycles vs. 1070 in Italy, under the proposed optimal level of demand calculated as 1500 of ART services per million inhabitants per year².

Table 2: Number of initiated ART cycle per million inhabitants and per million women of reproductive age (15-45 years) annually in Italy (2005-2016) and in Europe (2005-2014).

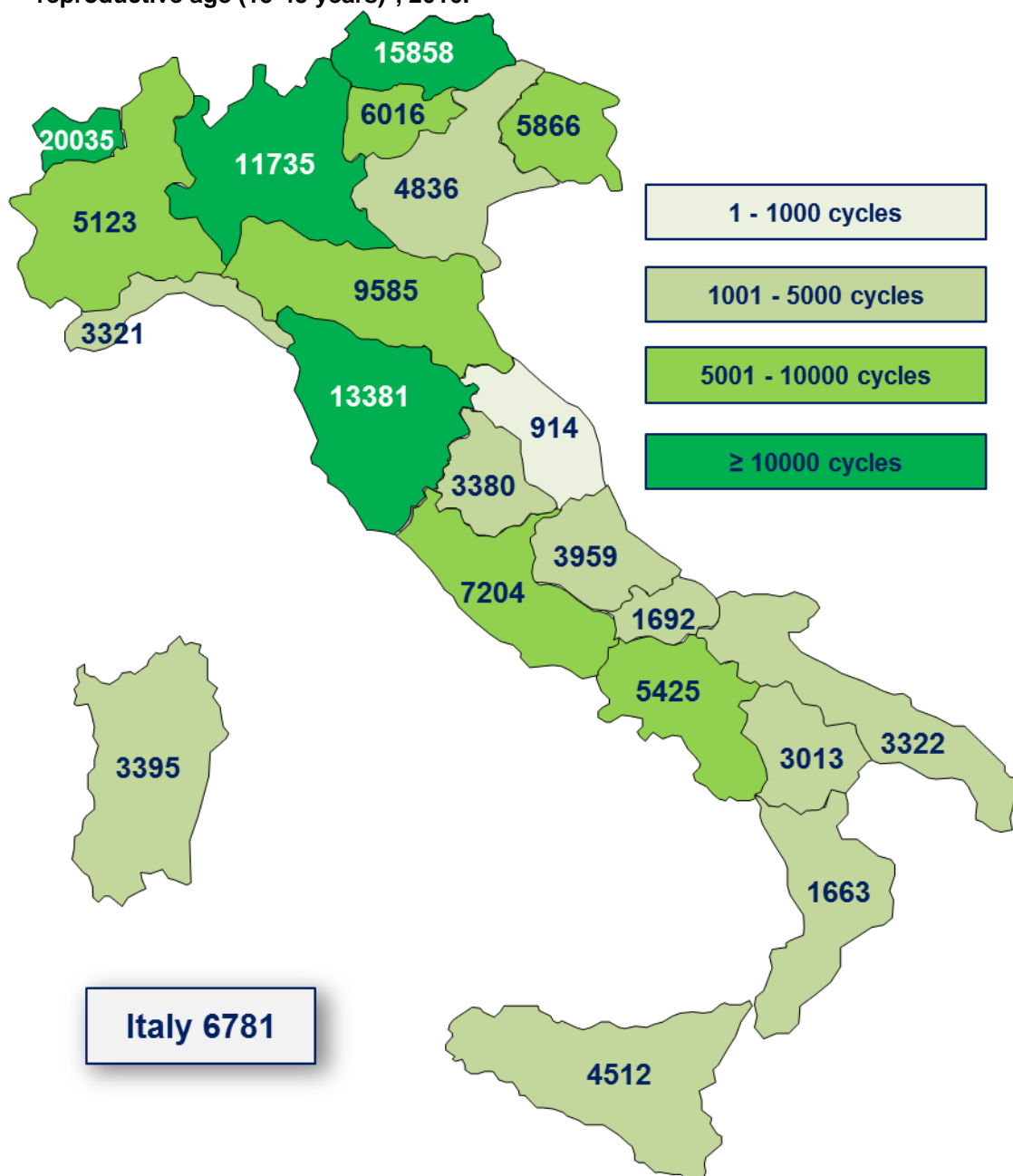
Years	ART Cycles/million population		ART cycles/million women (15 - 45 years)	
	Italy	Europe ^a	Italy	Europe ^a
2005	636	1115	2683 ^b	4008 ^b
2006	692	850	3328	3503
2007	736	886	3569	4320
2008	800	947	3905	4661
2009	865	1067	4265	5455
2010	973	1221	4863	6258
2011	1063	1269	5392	6556
2012	1078	1252	5562	6519
2013	1070	1175	5601	6210
2014	1102	1399	5855	7608
2015	1175	-	6341	-
2016	1237	-	6781	-

a: Data for Europe refers only to those country where data coverage was 100% in every year (range from 14 country in 2014 to 21 country in 2009).

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 20035 cycles offered in Valle d'Aosta to 914 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 (6781 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)*, 2016.



*Average resident population in Italy in 2016: Source ISTAT.

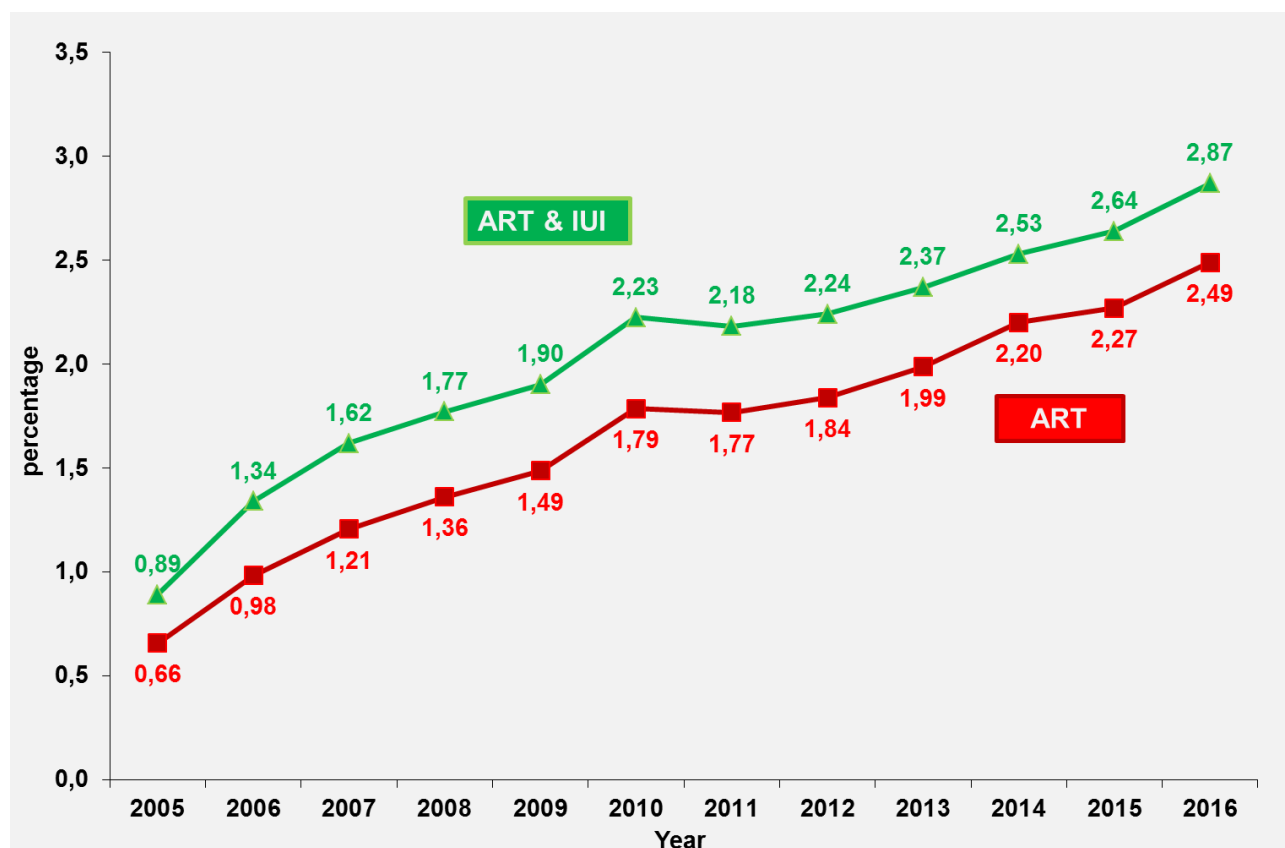
Since its establishment, IARTR collected data on 130353 infants, of which 105861 from ART and 24492 from IUI cycles. For the analysis of these data some caution may be required because of the proportion of pregnancies lost to follow-up, that however changed to the better: from 41% in 2005 and 21,5% in 2006 to 9,7% in 2016. In particular, in 2016, 11791 babies are born alive from ART techniques in Italy, that is a 2,5% of the national babies born in the country. These values are an expression of the application of the ART techniques in the different regions, but they do not faithfully reflect the number of births because the cycles carried out also include the techniques performed on patients coming from outside the region (for example in Tuscany, 65% of cycles are performed on patients from outside the region).

Figure 3: Regional distribution of the babies born in 2016 only from ART cycles, and the percentages in relation to the annual number of children born.



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 2016 the percentage of infants born with ART procedures increased more than 3 times.

Figure 4: 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, 2005-2016.



2.EFFICACY OF ART 2016 AND TIME TRENDS 2005-2016

2.1. Overview of ART.

2.1.1. What types of ART cycles were performed?

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

- **In vitro fertilization with embryo transfer (IVF):** an ART procedure that involves extracorporeal fertilization of gametes²;
- **Intra Cytoplasmic Sperm Injection (ICSI):** a procedure in which a single spermatozoon is injected into the oocyte cytoplasm.²

An ART treatment in which cryopreserved oocytes or embryos, are utilized it can be defined as a “**frozen/thawing cycle**”, and it includes:

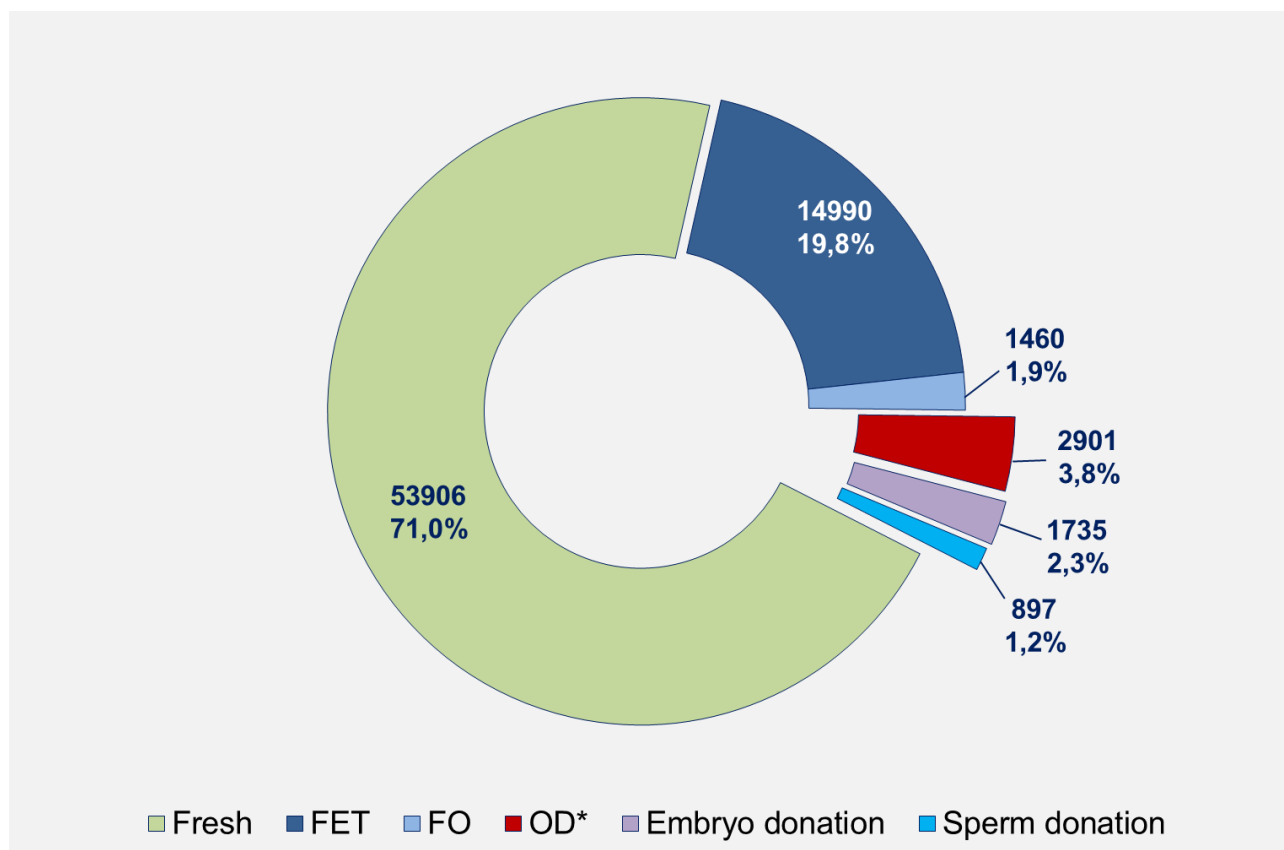
- **Frozen/thawed Embryo transfer (FET) cycle:** ART procedure in which cycle monitoring is carried out with the intention of transferring to a woman frozen/thawed or vitrified/warmed embryo(s)/blastocyst(s)²;
- **Frozen/thawed Oocyte (FO) cycle:** ART procedure in which cycle monitoring is carried out with the intention of fertilizing thawed/warmed oocytes and performing embryo transfer.²

An ART treatment in which are used gametes that did not originate from the female recipient and/or her male partner, it can be defined as a “**donation cycle**”, and it includes:

- **Oocyte donation (OD) cycle:** an ART cycle in which a woman receives oocytes from a donor to be used for reproductive purpose²;
- **Sperm donation:** a cycle in which a woman receives spermatozoa from a person who is not her sexually intimate partner²;
- **Embryo donation:** ART cycle which consists of the transfer of an embryo to the uterus of a female recipient, resulting from gametes that did not originate from the recipient and/or from her male partner²;
- **Double donation:** an ART cycle in which are used both oocytes and spermatozoa originate from donors.

The major part of the 74992 Art cycle performed in Italy in 2016 were made with a fresh procedure (71%), then 19,8% of the cycles were performed with a FET, the 1,9% with a FO and the remaining 7,4% with a donation of gametes (**Figure 5**).

Figure 5: ART cycles performed in 2016.

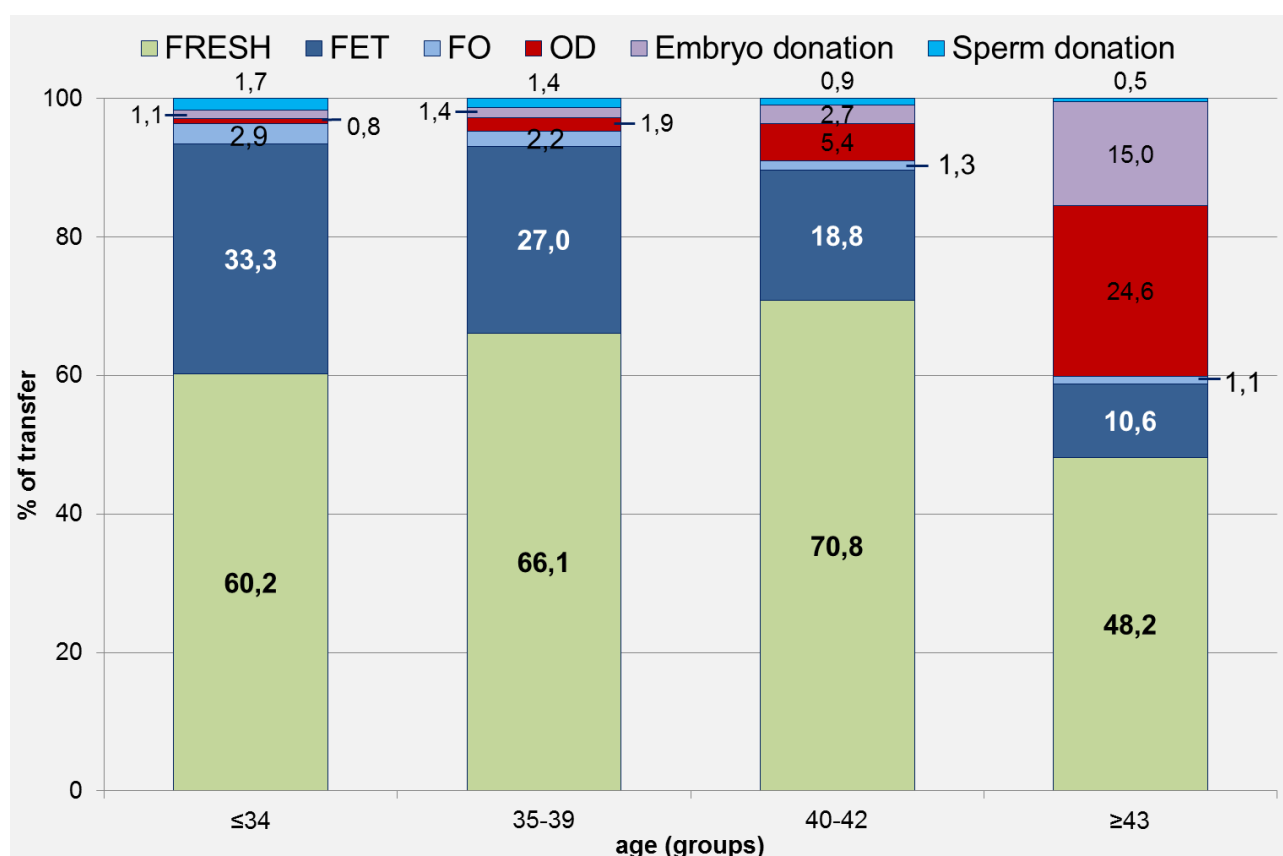


*It also includes 146 cycles performed after a double donation of gametes.

2.1.2. How did the types of ART transfers performed differ by a woman's age?

The patient's age is one of the variables that most influence the success of the application of assisted reproduction techniques, and therefore the probability of obtaining a pregnancy. **Figure 6** shows the percentage of ART transfers performed in 2016 according to the women underwent the procedures. Women that used her own oocytes (Fresh, FET and FO procedures) declined with the age, while the percentage of ART cycles using a donor oocytes (OD and Embryo donation) increased with age. The majority (96,3%) of women younger than age 35 used their own oocytes and only 2,0% used donor oocytes, while 39,6% of women older than age 42 used donor oocytes.

