EXECUTIVE SUMMARY for 2019

IARTR
THE ITALIAN ASSISTED REPRODUCTIVE TECHNOLOGY REGISTER

MONITORING THE ACTIVITY AND OUTCOMES OF ITALIAN ASSISTED REPRODUCTIVE TECHNOLOGY CENTRES 2019

MONITORING THE ACTIVITY AND OUTCOMES OF ITALIAN ART CENTRES IN 2019

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SUMMARY OF OUTPUTS GENERATED FROM IARTR, 2019

	Patient gametes			Donor gametes		
	Fresh cycles (IVF and ICSI)	**FET**	**FO**	**sperm donation**	**oocyte donation**	**double donation**
n° of patients	41.149	17.562	1.248	5.815	462	1.397
n° of initiated cycles	50.324	-	-	6.867	532	1.596
n° of aspirations/thawings	46.090	21.796	1.361	-	-	-
n° of transfers	28.731	21.078	1.071	6.346	502	1.224
with 1 embryo (%)	*44,8*	*76,0*	*43,8*	*72,4*	*70,5*	*60,4*
with 2 embryos (%)	*46,7*	*22,7*	*51,4*	*26,9*	*29,3*	*36,2*
with 3+ embryos (%)	*8,5*	*1,3*	*4,8*	*0,7*	*0,2*	*3,4*
n° of clinical pregnancies*	7.753	6.758	242	2.359	208	467
Pregnancies per initiated cycles (%)	15,4	-	-	34,4	39,1	29,3
Pregnancies per initiated cycles without freeze-all cycles (%)	18,1					
Pregnancies per aspirations/thawings (%)	16,8	31,0	17,8			
Pregnancies per aspirations/thawings without freeze-all cycles (%)	20,1					
Pregnancies per transfers (%)	27,0	32,1	22,6	37,2	41,4	38,2
Cumulative pregnancies per initiated cycles (%)	29,3					
Pregnancies lost to follow-up (%)	10,4	10,2	7,4	11,5	11,1	15,4
Pregnancies loss per monitored pregnancy (%)	25,8	27,3	33,5	22,8	27,0	25,3
n° deliveries	5.458	4.127	153	275	1.310	105
single (%)	*87,3*	*94,9*	*84,6*	*92,7*	*91,9*	*91,5*
twin (%)	*12,3*	*4,3*	*14,8*	*7,1*	*8,9*	*8,1*
triplets or more (%)	*0,3*	*0,1*	*0,7*	*0,2*	*0,0*	*0,3*
Deliveries per aspirations/thawings (%)	11,2	20,2	10,9	23,5	25,4	18,5
Estimated deliveries per aspirations/thawings (%)	12,5	22,6	11,8	26,5	28,6	21,9
Estimated deliveries per aspiration without freeze-all cycles (%)	15,4					
n° live born babies	6.186	4.393	172	311	1.466	118
Live born babies per initiated cycles (%)	11,5	21,3	12,7	25,1	27,3	20,1

*Clinical pregnancy: A pregnancy diagnosed by ultra-sonographic visualization of one or more gestational sacs or definitive clinical signs of pregnancy. In addition to intra-uterine pregnancy, it includes a clinically documented ectopic pregnancy[1].

SUMMARY OF OUTPUTS GENERATED FROM IARTR, 2019

	Intrauterine Insemination		
	patient semen	**donor semen**	**IUI total**
n° of patients	10.471	514	**10.985**
n° of initiated cycles	15.895	691	**16.586**
n° of inseminations	14.370	656	**15.026**
n° of clinical pregnancies*	1.638	129	**1.767**
Pregnancies per initiated cycles (%)	10,3	18,7	**10,7**
Pregnancies per inseminations (%)	11,4	19,7	**11,8**
Pregnancies lost to follow-up (%)	11,1	12,4	**11,2**
Pregnancies loss per monitored pregnancy (%)	20,4	20,4	**20,4**
n° deliveries	1.159	90	**1.249**
single (%)	*91,4*	*88,9*	***91,2***
twin (%)	*7,9*	*11,1*	***8,1***
triplets or more (%)	*0,8*	*0,0*	***0,7***
Deliveries per initiated cycles (%)	7,3	13,0	**7,5**
Estimated deliveries per initiated cycles (%)	8,2	14,9	**8,5**
n° live born babies	1.266	99	**1.365**
Live born babies per initiated cycles (%)	8,0	14,3	**8,2**

THE ITALIAN ASSISTED REPRODUCTION TECHNOLOGY REGISTER (IARTR)

IARTR has been established at the *Istituto Superiore di Sanità* (Italian National Institute of Health), by a Decree of the Ministry of Health issued on the 7th of October 2005 (G.U. n. 282 del 3rd December 2005) in implementation of article n° 11 paragraph 1 of Law 40/2004 (G.U. n. 45 del 24th February 2004).

The Register collects descriptive, technical, structural and organizational information of Assisted Reproductive Techniques (ART) centers authorized by their regional health authority, to conduct assisted reproductive technology, 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 Intrauterine Insemination (IUI) procedures in the country and the number of embryos created and cryopreserved;
- COLLECT and EVALUATE data regarding centres characteristics, 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 and 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 – European *In vitro* fertilization Monitoring) 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). Professor Jacques de Mouzon, Secretary of the ART World Register (ICMART), audited the activity of IARTR since 2018.

HOW DOES IARTR WORK?