Figure 6: Types of ART procedure performed by female patients age groups, 2016.



2.2. ART, non-donor cycles.

2.2.1. What are the causes of infertility of couples in ART treatment using fresh cycles in 2016?

- *Female factor:*

- **Tubal factor** - fallopian tubes are blocked or damaged, could prevent sperm from getting to the egg and eggs from getting to the uterus²;
- **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** – a disease characterized by the presence of endometrium-like epithelium and stroma outside the endometrium and myometrium. This condition can affect both fertilization of the egg and embryo implantation².
- **Diminished ovarian reserve** – indicate a reduced number and/or reduced quality of oocytes, such that the ability to reproduce is decreased²;
- **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.

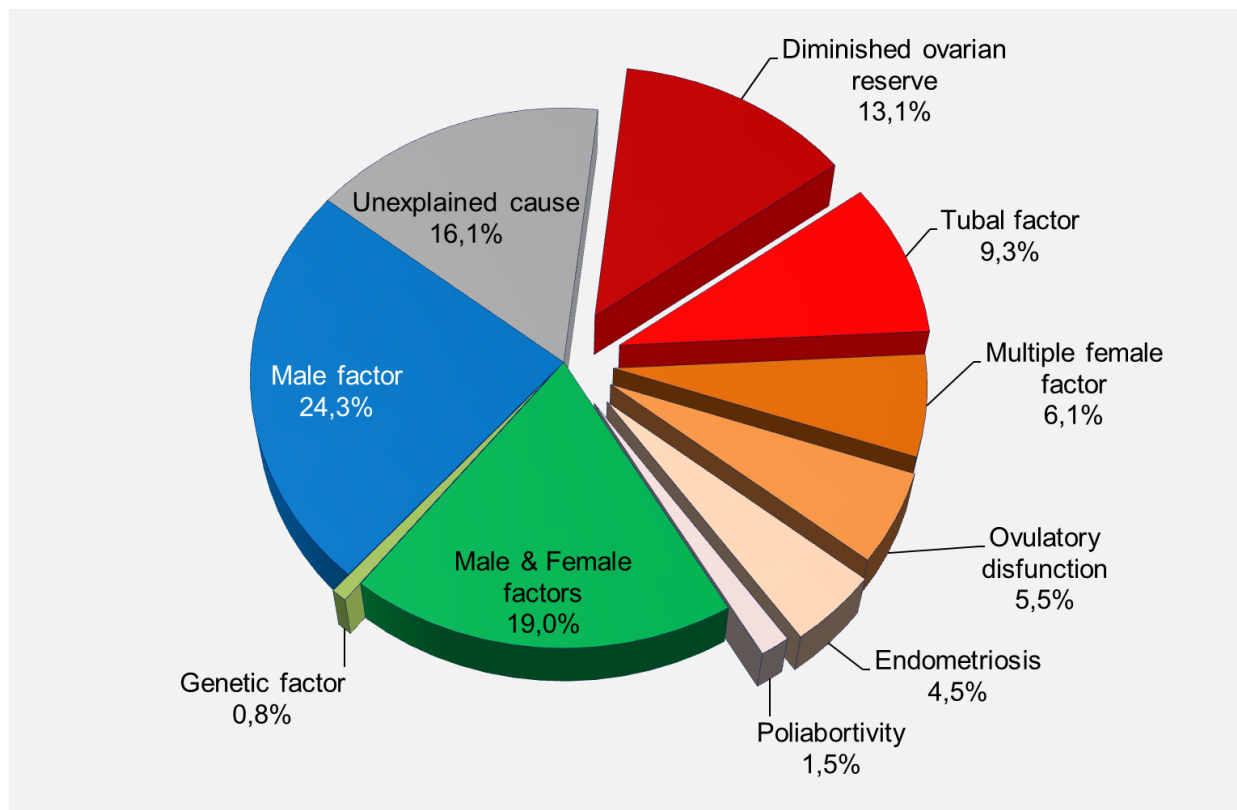
- **Male factor** – abnormal semen parameters or function; anatomical, endocrine, genetic, functional or immunological abnormalities of the reproductive system; chronic illness; and sexual conditions incompatible with the ability to deposit semen in the vagina².

- **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 infertility** - no cause of infertility is found in either woman or man².

Figure 7: Causes of infertility of couples in ART treatment using fresh cycle, 2016.



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

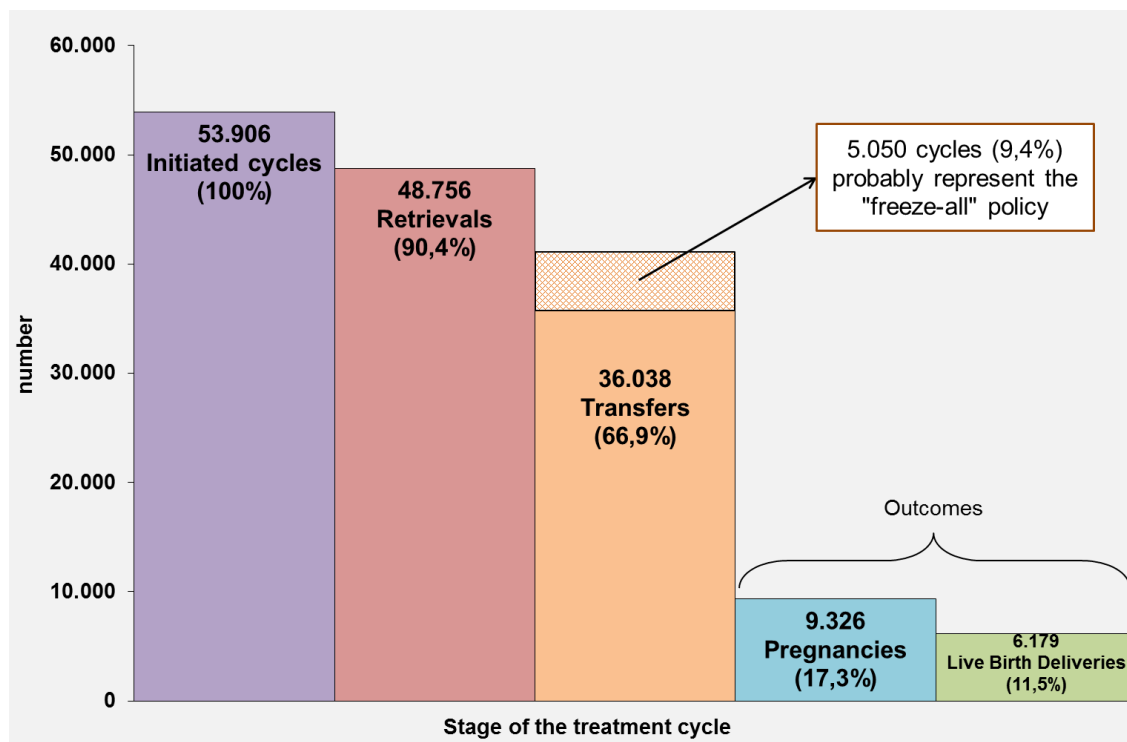
An ART cycle using fresh gametes:

- It 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 an ovarian follicular aspiration performed with the aim of retrieving oocytes (**retrieval**)
- After eggs collection, a process initiated by entry of a spermatozoon into a mature oocyte followed by formation of the pronuclei. (**fertilization**)
- If fertilization results, the embryo(s) at any embryonic stage from day 1 to day 7 is(are) transferred to the woman's womb (**transfer**)
- The attachment and subsequent penetration by a zona-free blastocyst into the endometrium (**implantation**)
- If implantation is successful, a pregnancy diagnosed by ultrasonographic visualization of one or more gestational sacs or definitive clinical sign of 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 8** outcomes resulting from various steps of fresh cycles performed in 2016 are shown.

Of 53906 fresh cycles, 90,4% resulted in an egg retrievals, 66,9% in an embryo transfers, 17,3% in a pregnancy and 11,5% in a live birth delivery. In the transfers' column, it was decided to show the weight of the 5050 cycles interrupted between the retrieval and the transfers due to the freezing of all the zygotes/embryos (9,4% of the initiated cycles and 10,4% of the retrievals), corresponding to an estimation of the "freeze-all" therapeutic protocol: if the possible cycles for the "freeze-all" strategy were not considered, the pregnancy rate per fresh initiated cycle could increase from 17,3% to 19,1%. Among the outcomes we must also consider 11,2% of pregnancies lost to follow-up and the 25,2% of monitored pregnancies that do not reach the delivery due to abortions or ectopic pregnancies (see **Figure 12**).

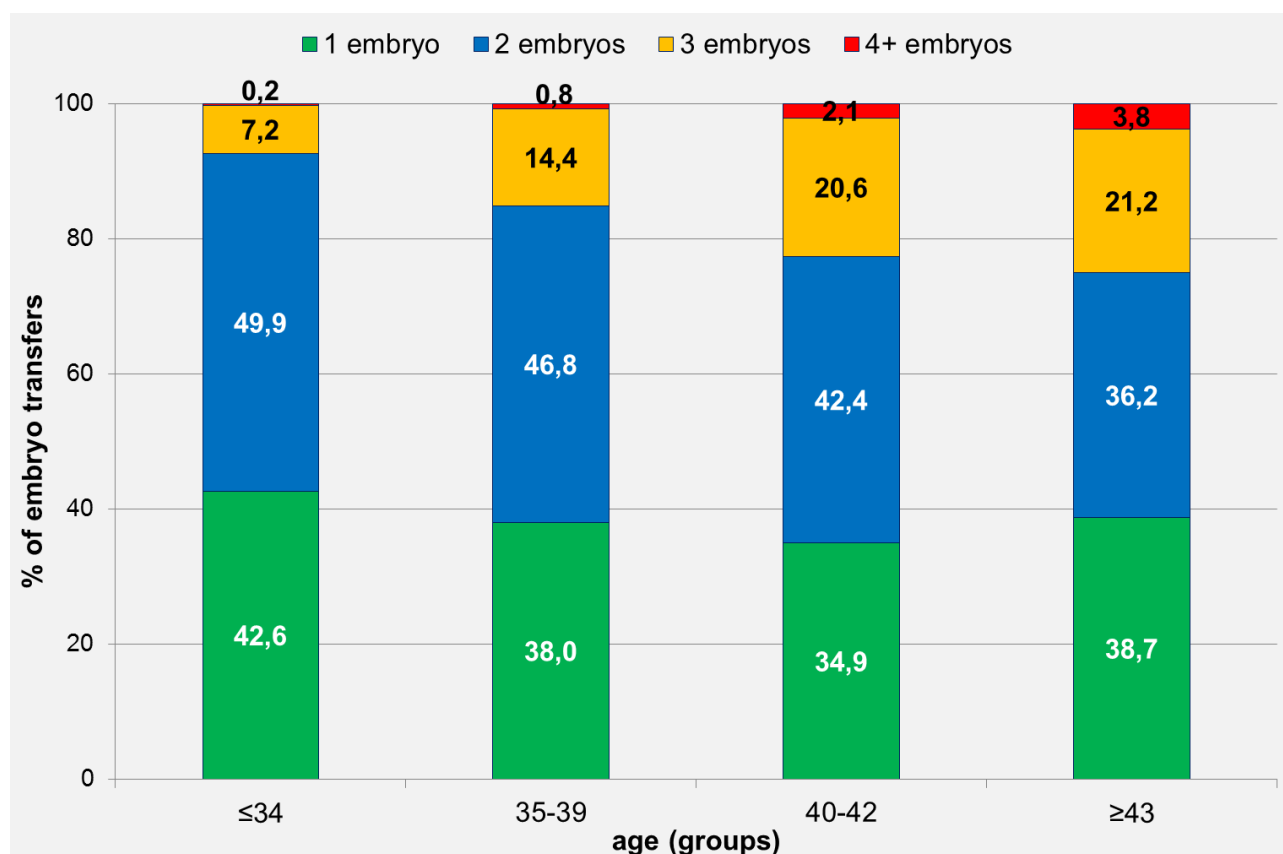
Figure 8: Outcomes of ART using fresh cycles by stage of the treatment cycle, 2016.



2.2.3. Did the number of embryos transferred differ among women of different age groups?

Figure 9 shows that in 2016, the transfers with at least three embryos increased with age of women underwent an ART procedure using own oocytes, while the transfers with one or two embryos declined with women age. Almost the 50% of transfers in the women under 35 involved the transfer of two embryos, while the majority (38,7%) of transfers in women older than 42 age were performed with one embryo.

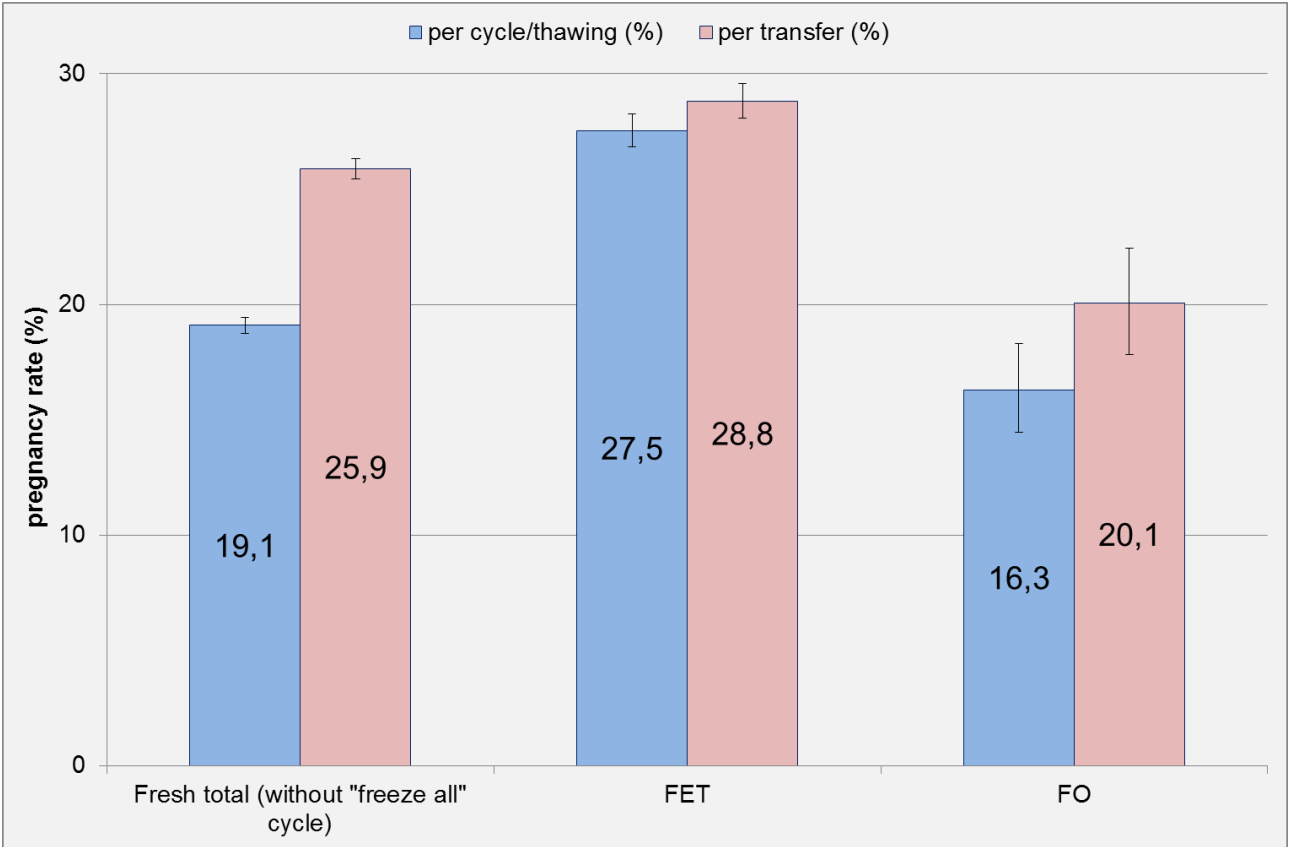
Figure 9: Distribution of embryo transfers according to the number of embryos transferred (ART total) by female patients age groups, 2016.



2.2.4. What are the percentages of initiated cycles or thawings, and transfers that result in pregnancies for ART cycles?

Figure 5 shows the pregnancy rates per initiated cycle and per transfer for the ART techniques. Overall, the rates after FET were higher than others techniques, while the FO ones were the lowest.

Figure 10: Pregnancy rates per initiated cycle/thawing and per transfer according to different ART procedures, 2016.



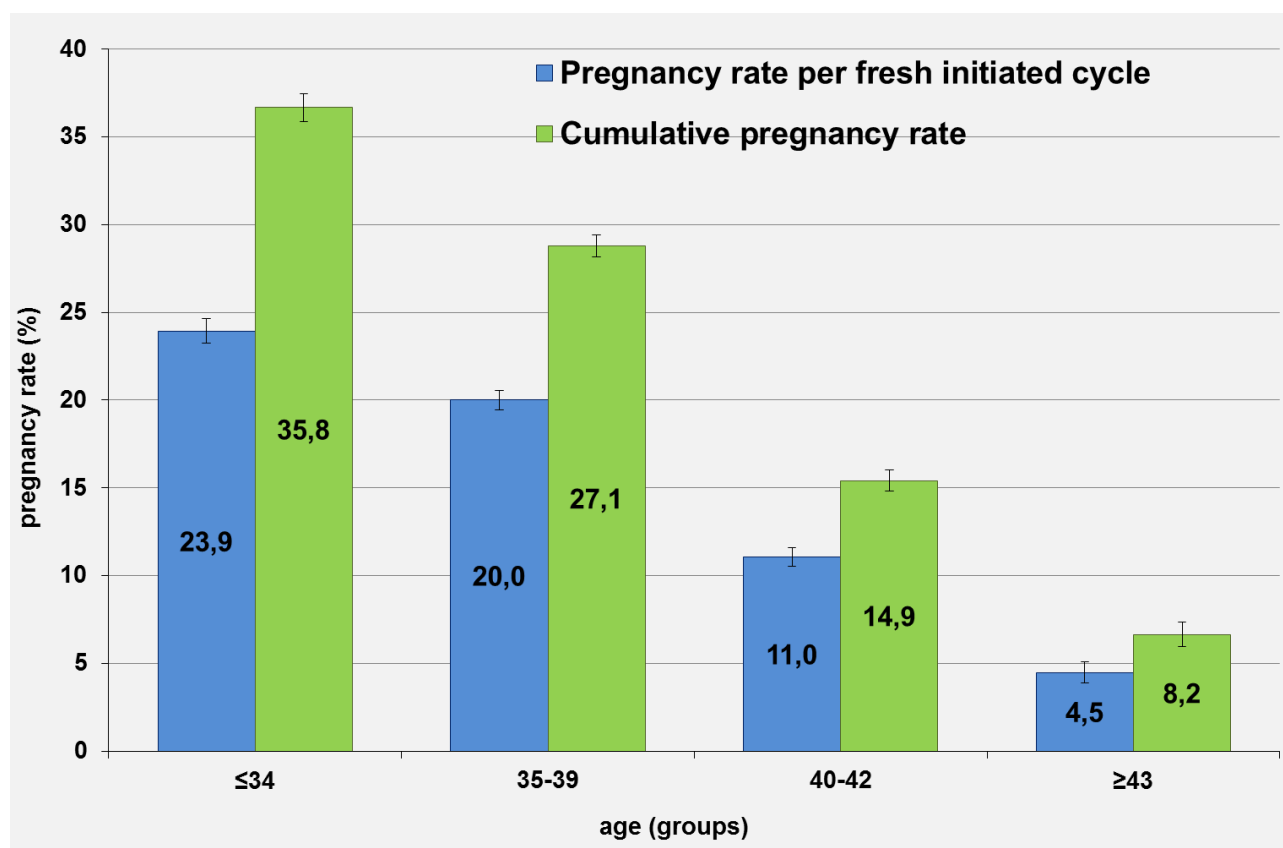
2.2.5. What is the “Cumulative Pregnancy Rate”?