Dr Giulia Scaravelli, MD-Gynaecologist and PhD-Obstetrics and Gynaecology, coordinates the staff. In the staff, there are varieties of skills: statistics, epidemiology, gynaecology, biology, psychology and informatics.

Data on efficacy, safety and outcomes of reproductive techniques, including IUI, are collected on a website on a reserved area with username and password. Data collection is based on summary data sent from each centre according to a national law on privacy protection (Dlg. 196/2003).

The data collection is organized in two different periods:

- The first phase of the collection is related to the activity conducted and the results obtained in 2019 and it was carried out from May to June 2020;
- The second phase of the collection is related to the outcomes of pregnancies obtained from ART treatments started in 2019 and it was carried out from October to December 2020.

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

THE IARTR WEBSITE

www.iss.it/rpma

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

There are different levels of interest in the website:

- A service to the citizens: they can consult the list of all the authorized ART centres by different regions and can 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 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. They can also see on their reserved area how they perform in respect with some national indicators.
- 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, last year, was visited by approximately 146.000 users, with a daily average of about 400 hits, and is the second most visited site in the National Institute of Health Portal.

1. ACCESS AND UTILIZATION OF ART SERVICES IN ITALY, 2019

1.1. Access to ART service

Figure 1 shows the regional distribution of the 203 ART authorized centers in 2019, but only 189 performed at least one ART cycle.

The largest number of ART centers is concentrated in northern Italy (81 centres the 39,9% of the total) and in the southern area (74 centres the 36,5% of the total), irrespective of the amount of their activity.

Figure 1. Regional distribution of the ART authorized centres and in brackets the number of centres per 100.000 women of reproductive age (15-45 years)*, 2019

*Average resident population in Italy in 2019: source ISTAT.

Table 1 shows the geographical distribution of ART centers according to the type of services offered. Overall, the number of centres active was 203 in 2019: 93 (45,8%) operating within the National Health Service (public and private) and 110 (54,2%) which provided only private service. The higher percentage of ART centres providing public service was concentrated in the north of Italy, i.e. in the North West 77,5%, while in the centre and in the south of Italy there were mainly private facilities (58,3% and 70,3%, respectively).

Table 1. ART authorized centres distribution by region and type of service, 2019

Region and geographical area	ART centres	Art centres by type of service					
		public		private covered by NHS		private	
		N	%	N	%	N	%
Piemonte	13	5	38,5	1	7,7	7	53,8
Valle d'Aosta	1	1	100	0	0	0	0
Lombardia	24	12	50,0	10	41,7	2	8,3
Liguria	2	2	100	0	0	0	0,0
north-west	**40**	**20**	**50,0**	**11**	**27,5**	**9**	**22,5**
A.P. Bolzano	3	1	33,3	0	0	2	66,7
A.P. Trento	1	1	100	0	0	0	0
Veneto	18	8	44,4	0	0,0	10	55,6
Friuli Venezia Giulia	3	2	66,7	1	33,3	0	0
Emilia Romagna	16	7	43,8	0	0	9	56,3
north-east	***41***	***19***	**46,3**	***1***	**2,4**	***21***	**51,2**
Toscana	15	5	33,3	5	33,3	5	33,3
Umbria	2	1	50,0	0	0	1	50,0
Marche	3	2	66,7	0	0	1	33,3
Lazio	28	6	21,4	1	3,6	21	75,0
central	***48***	***14***	**29,2**	***6***	**12,5**	***28***	**58,3**
Abruzzo	4	2	50,0	0	0	2	50,0
Molise	1	0	0	0	0	1	100
Campania	28	8	28,6	0	0	20	71,4
Puglia	11	2	18,2	0	0	9	81,8
Basilicata	1	1	100	0	0	0	0
Calabria	5	1	20,0	0	0	4	80
Sicilia	21	5	23,8	0	0	16	76,2
Sardegna	3	3	100	0	0	0	0
south and islands	***74***	***22***	**29,7**	***0***	**0,0**	***52***	**70,3**
Italy	**203**	***75***	**36,9**	***18***	**8,9**	***110***	**54,2**

1.2. Utilization of ART services

Table 2 shows the time-trends of ART initiated cycles per million inhabitants and per million women of reproductive age (between 15 and 45 years), in comparison with the same indicators for Europe. Since 2005 in Italy, both the indicators were constantly growing, with an increase of 705 cycles (+110,7%) and of 5.014 cycles (+186,9%), respectively. The latest European data available refers to the activity of year 2017[1].

The number of started cycles per million inhabitants (calculated only for the 20 countries that have reported data of 100% of the centers) was 1.435 cycles in Europe versus 1.275 in Italy, both under the proposed optimal level of demand calculated as 1.500 of ART services per million inhabitants per year[2].

Table 2. Number of initiated ART cycle per million inhabitants and per million women of reproductive age (15-45 years) annually in Italy (2005-2019) and in Europe (2005-2017)

Years	ART cycles/ million population		ART cycles/ million women (15 - 45 years)	
	Italy	Europe [a]	Italy	Europe [a]
2005	636	1.115	2.683 [b]	4.008 [b]
2006	692	850	3.328	3.503
2007	736	886	3.569	4.320
2008	800	947	3.905	4.661
2009	865	1.067	4.265	5.455
2010	973	1.221	4.863	6.258
2011	1.063	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	1.399	5.855	7.608
2015	1.175	1.432	6.341	7.795
2016	1.237	1.410	6.781	7.794
2017	1.275	1.435	7.106	7.662
2018	1.297	-	7.341	-
2019	1.341	-	7.697	-

a: data for Europe refers only to those countries 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.

Figure 2 shows the distribution of initiated cycles per million women of childbearing age per geographical region. There is a great difference in the number of cycles performed among regions. If we select regions with more than five hundred thousand women in reproductive age, the distribution of cycles range from 4.131 cycles offered in Puglia region to 15.405 cycles provided in Toscana region. More in general, only seven regions in northern and central area have numbers above the national average (7.697 cycles), while all the southern regions have numbers below the average.

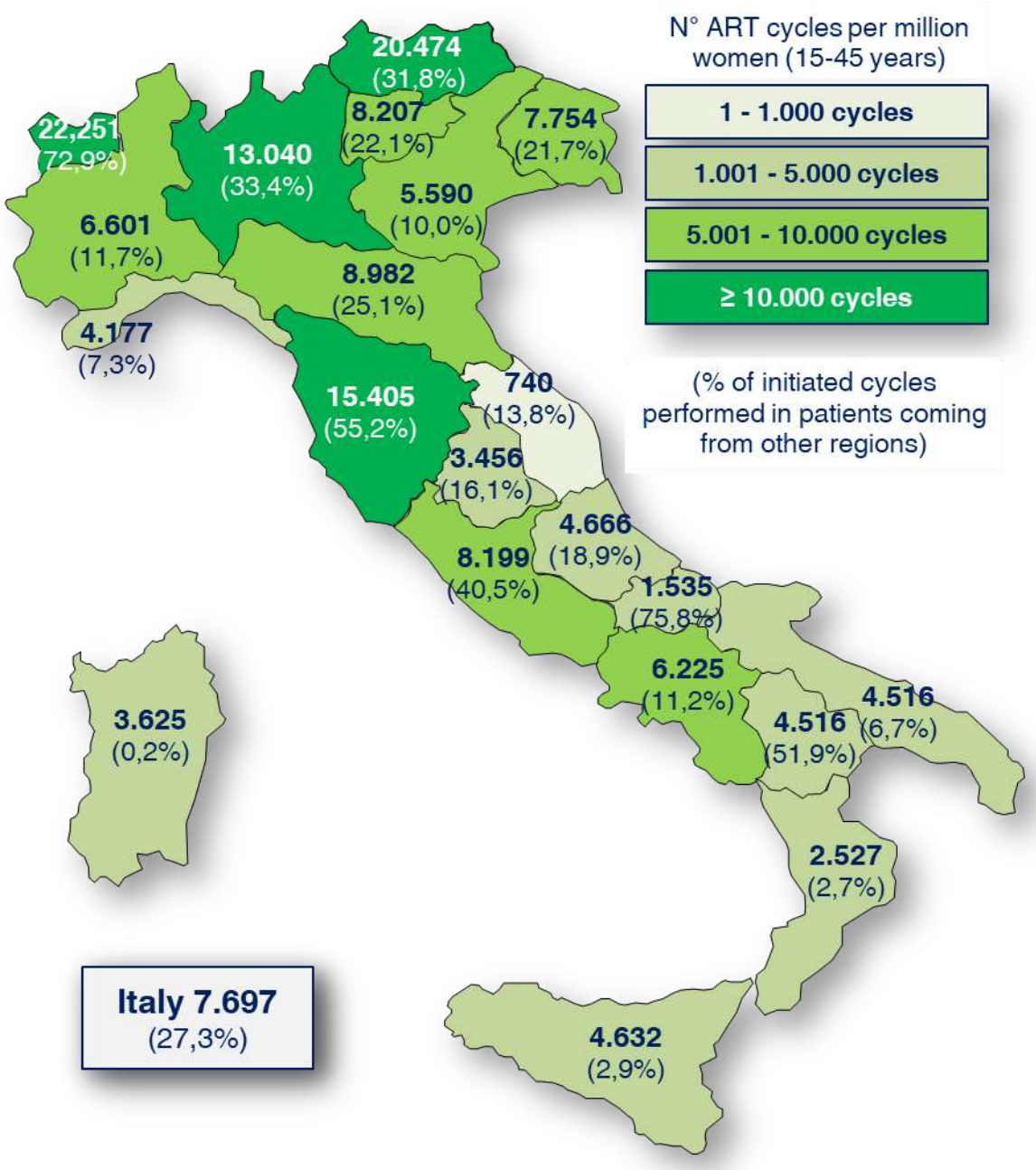


Figure 2. Regional distribution of the number of initiated ART cycles per million women of reproductive age (15-45 years)* and in brackets the percentage of initiated cycles performed in patients coming from other regions, 2019.

*Average resident population in Italy in 2019: source ISTAT.

Since its establishment, IARTR collected data on 172.627 infants, of which 143.758 born from ART and 28.869 born from IUI cycles. These data have to be considered with caution due to the proportion of pregnancies lost to follow-up that however changed to the better: from 21,5% in 2006 to 9,7% in 2018. In 2019, a number of 12.797 babies are born alive from ART techniques in Italy, that represent the 3,0% of the national babies born in the country in the same year. 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 Toscana region, 55,2% of cycles are performed on patients coming from other regions).