The cumulative pregnancy rate (CPR) is the overall chance of obtain a pregnancy from all fresh and frozen embryo transfers from one retrieval of eggs. To calculate the 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 11** 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 47%.

It should be emphasized that we cannot take into account the weight of the "freeze-all" policy in every age group of female patients (data not collected by the Registry), so the pregnancy rates per fresh initiated cycle for each age groups could be underestimated.

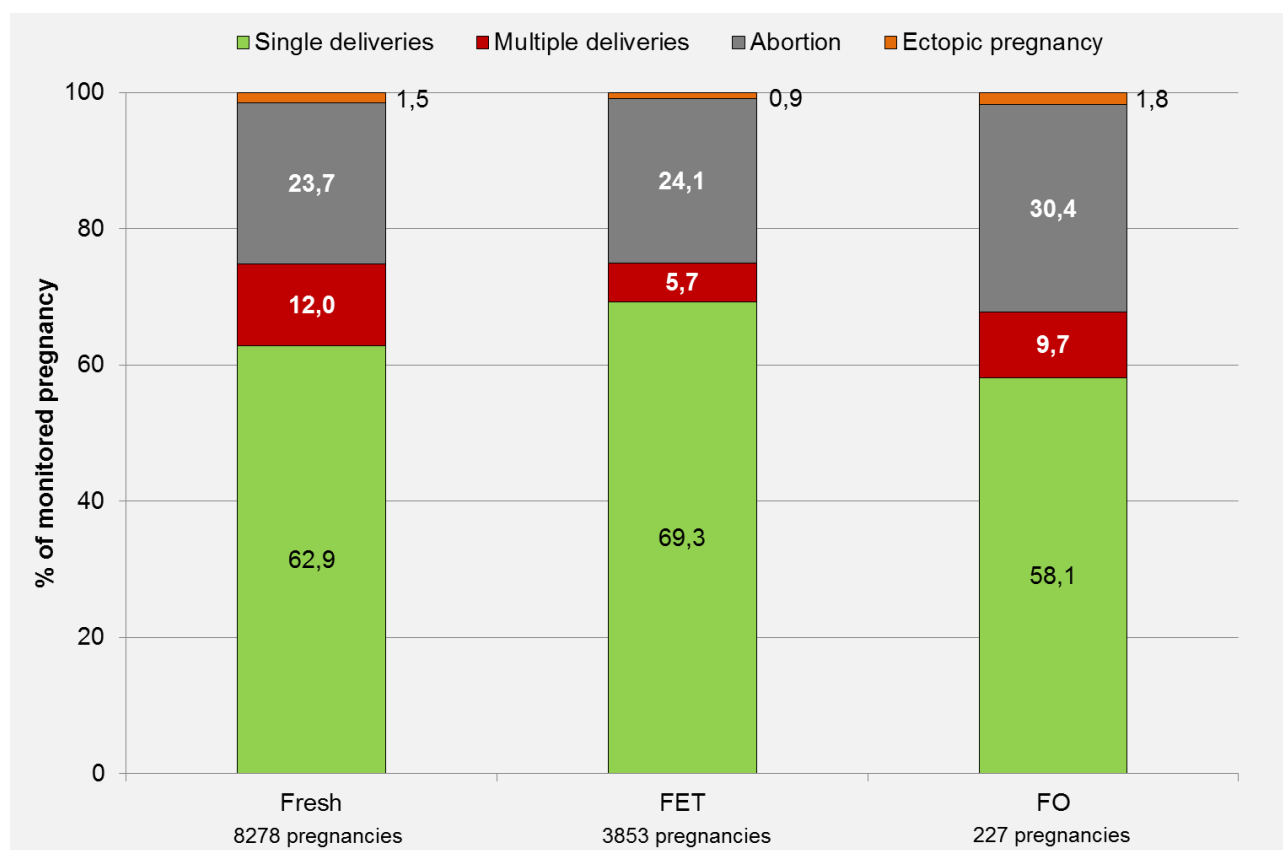
Figure 11: Pregnancy rates per initiated cycle for fresh and Cumulative pregnancy rates per initiated cycle, by female patients age groups, 2016.



2.2.6. What percentage of ART pregnancies resulted in a delivery?

Figure 12 shows the outcomes of the monitored clinical pregnancies obtained from the application of the ART non donor procedures in Italy in 2016. Of the 8278 monitored pregnancies resulted from fresh cycles 12% were resulted in multiple deliveries and the 23,7% were aborted. In FET and FO procedures the multiple deliveries are lower (5,7% and 9,7% respectively) then in fresh ones, but the percentage of abortion were higher (24,1% and 30,4%).

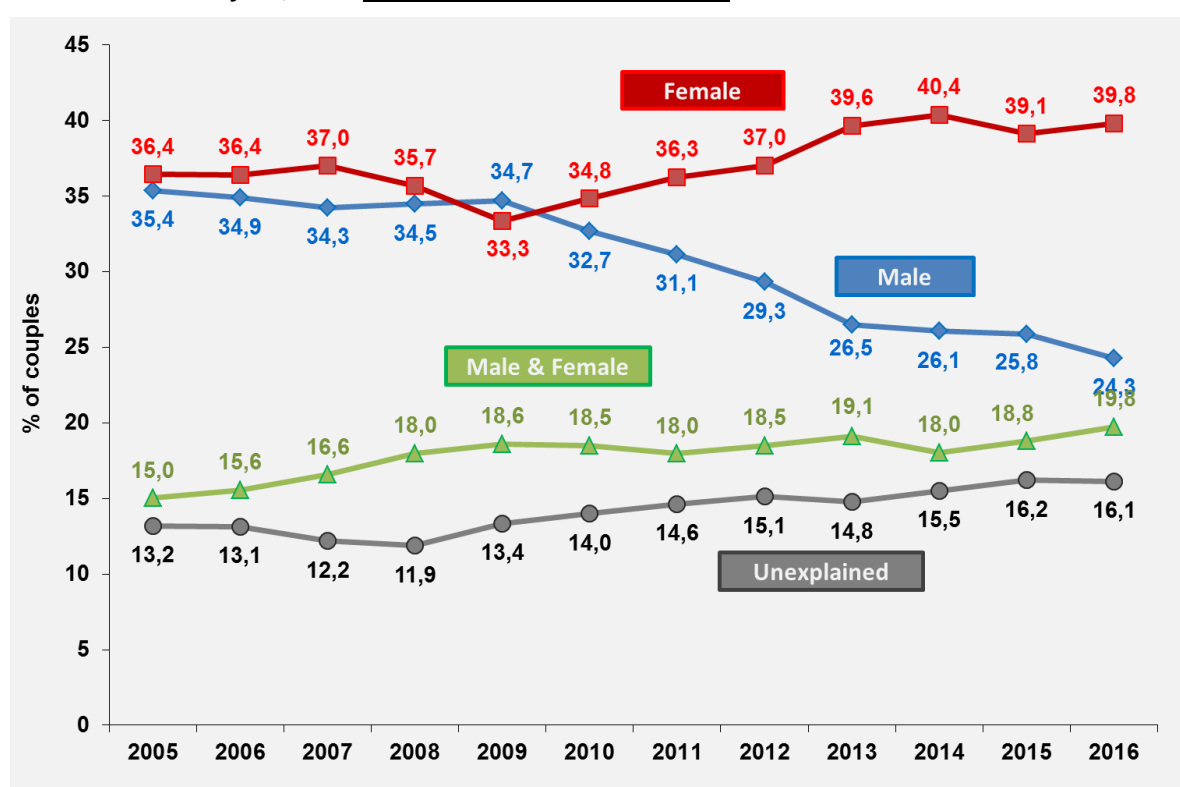
Figure 12: Comparison of the outcomes of monitored clinical pregnancies that resulted from ART non donor procedures, 2016



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

Figure 13 shows major causes of infertility among patients who had ART using fresh cycles in 2016. Diagnoses range from one infertility factor in the patient or partner to multiple infertility factors in either one or both members of the couple. The male factors are decreasing since 2009, while the female ones are now stable after rising rapidly from 2009 to 2013. Overall, considering also the causes of infertility present in both members of the couples, female factors were diagnosed in more than 50% of couples in each year of data collection.

Figure 13: Time-trends of gender distributions of infertility causes among patients who had ART using fresh cycle, 2016. Total couples treated: 44.965

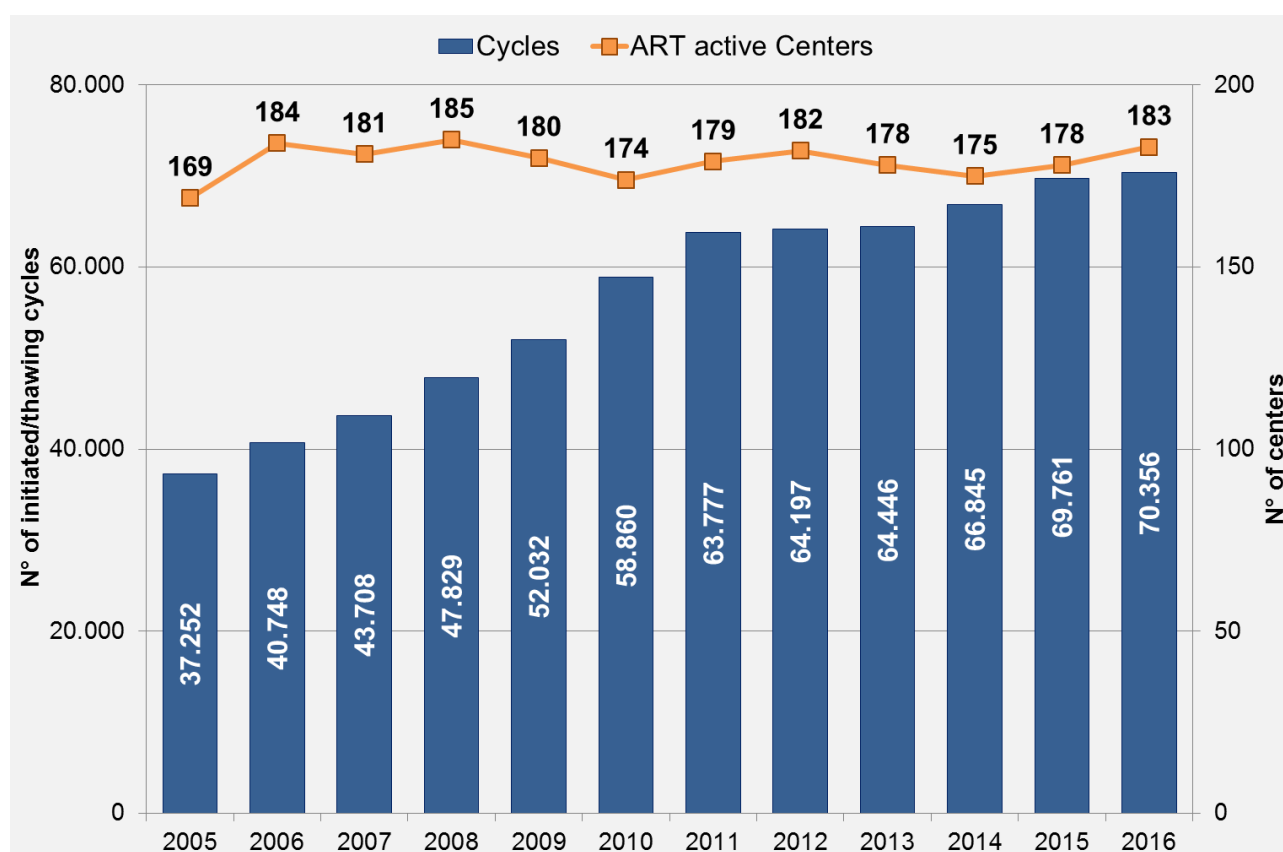


2.2.8. Is the use of ART increasing?

Figure 14 shows the number of ART non donor initiated/thawing cycle and the number of ART active centers (with at least 1 cycle performed in the year) from 2005 to 2016. Instead, the number of the ART authorized centers in Italy varies from a minimum of 194 in 2005 to a maximum of 207 in 2008.

The numbers of initiated cycles increased by 89% over time with an average increase of 8,1% for each year.

Figure 14: Time-trends of ART non donor initiated cycles and number of active ART centers, 2005–2016.



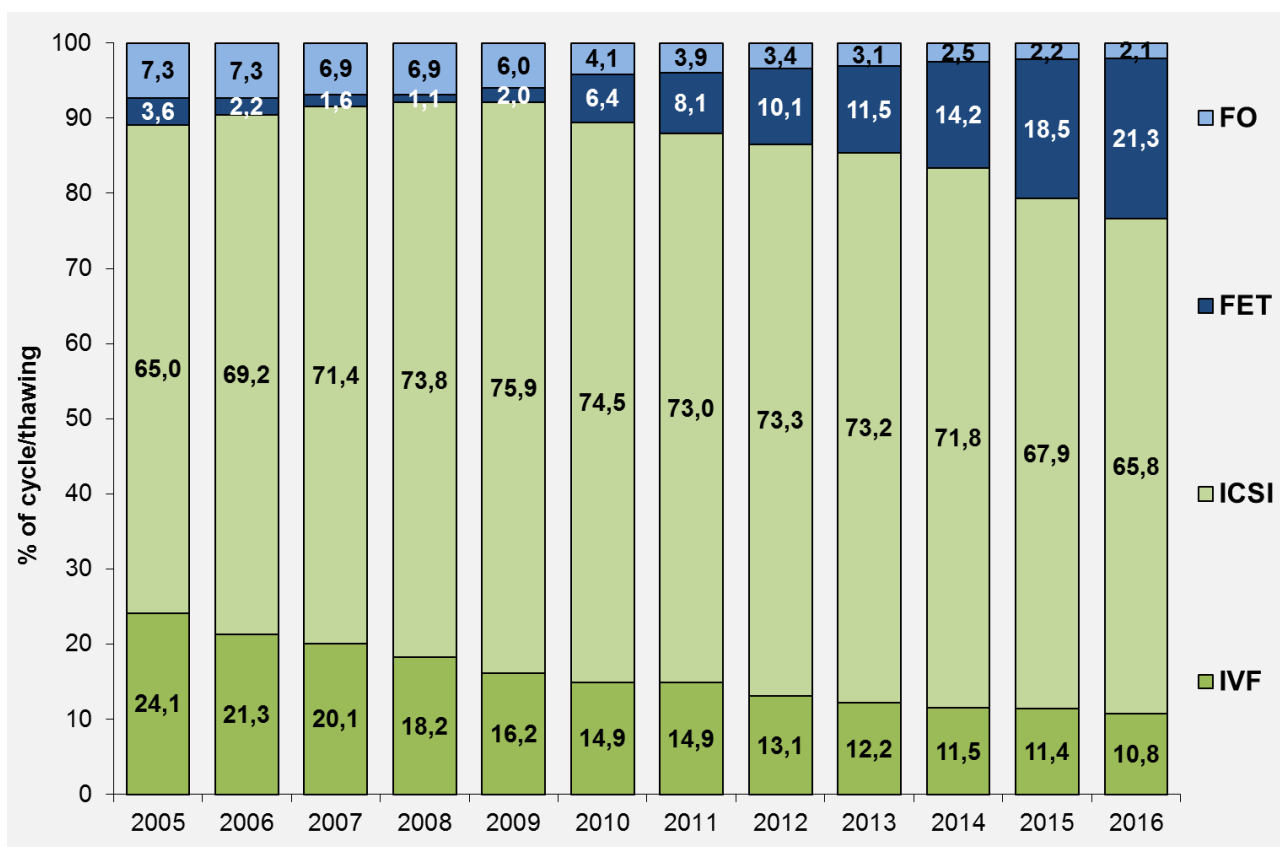
2.2.9. Did the use of different ART procedures change over time?

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 15 shows percentage of initiated cycles with fresh cycles (performed using ICSI and IVF procedures), and thawing with FET and FO from 2005 through 2016.

The number of ICSI cycles increased from 24209 in 2005 to 46322 in 2016, while IVF cycles decreased from 8994 to 7584. Also FET thawing increased from 1338 to 14990, while FO procedures decreased from 2711 to 1460.