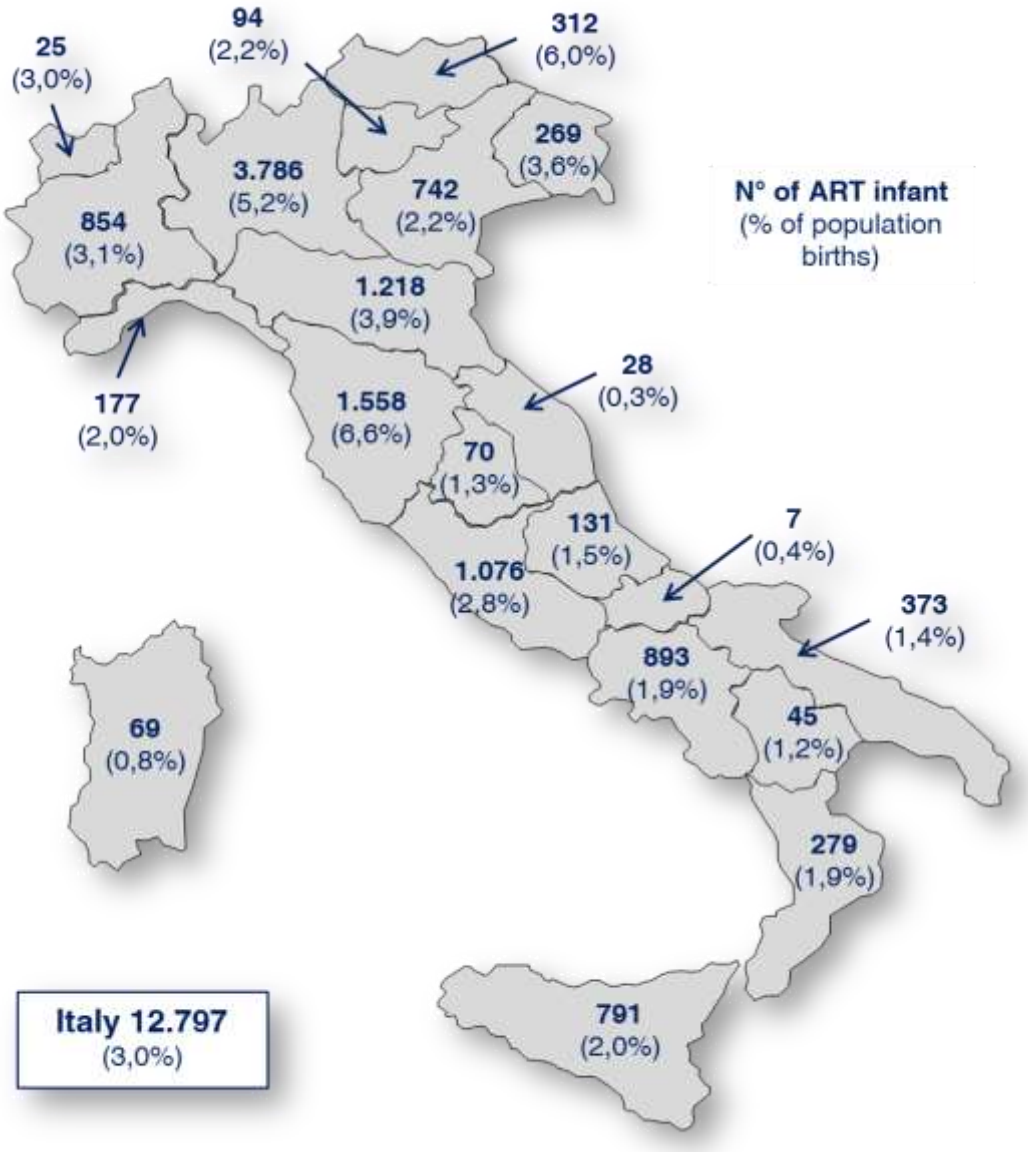


Figure 3. Regional distribution of the babies born in 2019 from ART cycles, also with donation, and the percentages in relation to the annual number of children born*.

*Number of live babies born in Italy in 2019: source ISTAT.

Figure 4 shows the percentages of live-born babies conceived by ART compared with the national total number of children born in Italy. The percentage of infants born with ART procedures increased more than 4,5 times from 2005 to 2019. The value of 3,1% for ART techniques in 2019 is equal to that of the European average in 2017 and it is higher than 2,7% in France and 2,9% in the United Kingdom. However, it should be considered that part of this increase is due to a strong contraction in births in Italy.

Figure 4. Time-trends of the percentage of live babies born after ART also with donation cycles and after ART & IUI with donation cycles in relation to the annual national number of children born in Italy, 2005-2019.

2. EFFICACY OF ART IN 2019 AND TIME TRENDS FROM 2005 TO 2019

2.1. Overview of ART

2.1.1. What types of ART cycles were performed?

When an ART treatment is applied without using cryopreserved oocytes or embryos, is defined as a **"fresh cycle"**, and it includes:

- **In Vitro Fertilization with embryo transfer (IVF)**: an ART procedure that involves extracorporeal fertilization of gametes[3];
- **Intra Cytoplasmic Sperm Injection (ICSI):** a procedure in which a single spermatozoon is injected into the oocyte cytoplasm[3].

An ART treatment in which cryopreserved oocytes or embryos are utilized is 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 a frozen/thawed or vitrified/warmed embryo(s)/blastocyst(s)[3];
- **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[3].