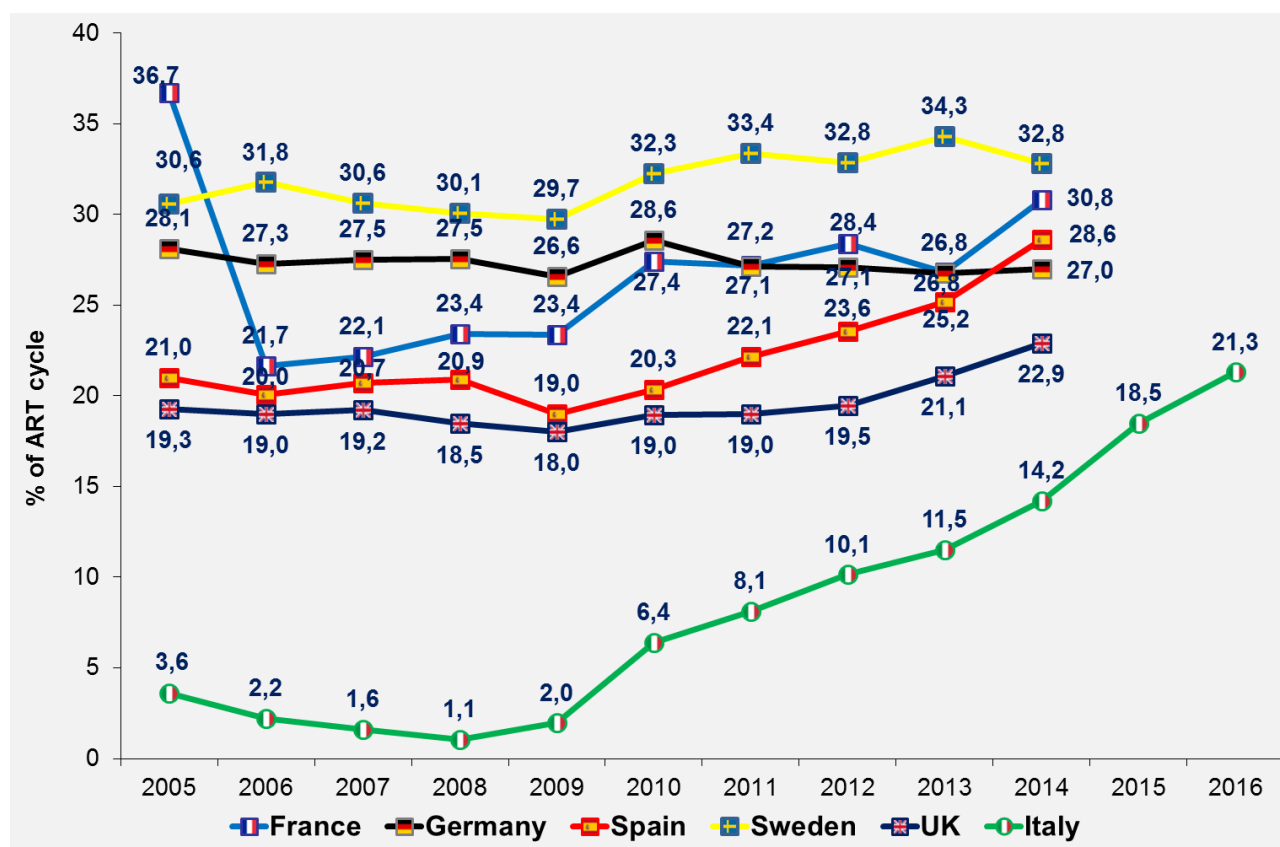
Figure 15: Time-trends of different ART procedures, 2005-2016.



2.2.10. Did the use of FET 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 FET has declined consistently after 2004 and resumed steadily after 2009 (**Figure 15**). As it shown in **Figure 16** percentage of FET cycles performed increased from 3,6% in 2005 to 21,3% in 2016. In comparison with some European countries, like France, Germany and Sweden, Italy still show the lowest number of FET cycles performed, but they are steadily increasing.

Figure 16: Time- trends of percentages of FER thawing on total ART non-donor initiated cycles in Europe, 2005-2014.

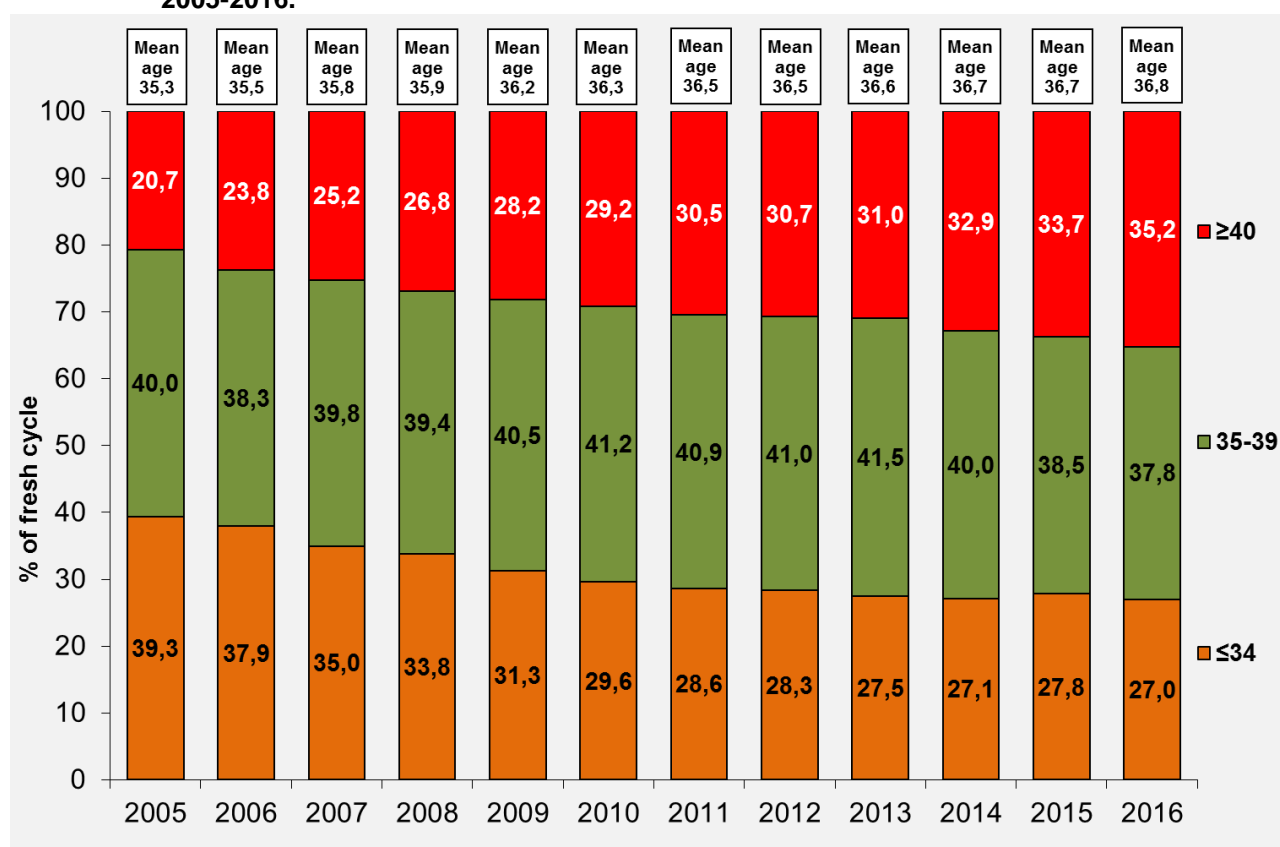


2.2.11. Has the age of ART female patients changed over time?

Figure 17 shows the distribution of fresh cycles by women age groups, from 2005 to 2016.

For women older than 40 the percentage of fresh cycles performed increased from 20,7% in 2005 to 35,2% in 2016, whilst the percentage of fresh cycles performed in women ≤ 34 years old decreased from 39,3% in 2005 to 27,0% in 2016. Overall, the mean age of women who had fresh cycles increase from 35,3 to 36,8 years over time.

Figure 17: Time-trends of fresh initiated cycles distributions by age classes of female patients, 2005-2016.

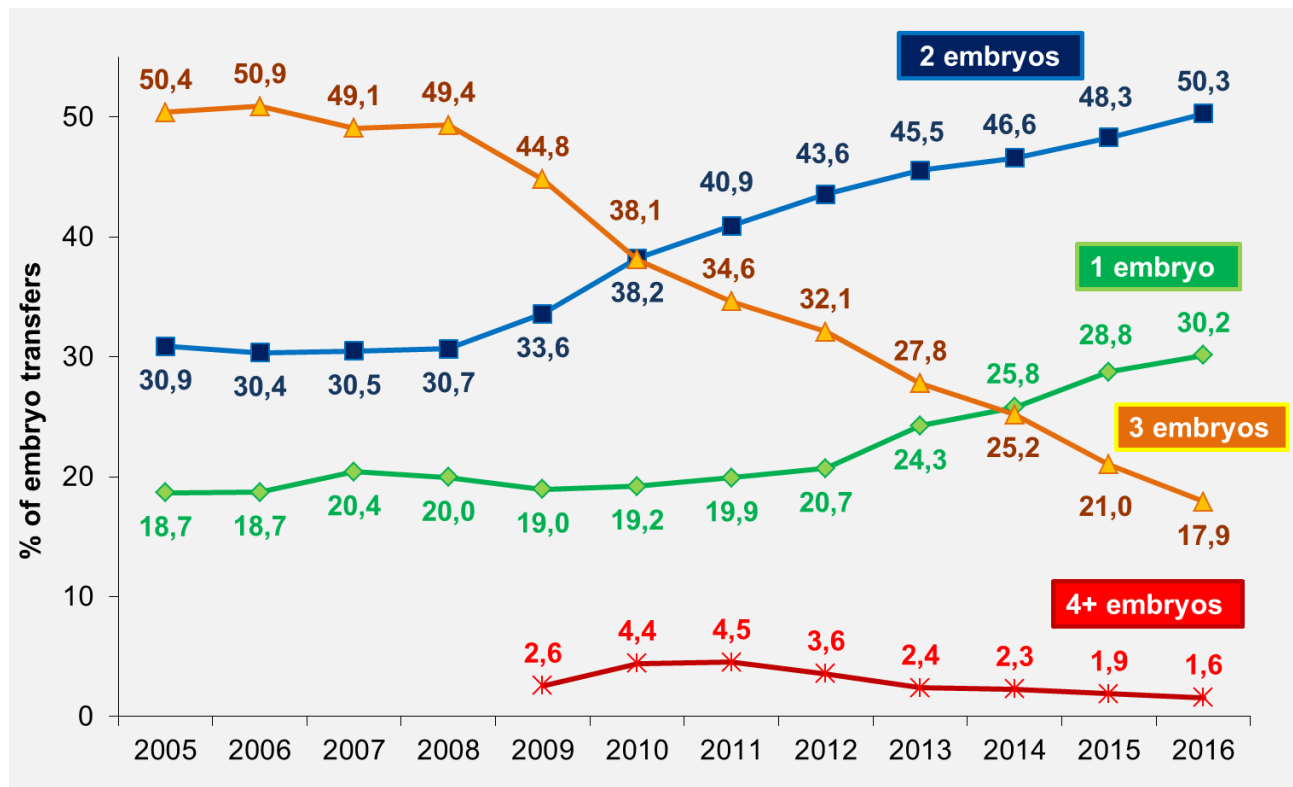


2.2.12. Has the number of embryos transferred changed in fresh cycles?

Figure 18 shows trends with the percentage of the number of embryos transferred in fresh cycles.

From 2005 to 2016 the transfer with one and two embryos increased from 18,7% and 30,9% to 30,2% and 50,3%, respectively. On the other hand transfers with 3 embryos dramatically decreased from 50,4%, first to 38,1% in 2010 to reach the 17,9% in 2016. 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 1,6% in 2016. The average number of embryos transferred decreased from 2,3 embryos per transfer in 2005 to 1,9 in 2016.

Figure 18: Time-trends of transfer by number of embryos transferred, 2005-2016.

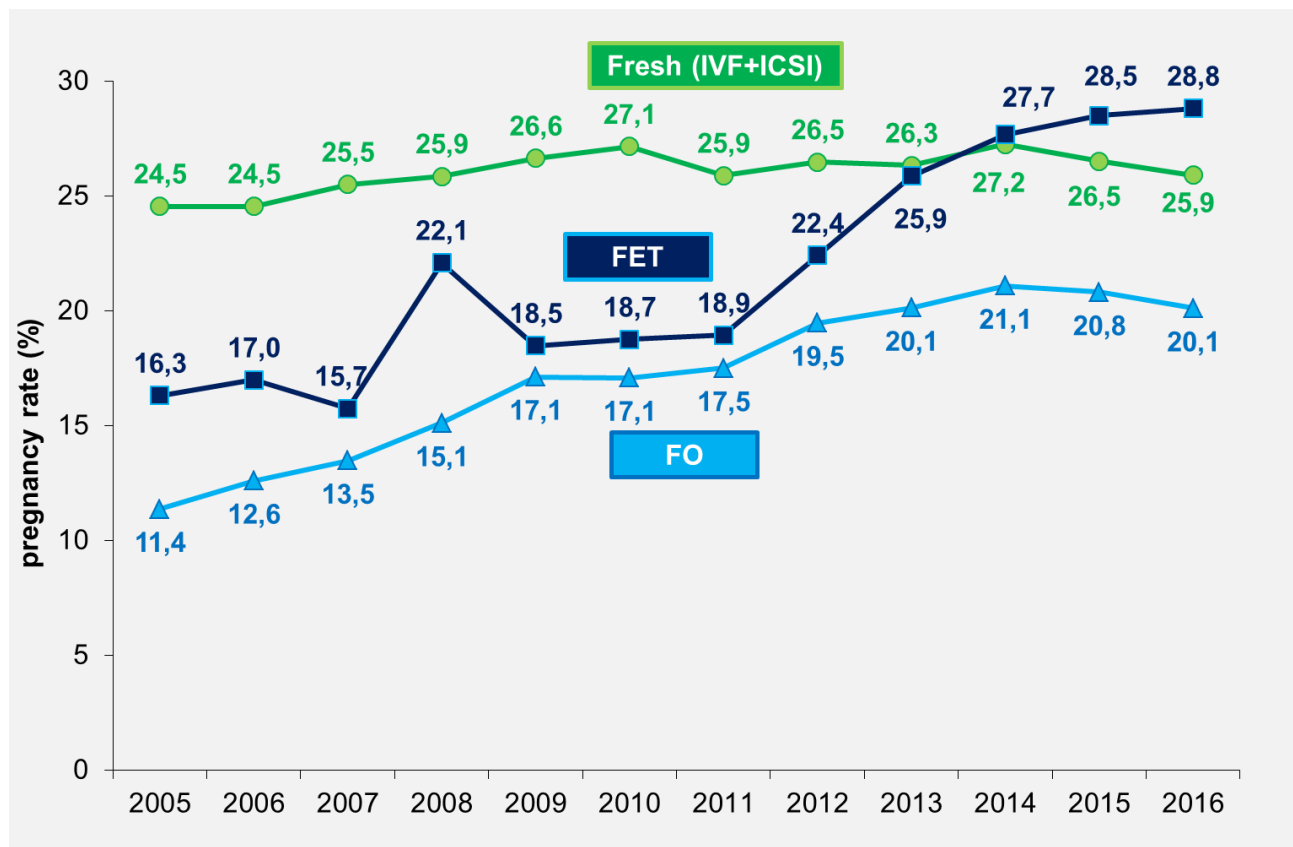


2.2.13. Did pregnancy rates per transfer changed over time among different ART procedures ?

Figure 19 shows pregnancy rates per transfer in order to compare cycles with fresh oocytes vs. those using frozen embryos (FET) or frozen oocytes (FO).

Overall, FET cycles showed the best pregnancy rates increasing highly from 16,3% in 2005 to 28,8% in 2016, those with fresh oocytes slightly increased from 24,5% to 25,9%, and those with frozen oocytes from 11,4% to 20,1%.

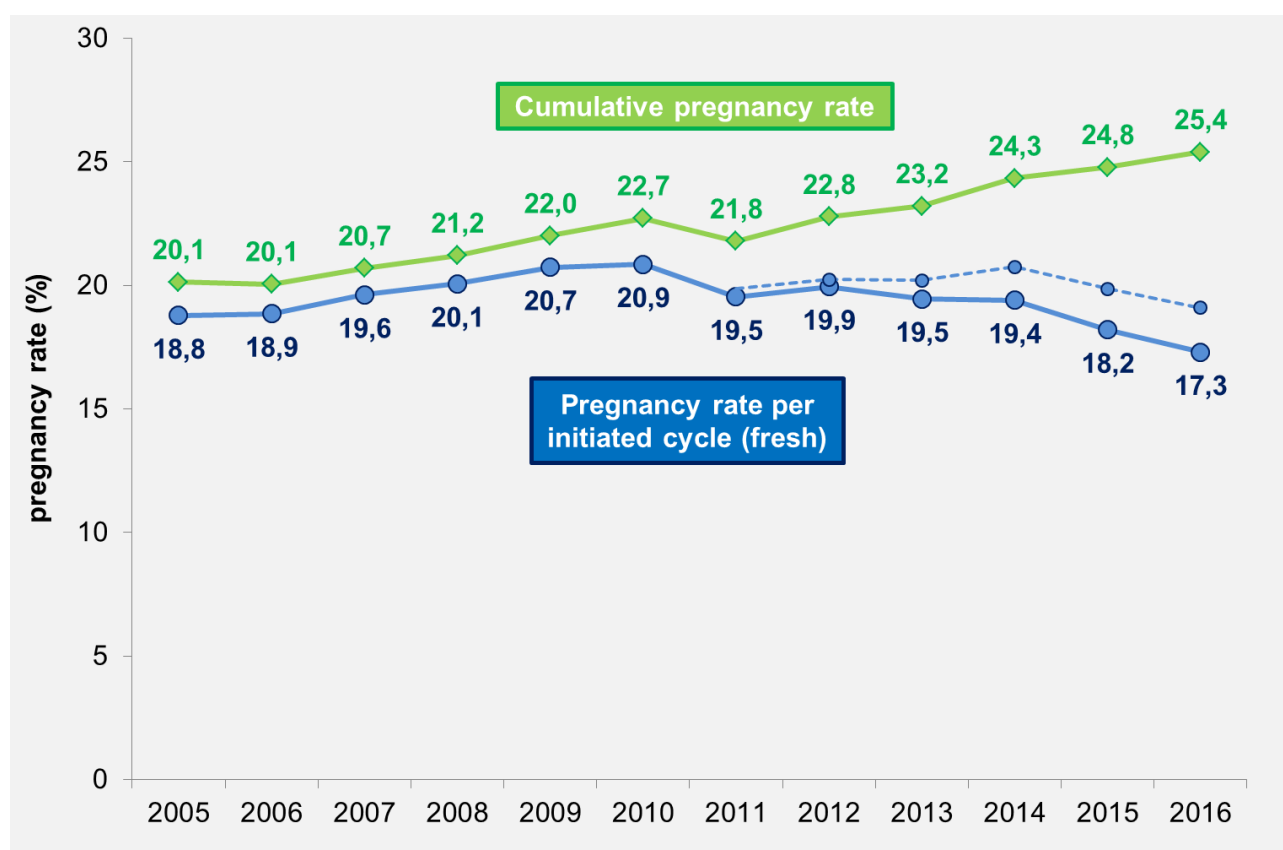
Figure 19: Time-trends of pregnancy rate per transfer for fresh, thawed embryos (FET) and thawed/warmed oocytes cycles (FO), 2005-2016.



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

Figure 20 compares the percentage of pregnancies obtained on fresh initiated cycles with the Cumulative Pregnancy Rate over time. As described in **chapter 2.2.5**, CPR is presented as the sum of pregnancies obtained from fresh cycles and with frozen/thawing cycles (FET and FO) 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 20** show this value is constantly growing from +7,2% in 2005 to a 46,8% in 2016.

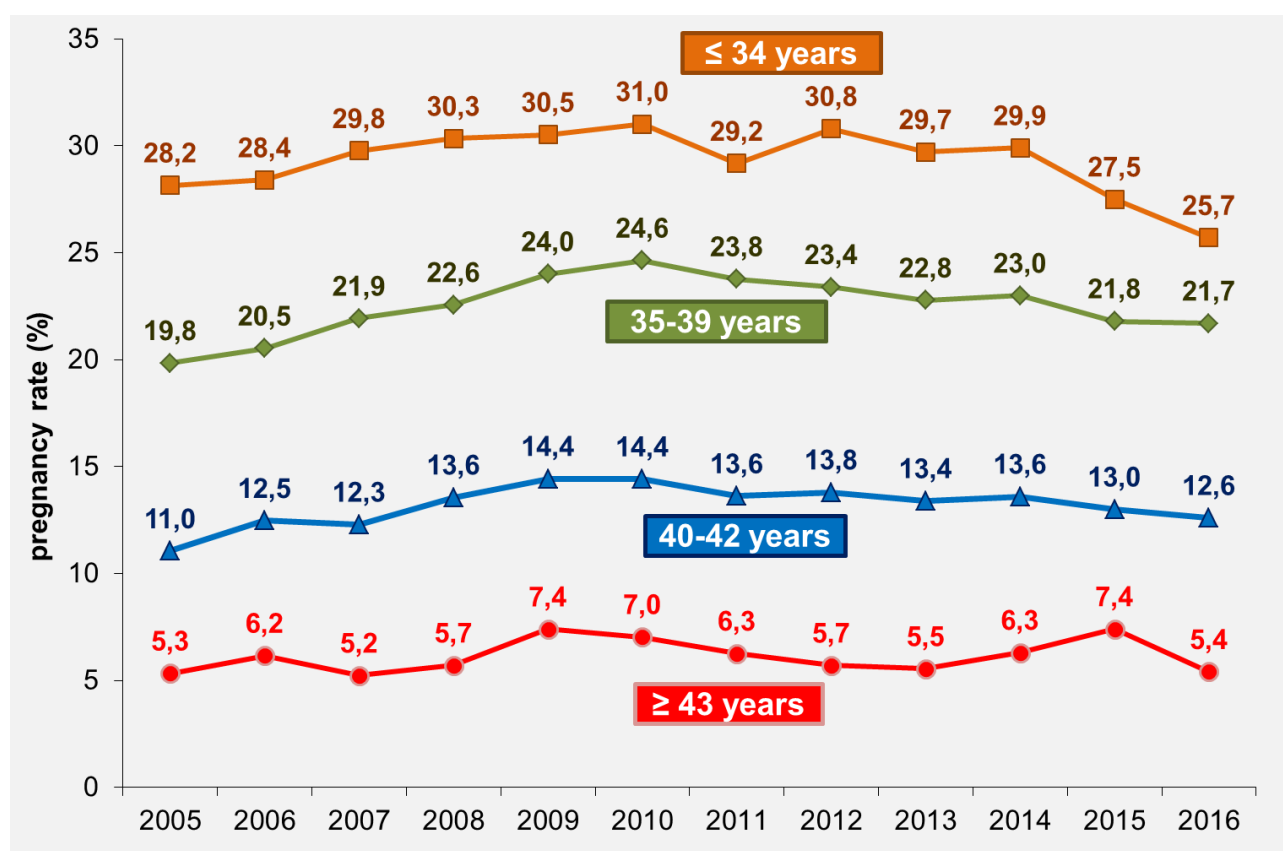
Figure 20: Time-trends of pregnancy rate per initiated cycle for fresh and cumulative pregnancy rate per initiated cycle, 2005-2016.



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

Figure 21 shows pregnancy rates per retrieval according to women age groups, after fresh cycles. From 2005 to 2016 pregnancy rates per retrieval decreased from 28,2% to 25,7% for women aged less than 34, while they increased from 19,8% to 21,7% for women aged 35-39, from 11,0% to 12,6% for women aged over 40-42 and from 5,3% to 5,4% in women aged more than 42 years.

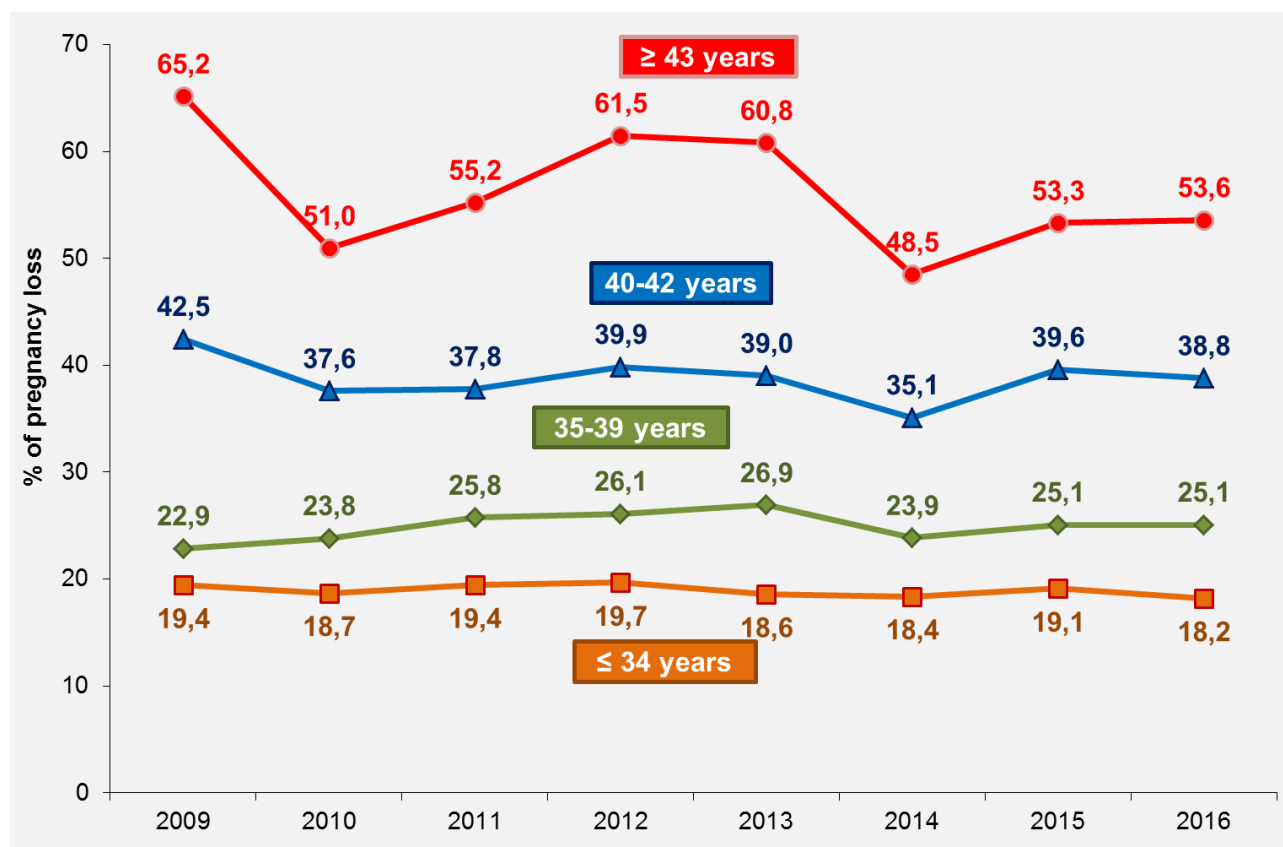
Figure 21: Time-trends of pregnancy rates per retrievals with fresh cycles by age groups of female patients, 2005-2016.



2.2.16. 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 22** rates in older age groups were much higher. Rates decreased over time from 65,2% to 53,6% for women older than 43 years old and from 42,5% to 38,8% for women aged 40-42. Rates for the age classes younger than 40 were quite stable from 2009 to 2016.

Figure 22: Time-trends of percentages of total pregnancy loss using ART cycles by female age groups, 2009-2016.



2.3. ART donor cycles.

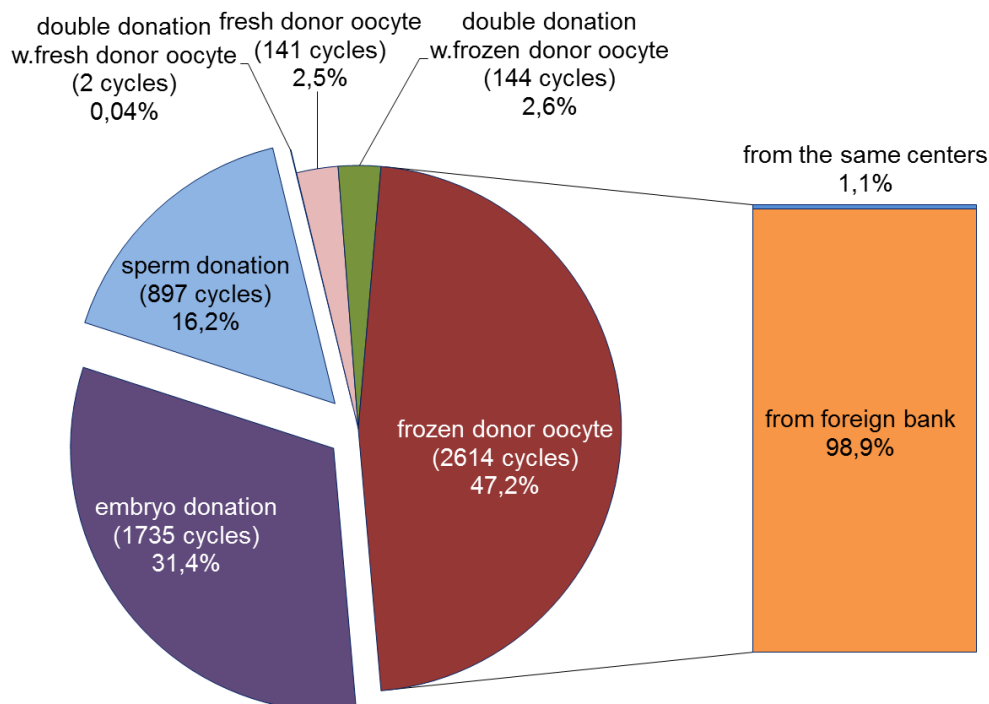
In April 2014 Italian Constitutional Court removed the prohibition, set out in the law, regarding the practice of ART techniques using donor gametes, now permitted under specific conditions.

For more detailed data on activity and outcomes regarding ART donor cycles, please check on Summary table for 2016 (on page 58).

2.3.1. Which gametes were used in ART donor cycles in 2016?

Figure 23 shows the distribution of types of ART cycles using donor gametes applied in Italy in 2016 and the origin of the donated frozen oocytes. In about 50% of ART donor cycles, fresh or frozen eggs were used, in almost 16% of cycles there was a sperm donation, more than 31% of cycles were performed using cryopreserved embryos obtained from donation of gamete(s) and in 2,5% of cycles there were a double donation. In cycles involving a cryopreserved oocyte donation, almost all (98,9%) was performed with oocytes from foreign banks.

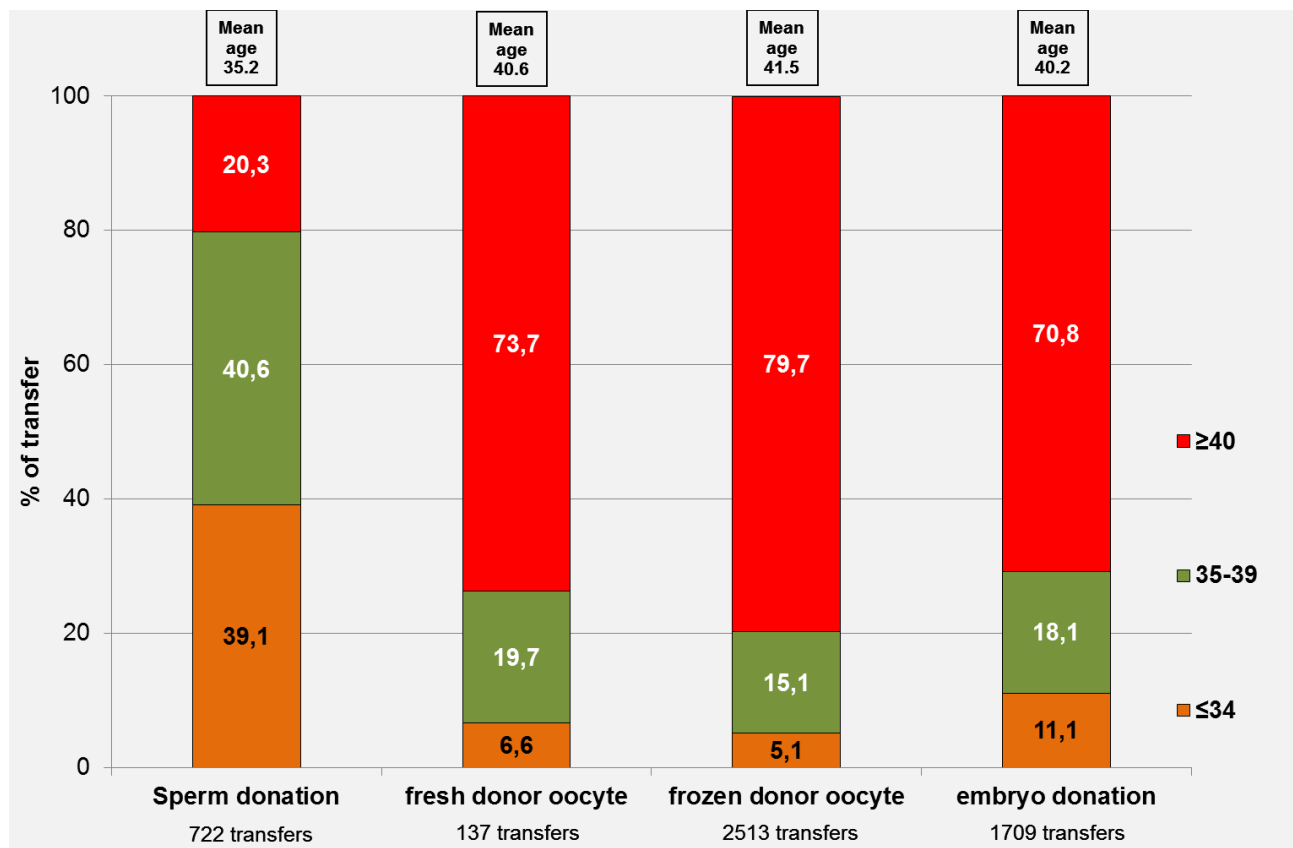
Figure 23: Distribution of all ART cycles using donor gametes or cryopreserved embryos after donation and origin of the oocytes for the frozen donor oocyte cycles, 2016. Total cycles = 5533.



2.3.2. What is the age of recipient female patients in ART donor cycles in 2016?

Figure 24 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.

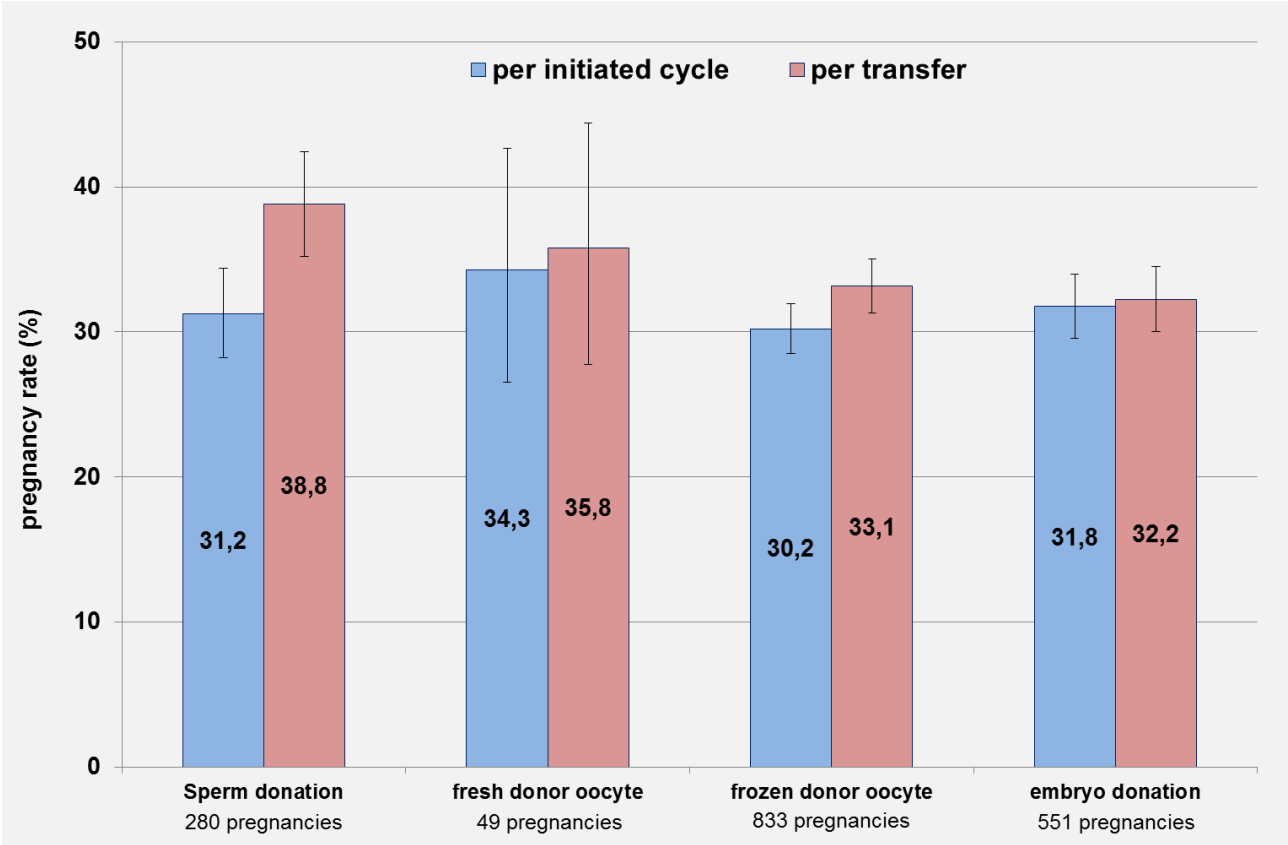
Figure 24: Distribution of transfers cycles using donor gametes or cryopreserved embryos after donation by recipient female age groups, 2016.