An ART treatment in which are used gametes that did not originate from the female recipient and/or her male partner is 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 purpose[3];
- **sperm donation**: a cycle in which a woman receives spermatozoa from a person who is not her sexually intimate partner[3];
- **double donation:** an ART cycle in which oocytes and spermatozoa both originating from donors are used.

The major part of the 82.476 ART cycle performed in Italy in 2019 was made with a fresh procedure with partner gametes (61%). Then 26,4% of the cycles were performed with a FET, 1,7% with a FO and the remaining 10,9% (8.995 cycles) with a gamete donation (see **Figure 5**).

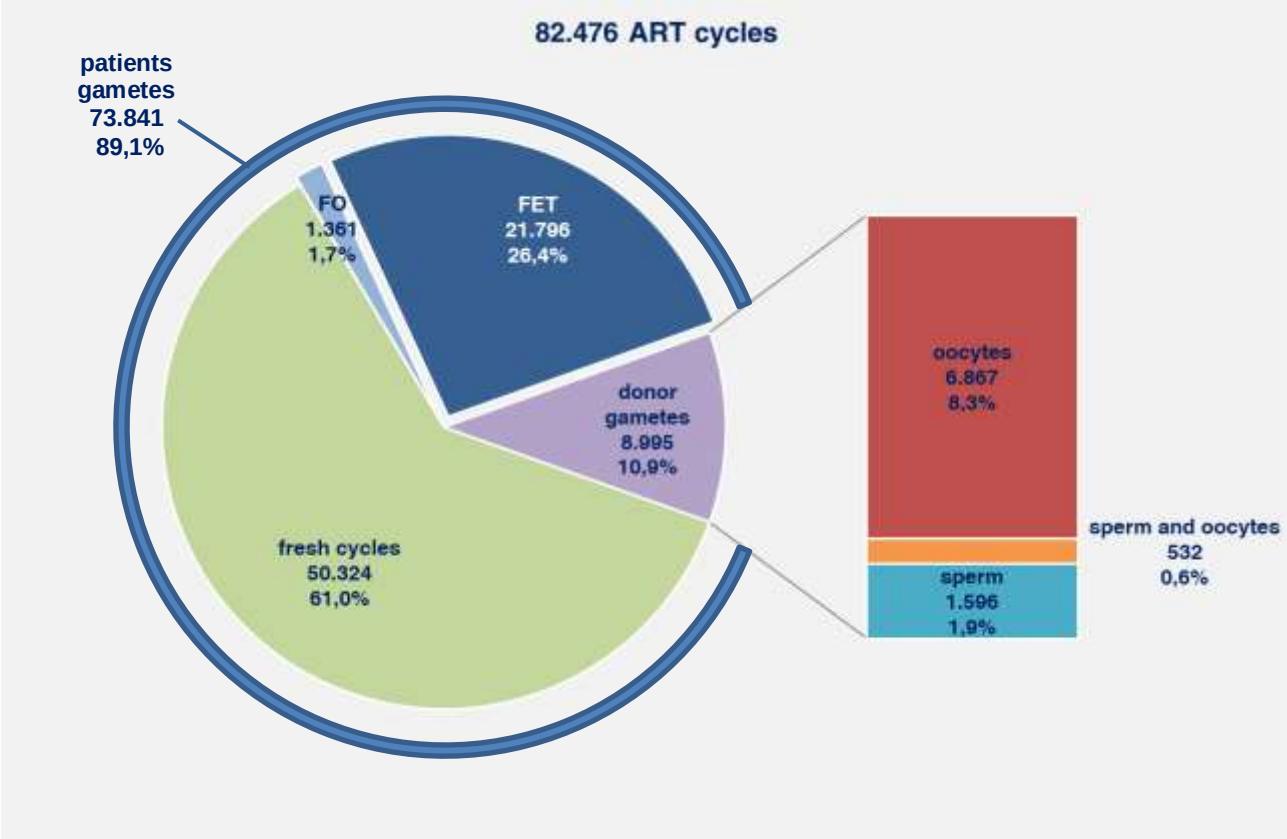


Figure 5. ART cycles performed in 2019.

2.1.2. How did the types of ART techniques change according to transfers among women of different ages?

The patient's age is the variable that influences at the most the success of assisted reproduction techniques, and therefore the probability of obtaining a pregnancy. **Figure 6** shows the percentage of ART transfers performed in 2019 according to women's age. As expected, ART treatment with their own oocytes are the most applied techniques in women from ≤34 years till 42 years of age, while after 42 years of age the cycles performed with donor gametes reach 52,4% of application. In younger patients, FET was the most commonly used ART procedure.