2.3.3. What is the percentage of initiated cycles and transfer that result in pregnancies in ART donor cycles in 2016?

In **Figure 25** the pregnancy rate per initiated cycle and per transfer in ART donor techniques are shown.

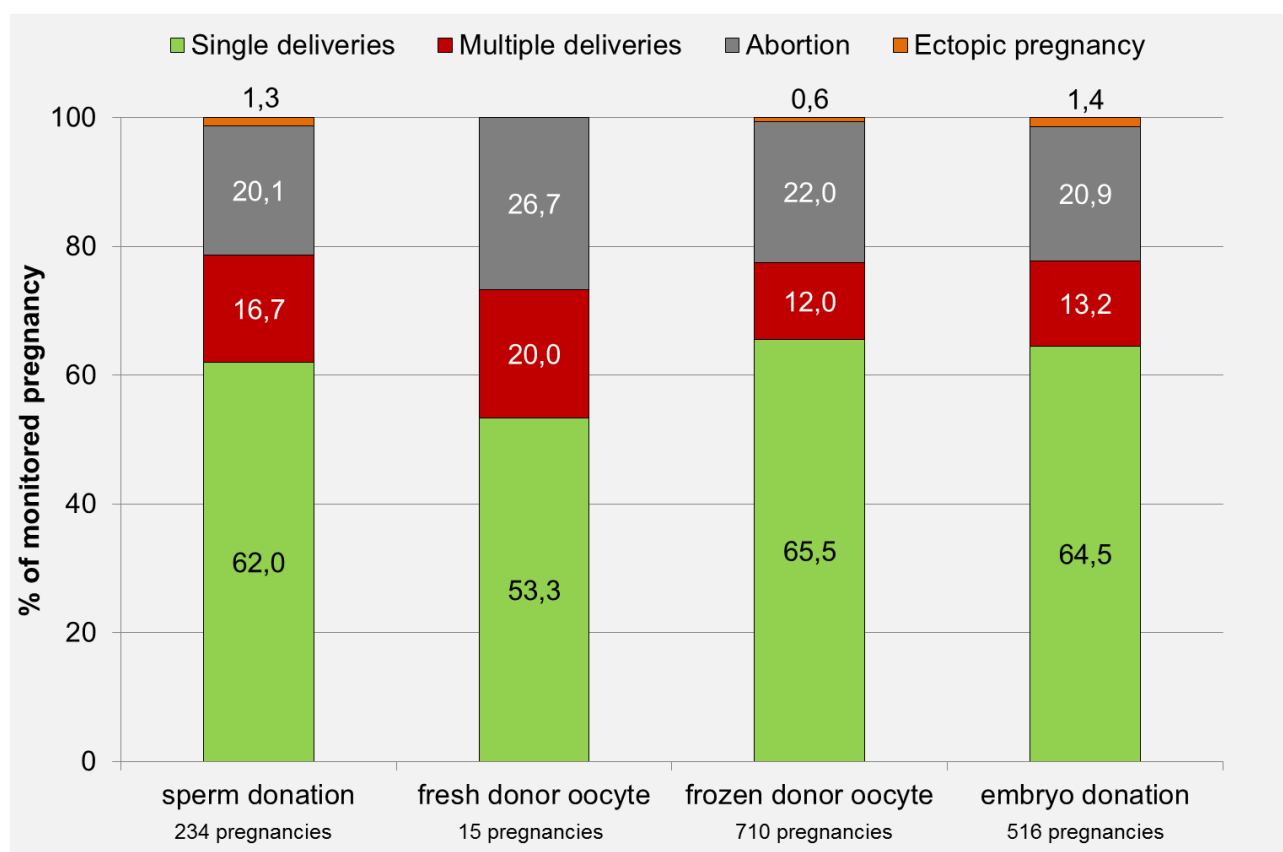
Figure 25: Distribution of pregnancy rate per initiated cycle and per transfer using donor gametes or cryopreserved embryos after donation, 2016.



2.3.3. What are the outcomes of the pregnancies obtained in ART donor cycle in 2016?

Figure 26 shows the outcomes of the monitored clinical pregnancies obtained from the application of the ART donor procedures in Italy in 2016. Of the 234 monitored pregnancies resulted from sperm donation 16,7% were resulted in multiple deliveries and the 20,1% were aborted. In frozen donor oocyte cycles and in embryo transfer after a gametes donation cycle the multiple deliveries are lower (12% and 13,2% respectively), and the percentage of abortion were similar (22% and 20,9%).

Figure 26: Comparison of the outcomes of monitored clinical pregnancies that resulted from ART donor cycles, 2016.



2.4. PGD/PGS activity.

During an ART treatment some investigation should be performed with the aim of the evaluation of the embryo's health status regarding the detection of possible genetic disorder.

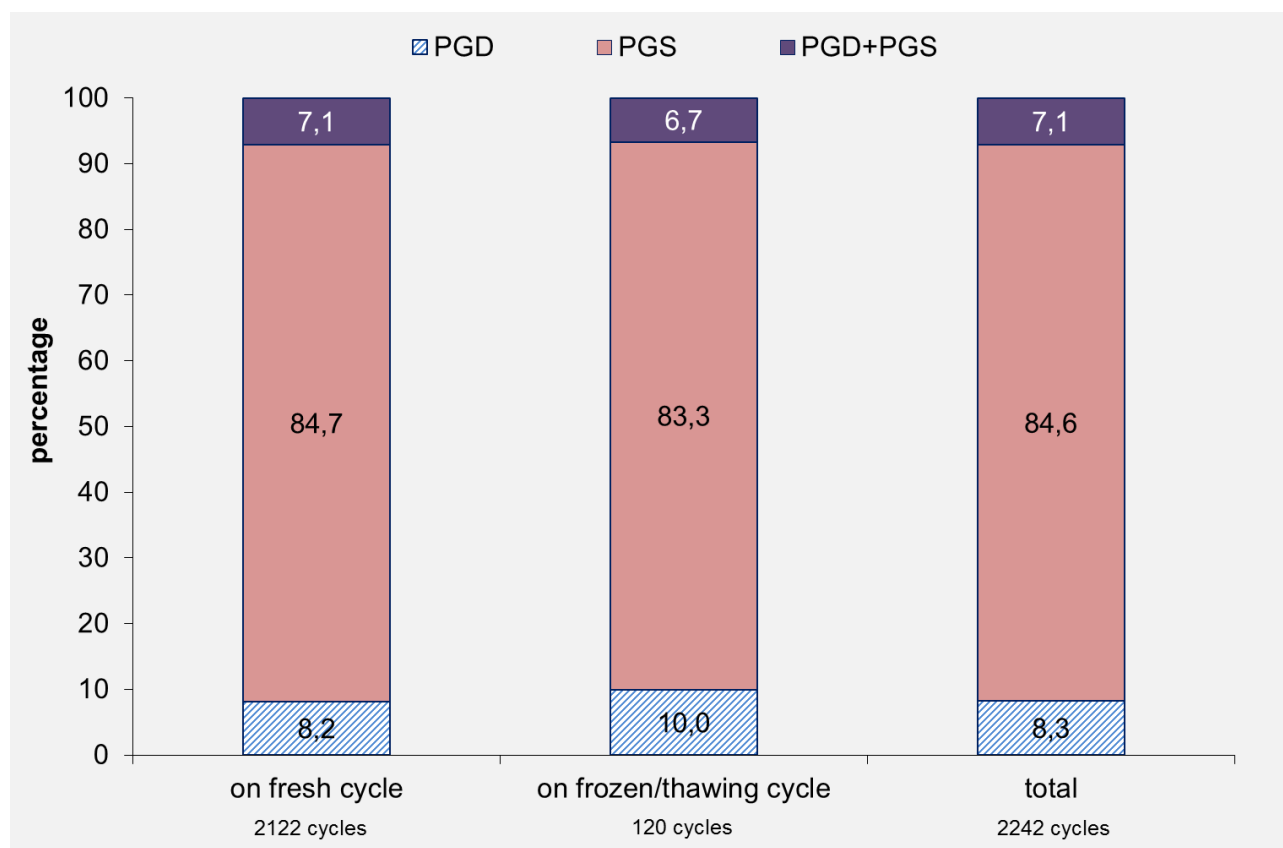
For the analysis may be used the Preimplantation Genetic Diagnosis (PGD) technique or Preimplantation Genetic Screening (PGS) or a combination of the two:

- **PGD:** analysis of polar bodies, blastomeres or trophoctoderm from oocytes, zygotes or embryos for the detection of specific genetic, structural and/or chromosomal alterations;
- **PGS:** analysis of polar bodies, blastomeres or trophoctoderm from oocytes, zygotes or embryos for the detection of aneuploidy, mutation and/or DNA rearrangement.

2.4.1. Which types of genetic analysis were performed in ART cycles in 2016?

PGD/PGS activity, recorded from 35 centers, involved 2122 analysis on fresh and 120 analysis on thawing cycles, resulting in 1587 fresh and 38 frozen embryo transfers. **Figure 27** shows the distribution of the application of PGD/PGS cycles in Italy. A total of 700 pregnancies (44,1% per transfer) and 569 deliveries (35,9% per transfer) resulted from fresh cycles, while 21 pregnancies (55,3% per transfer) and 13 deliveries (34,2% per transfer) resulted from frozen embryo cycles.

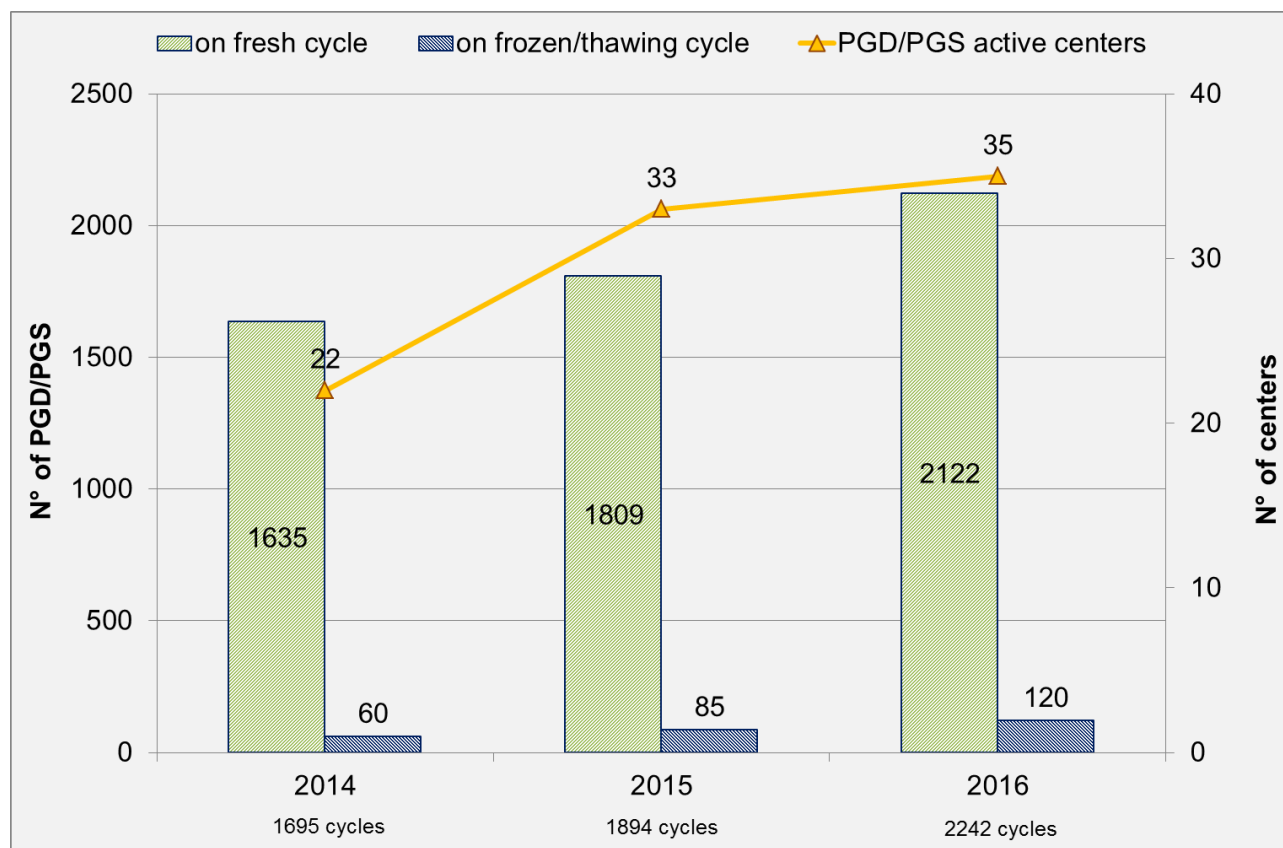
Figure 27: Distribution of PGD/PGS cycles, 2016



2.4.2. Did the use of different genetic analysis in ART change over time?

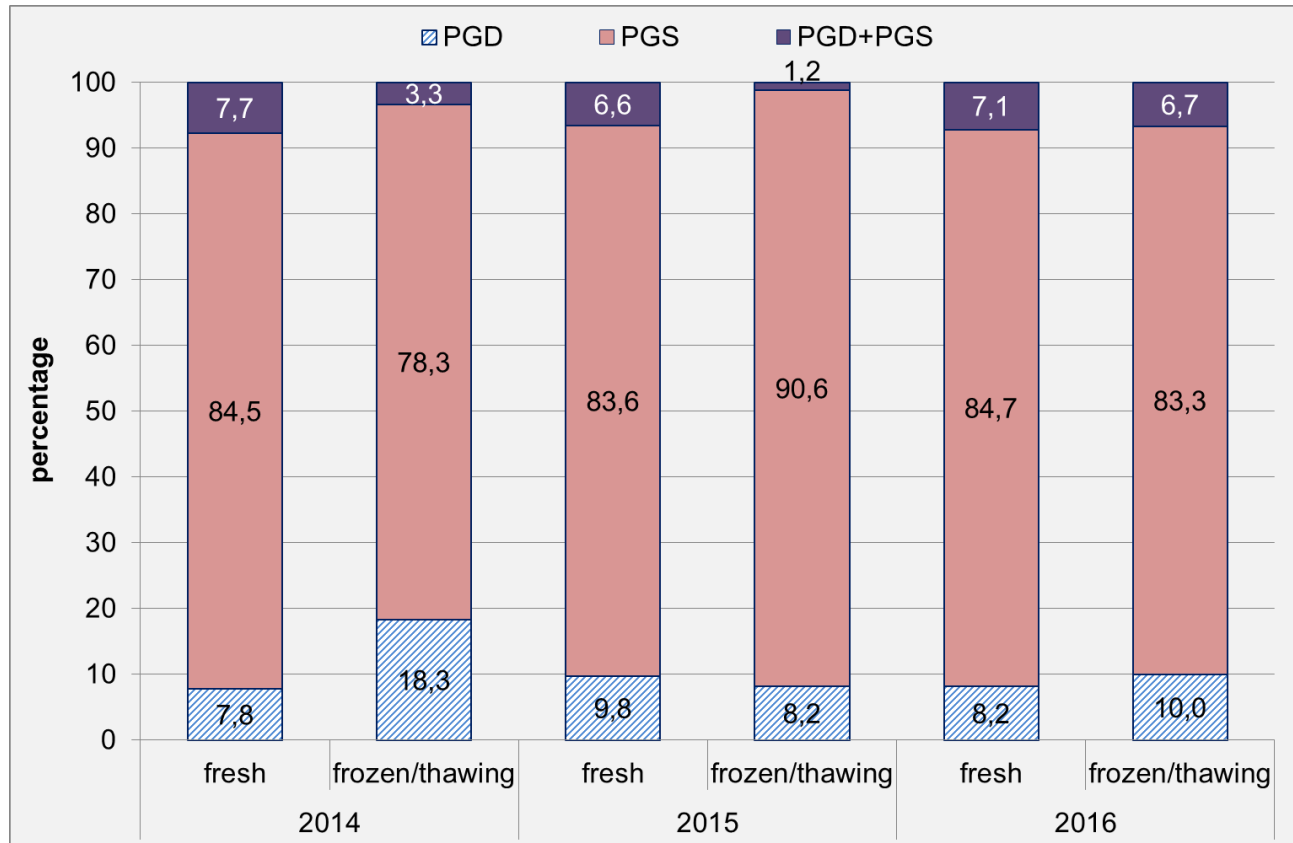
Since the first data collection on PGD/PGS cycles performed on 2014 activity, the number of centers performing at least one PGD/PGS cycle increased from 22 in 2014 to 35 in 2016. At the same time also the number of analysis performed increased from 1695 cycles in 2014 to 2242 cycles in 2016 (Figure 28).

Figure 28: Time-trend of number of PGD/PGS cycles according to ART procedure performed, and of n° of ART centers performing at least one PGD/PGS cycle, 2016



The time-trend of the different analysis performed according to the different ART cycle in **Figure 29**, shows no difference in the application of the genetic analysis both in fresh and in thawing cycles. The distributions were more stable in fresh cycle then in frozen ones because of the large number of cycles involved, however PGS analysis is the most common in all the three data collection.

Figure 29: Time-trend of distribution of PGD/PGS cycles according to the type of the analysis and the ART procedure performed, 2016



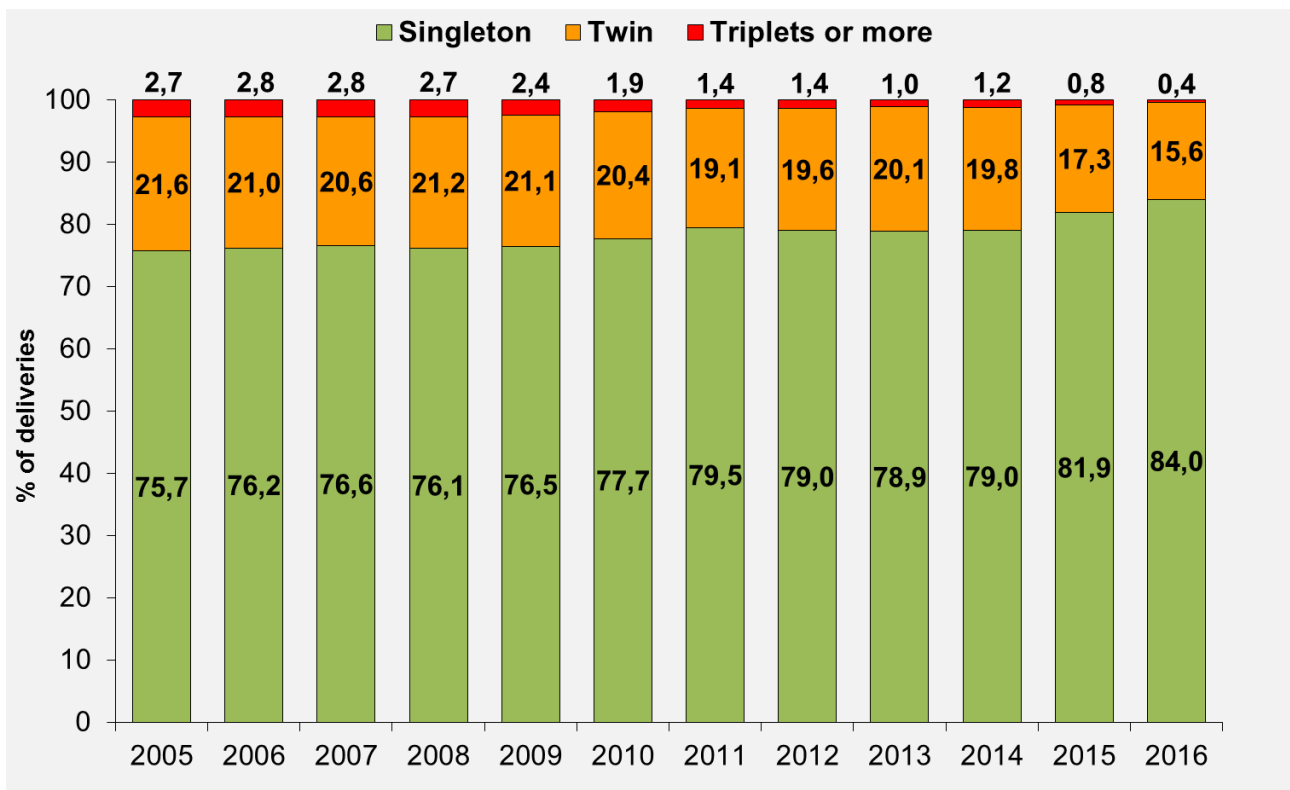
3.INDICATORS OF ART SAFETY

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

Figure 30 shows trends for singleton and triplet deliveries in fresh cycles.

From 2005 to 2016 twin delivery rates decreased from 21,6% to 15,6% while numbers of triplets and more deliveries decreased from 2,7% to 0,4%, similar to the 0,5% average value in Europe, as reported in 2013 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 30: Time-trends of deliveries from fresh cycles according to gestational order, 2005-2016.

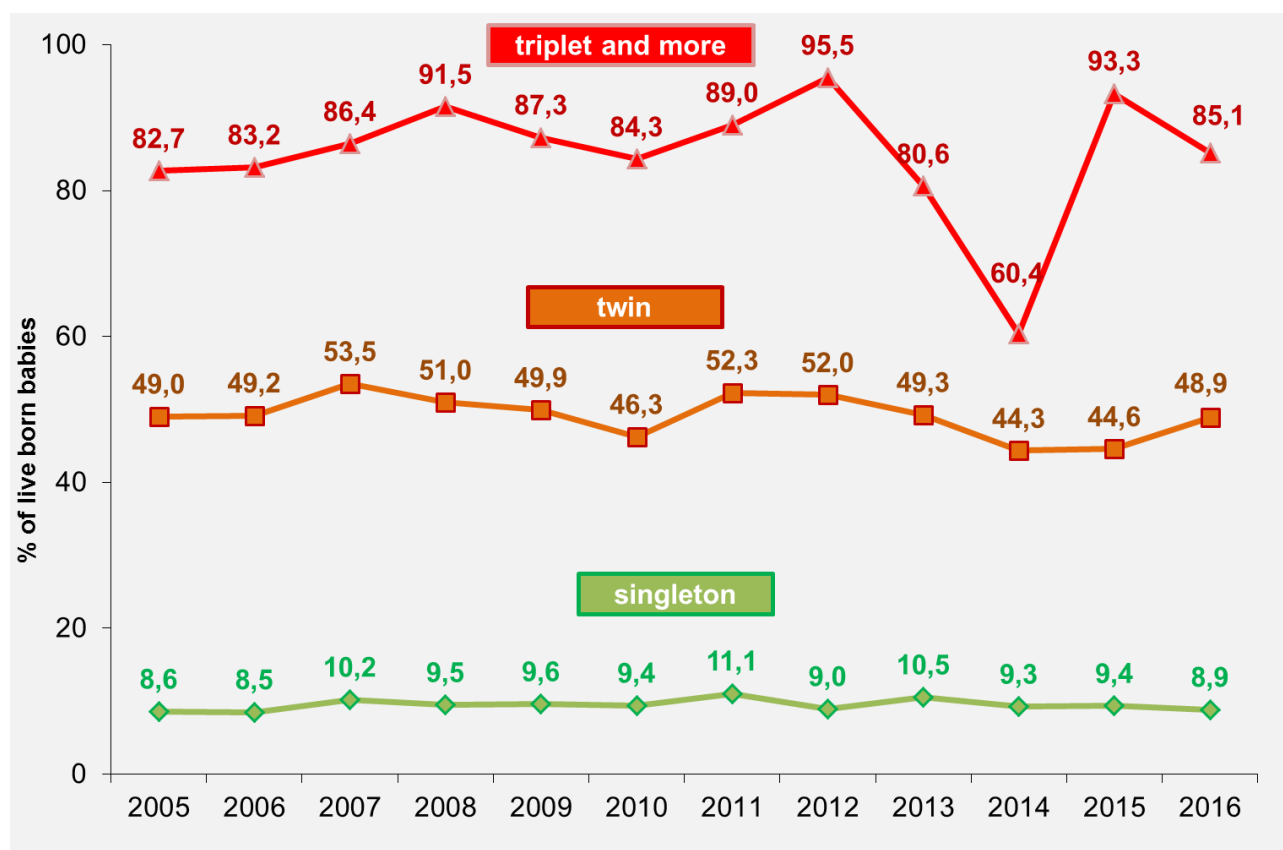


3.1.2. Did the percentages of preterm live babies change over time?

Figure 31 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 and twin deliveries are quite stable during all the period. Otherwise in triplets deliveries there is a variability from year to year, but overall the trend is upwards from 82,7% in 2005 to 85,1% in 2016.

Figure 31: Time-trends of percentage of preterm ART live born babies (<37 week of gestation) by gestational order, 2005-2016.

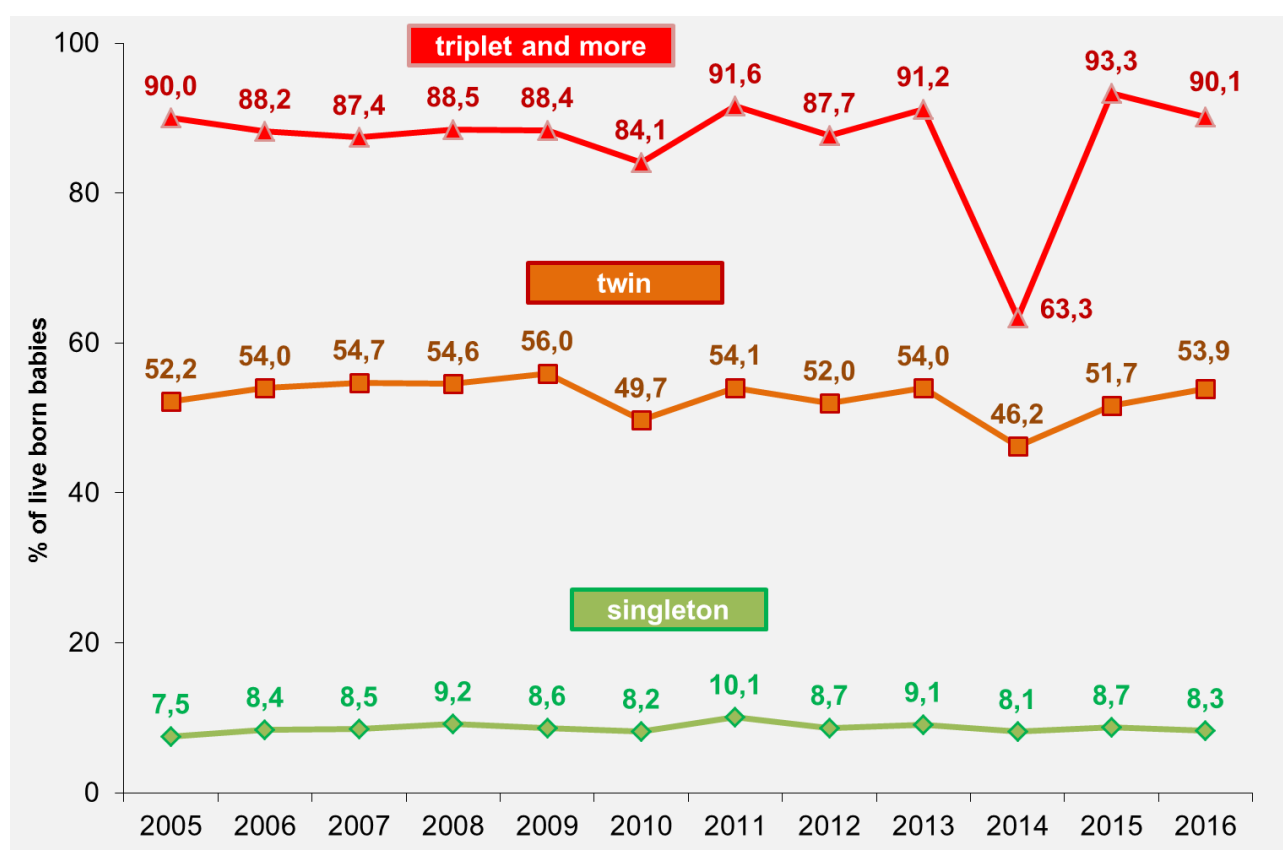


3.1.3. Did the percentage of underweight live babies change over time?

Figure 32 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 and twin deliveries are quite stable during all the period. Overall the trend is also quite stable for triplets and more deliveries from 90% in 2005 to 90,1% in 2016 with a minimum value of 63,3% in 2014 due to variability of the small number.

Figure 32: Time-trends of percentage of ART live born babies underweight (<2,500 gr) by gestational order, 2005-2016.



4.IUI PROCEDURES

4.1. Access to IUI service

In **Figure 33** the regional distribution of the 360 IUI authorized centers in 2016 is represented, but only 301 are performed at least 1 homologous IUI cycle.

The largest number of the centers is concentrated in Norther 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 33: Regional distribution of IUI + ART authorized centers and in brackets the number of centers per 100000 women of reproductive age (15-45 years), 2016



As shown in **Table 3**, in 2016 there were 360 authorized centers to perform IUI of which only 134 operating within the National Health System (public and private 37,2%) and 226 providing private service (62,8%).

Most of public centers that could performs IUI in Italy were in North: 69 out of 112 centers (61,6%).

Table 3: IUI authorized centers distribution by region and type of service, 2016.

Region and Geographical Area	Total	Type of Service					
		Public		Private covered by NHS		Private	
		N	%	N	%	N	%
Piemonte	28	12	42,9	1	3,6	15	53,6
Valle d'Aosta	1	1	100	0	-	0	-
Lombardia	62	20	32,3	10	16,1	32	51,6
Liguria	10	5	50,0	0	-	5	50,0
Northwest	101	38	37,6	11	10,9	52	51,5
P.A. Bolzano	5	4	80,0	0	-	1	20,0
P.A. Trento	1	1	100	0	-	0	-
Veneto	38	13	34,2	2	5,3	23	60,5
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	31	43,7	3	4,2	37	52,1
Toscana	22	8	36,4	5	22,7	9	40,9
Umbria	2	1	50,0	0	-	1	50,0
Marche	7	3	42,9	0	-	4	57,1
Lazio	38	6	15,8	3	7,9	29	76,3
Central	69	18	26,1	8	11,6	43	62,3
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	15	3	20,0	0	-	12	80,0
Basilicata	2	2	100	0	-	0	-
Calabria	9	1	11,1	0	-	8	88,9
Sicilia	39	4	10,3	0	-	35	89,7
Sardegna	3	3	100	0	-	0	-
South and Islands	119	25	21,0	0	-	94	79,0
Italy	360	112	31,1	22	6,1	226	62,8

4.2. Efficacy and safety of IUI and trends

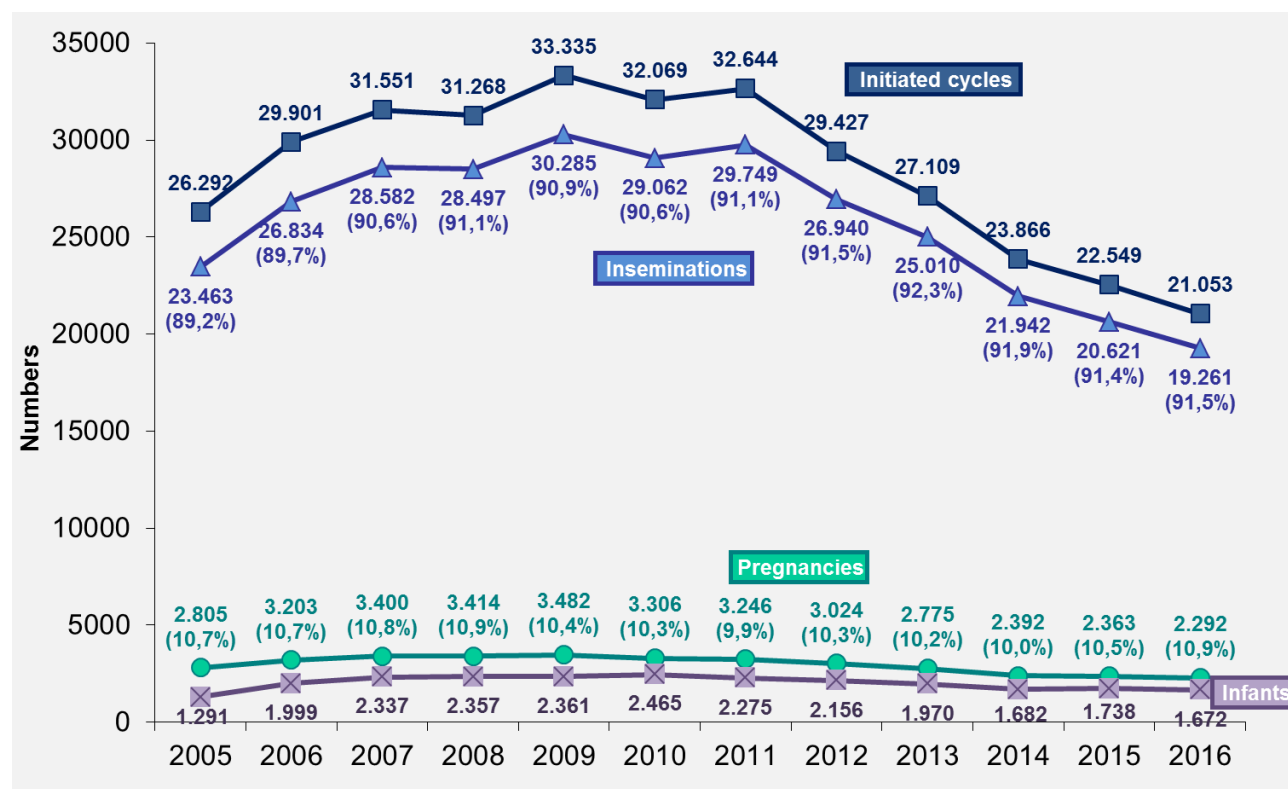
4.2.1. Is the use of IUI-H increasing?

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 36) 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 2016, please check on Summary table for 2016 (on page 58) for more detailed data.

In **Figure 34** the use of IUI-H from 2005 to 2016 is represented. Number of IUI-H cycles decreased from 26292 to 21053 after having reached his maximum of 33335 cycles in 2009. There were no changes in pregnancy rate from 10,7% in 2005 to 10,9% in 2016. Average women age increase of 0.5 year during time.

Figure 34: Time-trends of outcomes of IUI-H cycles, 2005-2016.

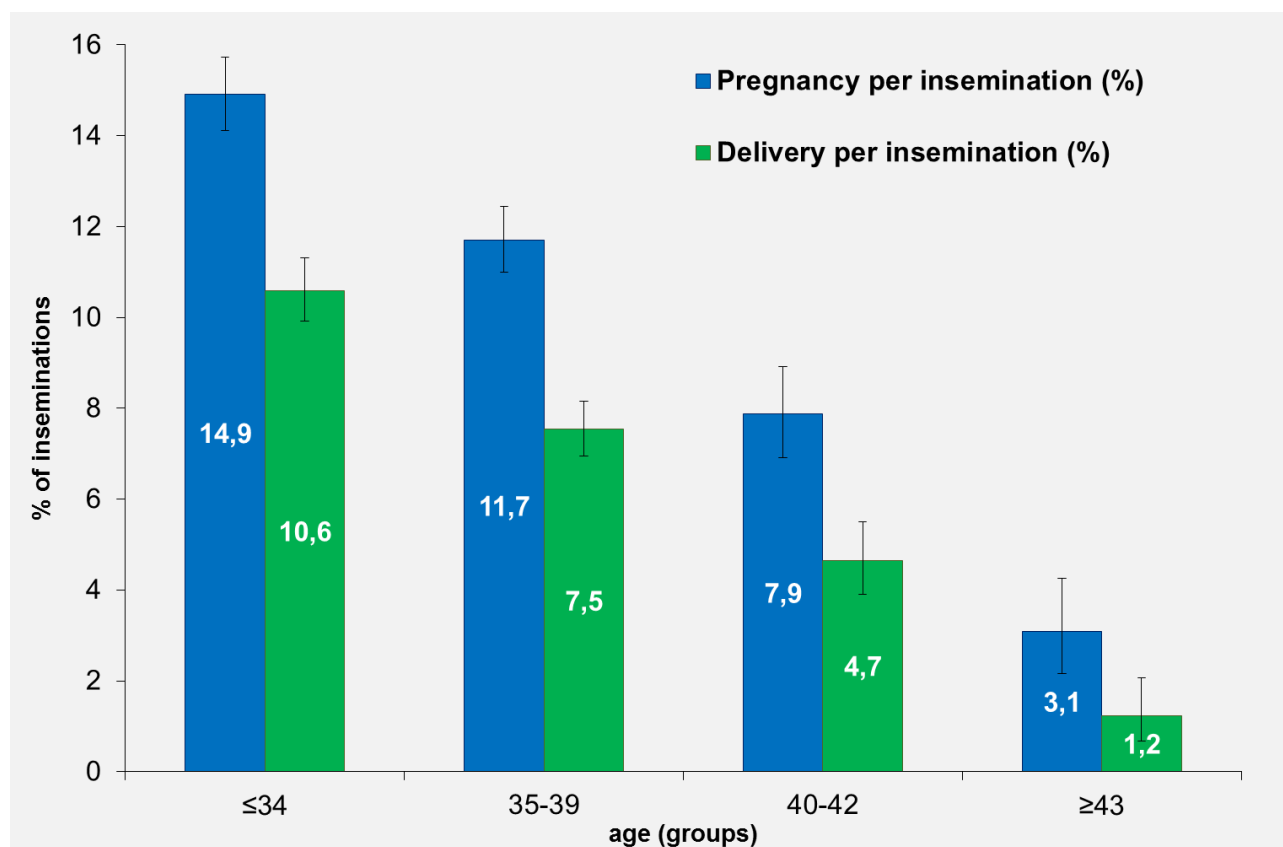


4.2.2. Do percentages of IUI-H cycles resulting in pregnancy, differ among women of different age groups?

Figure 35 shows percentages of insemination cycles for IUI-H that resulted in pregnancies and in deliveries 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 3,1% for pregnancy and 1,2% for delivery.