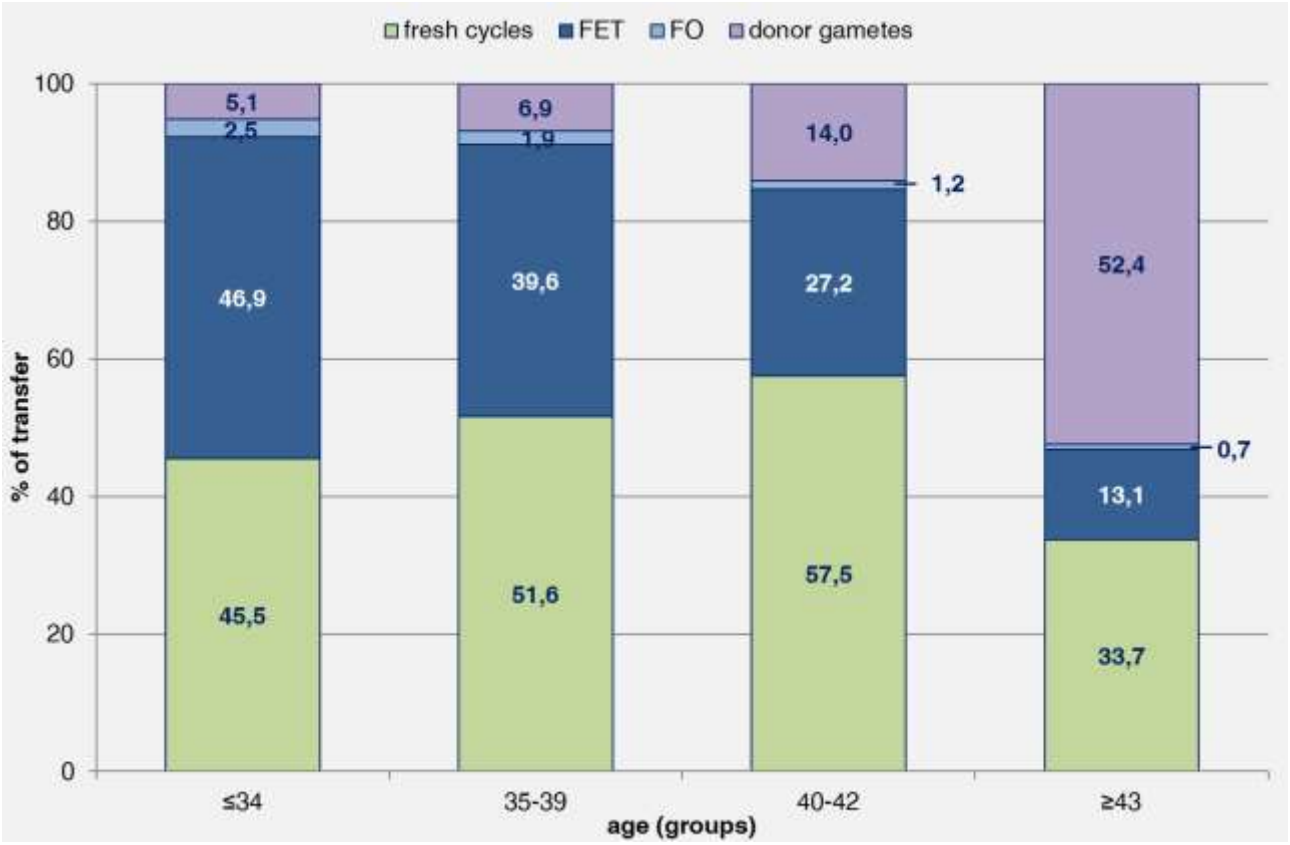


Figure 6. Types of ART procedure performed by female patients' age groups, 2019.

2.2. ART non-donor cycles

2.2.1. What are the causes of infertility of couples in ART treatment using fresh cycles in 2019?

- ***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[3];
- **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 implantation[3].
- **diminished ovarian reserve –** indicate a reduced number and/or reduced quality of oocytes, such that the ability to reproduce is decreased[3];
- **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 vagina[3].

- ***Male and female factors*** - one or more female and male 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 was found in either woman or man[3].

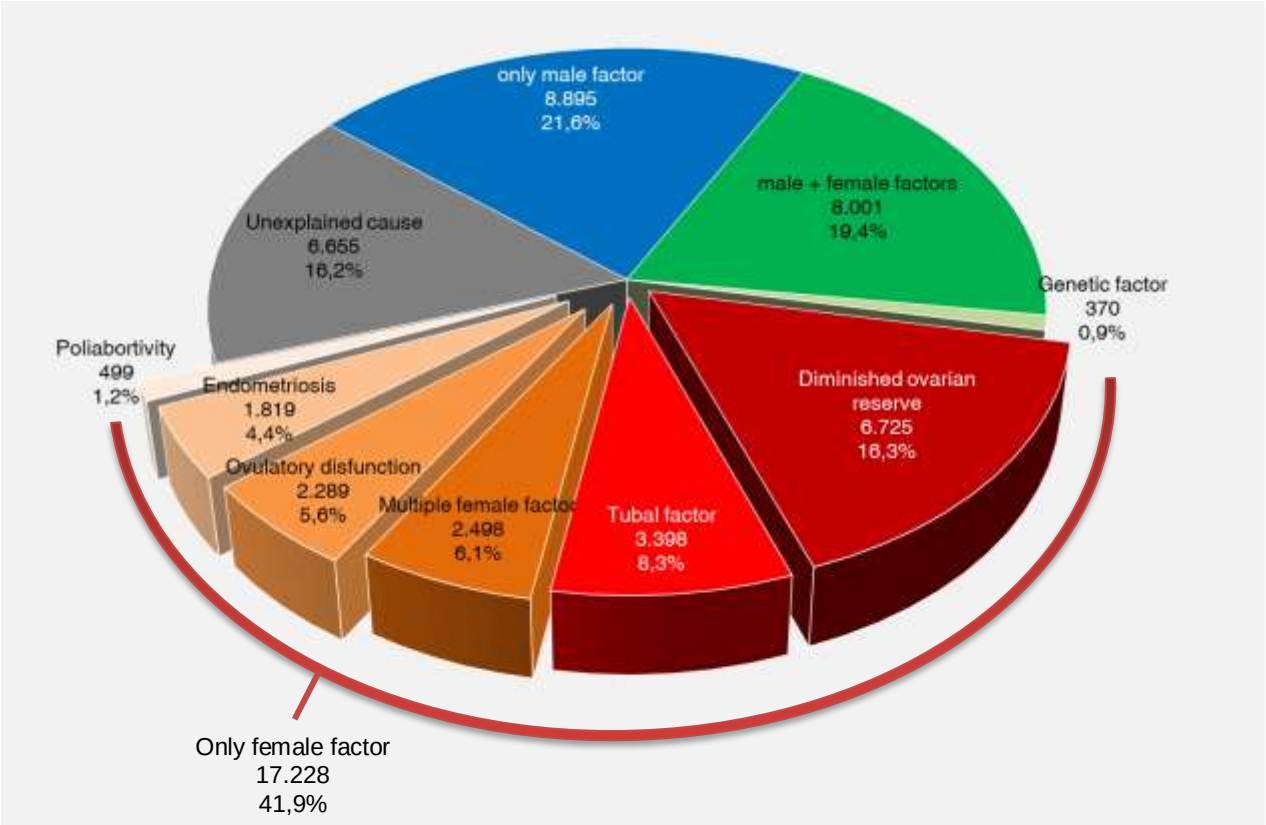


Figure 7. Causes of infertility of couples in ART treatment using fresh cycle, 2019

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

An ART cycle using fresh gametes:

- starts 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)**;
- 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 spermatozoa into a mature oocyte followed by formation of the pronuclei **(fertilization)**;
- if fertilization occurs, the embryo(s) are cultured from day 1 to day 7, and then embryo(s) (generally 1 or 2) is(are) transferred to the woman's womb either at day 2 to 3 (cleavage stage) or at day 5 to 7 (blastocyst stage) **(transfer)**;
- the attachment and subsequent penetration by a zona-free blastocyst into the endometrium **(implantation)**;
- if implantation is successful, a pregnancy diagnosed by ultra-sonographic visualization of one or more gestational sacs or definitive clinical sign of pregnancy occurs **(clinical pregnancy)**;
- generally in 75-80% of cases a **live birth delivery** occurs. A birth of twins, triplets or more are counted as one live birth.

Figure 8 shows outcomes resulting from various steps of fresh cycles performed with partner gametes in 2019. Of the 50.324 cycles, 91,6% resulted in an egg retrieval, 57,1% in an embryo transfer, and 17,6% in "freeze-all" cycles. We could choose to use the "freeze-all" strategy for different reasons: either to avoid the risk of OHSS (*Ovarian Hyper Stimulation Syndrome*) or to perform PGT (*Pre-implantation Genetic Testing*). Because of the "freeze-all cycles", we decided to compute the pregnancy rate per cycle removing them from the results of the fresh cycles. They will be included only when we computed the cumulative pregnancy rate (see Figure 11 and 20). Among the outcomes, we must also consider the 10,4% of pregnancies lost to follow-up and the 25,8% of monitored pregnancies that do not reach the delivery due to miscarriages or ectopic pregnancies (see **Figure 12**).

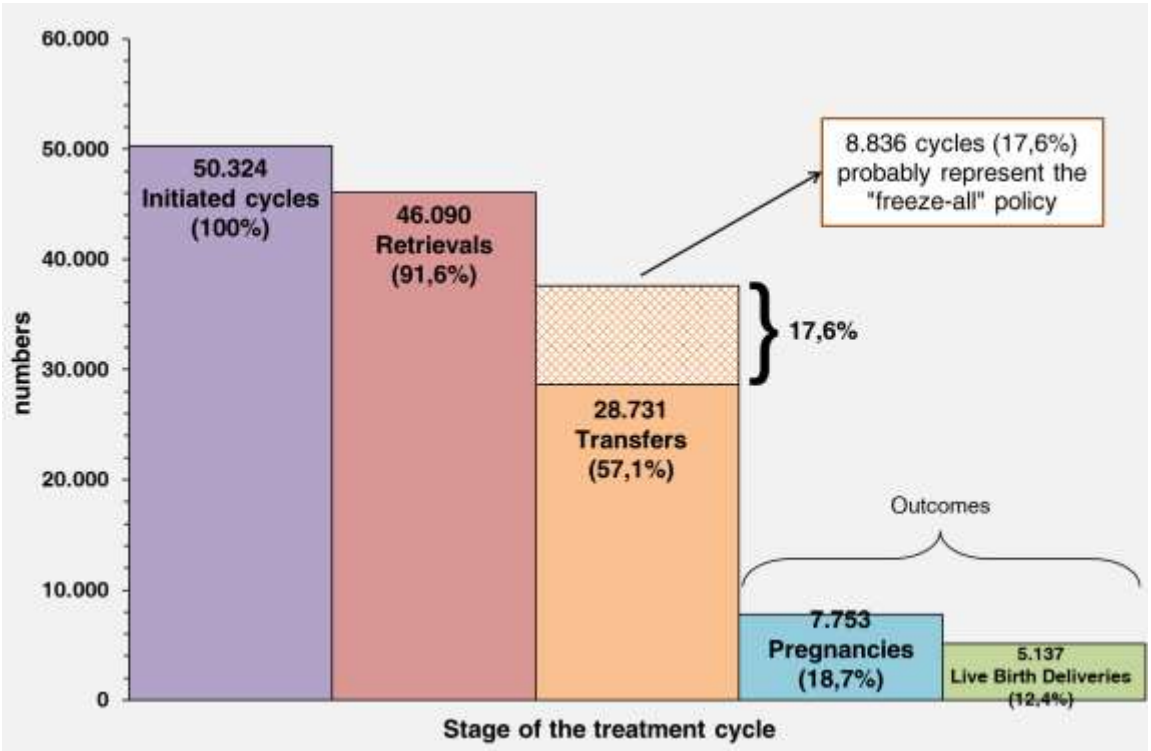


Figure 8. Outcomes of ART using fresh cycles by stage of the treatment cycle, 2019.