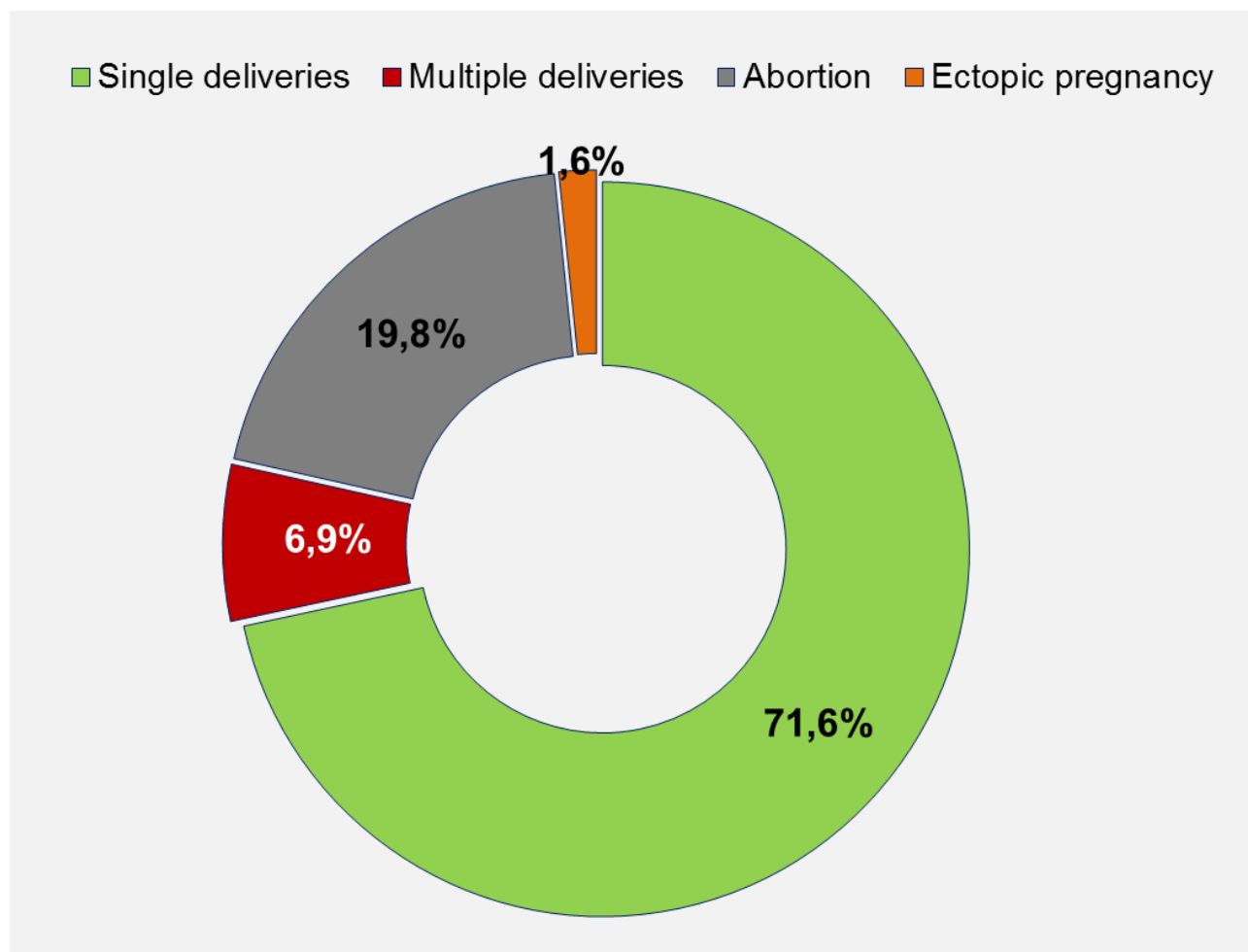
Figure 35: Pregnancy rates and delivery rates per insemination for IUI-H cycles by age groups of female patients, 2016.



4.2.3. What are the outcomes of the pregnancies obtained in H-IUI cycles in 2016?

Figure 36 shows the outcomes of the monitored clinical pregnancies obtained from the application of the homoulogous IUI in Italy in 2016. Of the 1950 monitored pregnancies resulted from homoulogous IUI cycles 6,9% were resulted in multiple deliveries and the 19,8% were aborted.

Figure 36: Outcomes of clinical pregnancies that resulted from H-IUI cycles, 2016.

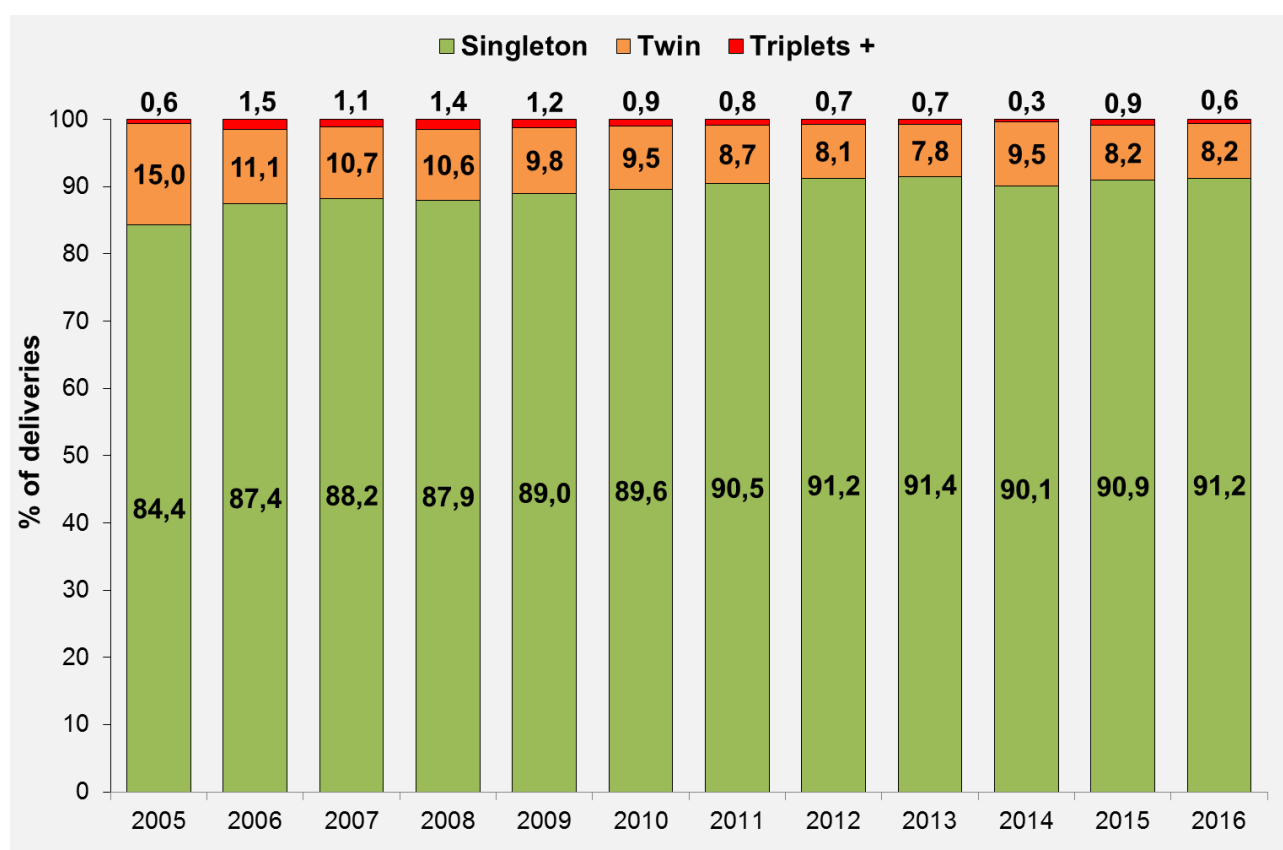


4.2.4. Did the percentages of singletons, twins and triplets- or- more deliveries change over time for intrauterine insemination cycles?

Figure 37 shows time trends for multiplicity of deliveries in IUI-H cycles.

From 2005 to 2016 twin deliveries rates decreased from 15% to 8.2% while percentage of triplets and more deliveries are quite stable: in 2016, 9 deliveries out of 10 were singleton.

Figure 37: Time-trends of deliveries from H-IUI cycles according to gestational order, 2005-2016.

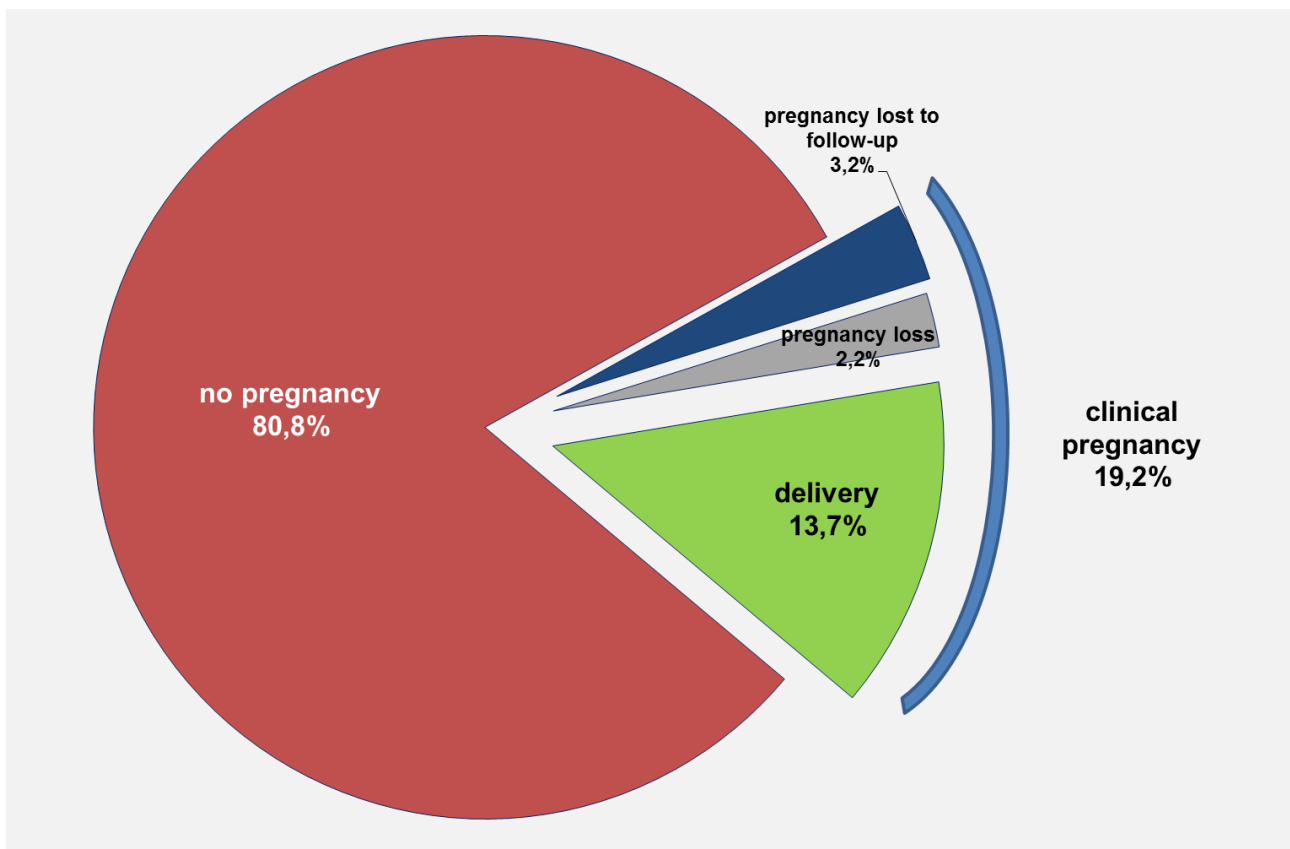


4.3. IUI donor cycles.

4.3.1. What is the outcome in IUI donor cycles in 2016?

In total, 19,2% of the 714 initiated cycles using donor sperm in IUI cycle started in 2016 resulted in a clinical pregnancy and 13,7% has resulted in a delivery. However most of these cycles (about 80%) did not produce a pregnancy while a small proportion (2,2%) resulted in a pregnancy loss (i.e. ectopic pregnancy or abortion).

Figure 38: Outcome of IUI-D cycles, 2016 (714 initiated cycles)



APPENDIX. SUMMARY TABLE OF ACTIVITY
AND OUTCOMES OF ART PROCEDURES,
YEARS 2010 – 2016

Summary table of activity and outcomes of all procedures, 2010 – 2016

	2010	2011	2012	2013	2014	2015	2016
N° Clinics	357	354	355	369	362	366	360
% of clinics reporting data to ISS	100	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	77.522
N° Initiated cycles	90.944	96.427	93.634	91.556	90.957	95.110	97.656
N° Live born	12.506	11.933	11.974	12.187	12.720	12.836	13.582
H-IUI and D-IUI activity							
N° Patients	19.707	20.012	18.085	17.218	14.967	14.545	13.798
N° Initiated cycles	32.069	32.644	29.427	27.109	23.903	23.062	21.767
N° Pregnancies	3.306	3.246	3.024	2.775	2.399	2.466	2.429
% Pregnancy Rate per cycle	10,3	9,9	10,3	10,2	10,0	10,7	11,2
% Pregnancies lost to follow-up	15,5	18,1	17,1	16,8	18,2	16,8	15,0
N° Deliveries	2.220	2.062	1.974	1.810	1.530	1.649	1.629
N° Live born	2.465	2.275	2.156	1.970	1.683	1.807	1.791
ART activity (Fresh-non donor, Thawing-non donor, donor)							
N° Patients	50.090	53.558	54.458	54.523	55.859	59.747	63.724
N° Initiated cycles	58.875	63.783	64.207	64.447	67.054	72.048	75.889
N° Pregnancies	11.968	12.221	12.646	12.775	13.642	14.391	15.405
Cumulative Pregnancy Rate per couple treated with fresh cycle	27,0	26,3	27,2	27,5	29,7	31,5	34,3
% Pregnancies lost to follow-up	10,2	12,2	13,2	10,3	10,8	11,3	10,2
N° Deliveries	8.167	8.003	8.127	8.495	9.252	9.512	10.386
N° Live born	10.041	9.658	9.818	10.217	11.037	11.029	11.791
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	6.781
ART Initiated cycles per 1 million inhabitants	973	1.050	1.078	1.070	1.103	1.175	1.237

	2010	2011	2012	2013	2014	2015	2016
ONLY FRESH CYCLES (Non Donor)							
N° Patients	44.365	46.491	46.491	46.433	45.985	45.689	44.965
N° Initiated cycles	52.676	56.092	55.505	55.050	55.705	55.329	53.906
Average age calculated	36,34	36,48	36,50	36,55	36,68	36,68	36,80
N° Pregnancies	10.988	10.959	11.077	10.712	10.834	10.081	9.326
% Pregnancies rate per cycles	20,9	19,5	20,0	19,5	19,4	18,2	17,3
% Pregnancies rate per aspirations	23,2	21,6	22,1	21,3	21,3	20,1	19,1
% Pregnancies rate per transfers	27,2	25,9	26,5	26,3	27,2	26,5	25,9
% Twin Pregnancies	20,2	18,8	18,9	19,4	19,5	17,0	15,6
% Triplet or more Pregnancies	2,3	1,8	1,8	1,6	1,4	0,9	0,6
% Pregnancies lost to follow-up	10,8	12,7	13,9	10,9	11,9	13,1	11,2
N° Deliveries	7.512	7.193	7.116	7.125	7.277	6.498	6.196
N° Live born	9.286	8.734	8.680	8.677	8.848	7.695	7.172
ONLY THAWING CYCLES (Non Donor)							
N° Patients	5.725	7.067	7.967	8.090	9.669	11.975	13.826
N° Initiated cycles	6.199	7.691	8.702	9.397	11.140	14.432	16.450
N° Pregnancies	980	1.262	1.569	2.063	2.721	3.633	4.366
% Pregnancies lost to follow-up	4,3	7,8	8,0	6,9	5,7	5,6	6,6
N° Deliveries	655	810	1.011	1.370	1.926	2.573	3.044
N° Live born	755	924	1.138	1.540	2.128	2.802	3.281

Summary table of activity and outcomes of procedures with gamete/embryo donation, 2014-2016

Donor activity			
	2014	2015	2016
ART-Donor activity			
N° clinics reporting data (with at least 1 patients treated)	17	69	83
N° Patients	205	2.083	4.933
N° Initiated cycles	209	2.287	5.533
N° Pregnancies	87	677	1.713
% Pregnancies lost to follow-up	26,4	15,7	13,9
N° Deliveries	49	441	1.146
N° Live born	61	532	1.338
IUI-D activity (sperm donation)			
N° clinics reporting data (with at least 1 patients treated)	13	52	65
N° Patients	32	379	517
N° Initiated cycles	37	513	714
N° Pregnancies	7	103	137
% Pregnancies rate per cycles	18,9	20,1	19,2
N° lost to follow-up pregnancies	6	31	23
N° Deliveries	1	61	98
N° Live born	1	69	119

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