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

Figure 9 shows the distribution of the ART transfers performed with partner gametes, divided by the number of embryo(s) transferred according to women's age (due to the aggregate data collection we cannot have this information for each ART techniques). The number of transfers with three embryos increased with women's age when they use their own oocytes, while the number of transfers performed with one or two embryos declined with women's age. The single embryo transfers (SET) are increasing both generally and in every age classes. In particular SET have increased from 55,5% in 2018 to 62,3% in 2019 in younger patients and from 43,5% to 50,7% in older ones.

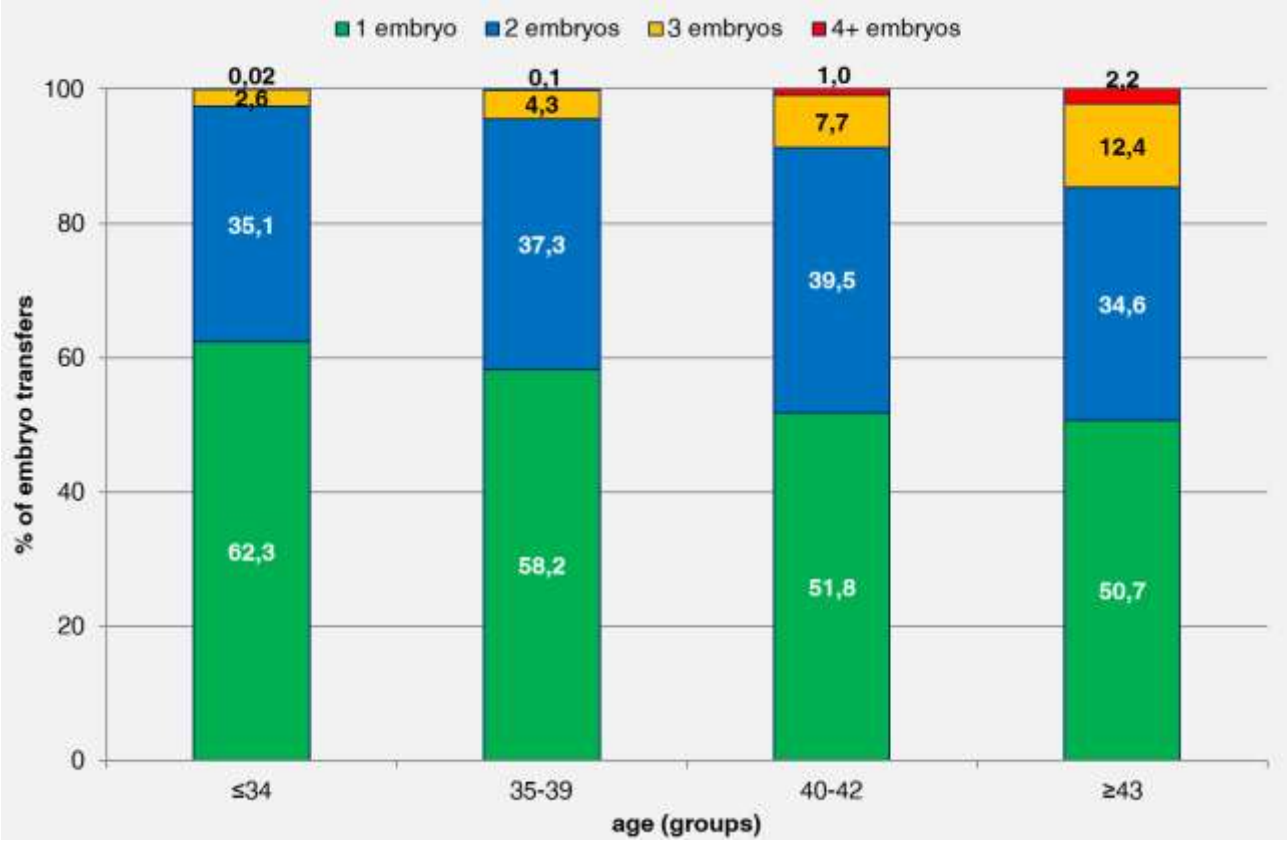


Figure 9. Distribution of embryo transfers according to the number of embryos transferred (ART total) by female patients' age groups, 2019.

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

Figure 10 shows the pregnancy rates per aspiration/thawing and per transfer for the ART techniques. Overall, the rates after FET (Frozen Embryo Transfer) were higher than others techniques, while the FO (Frozen Oocytes) ones were the lowest. The better results obtained with frozen embryos could be partially due to the selection of "good prognosis" patients (freeze-all strategy and/or more efficient single embryo transfer) in cryopreservation techniques. These results are observed also at the European level[1].

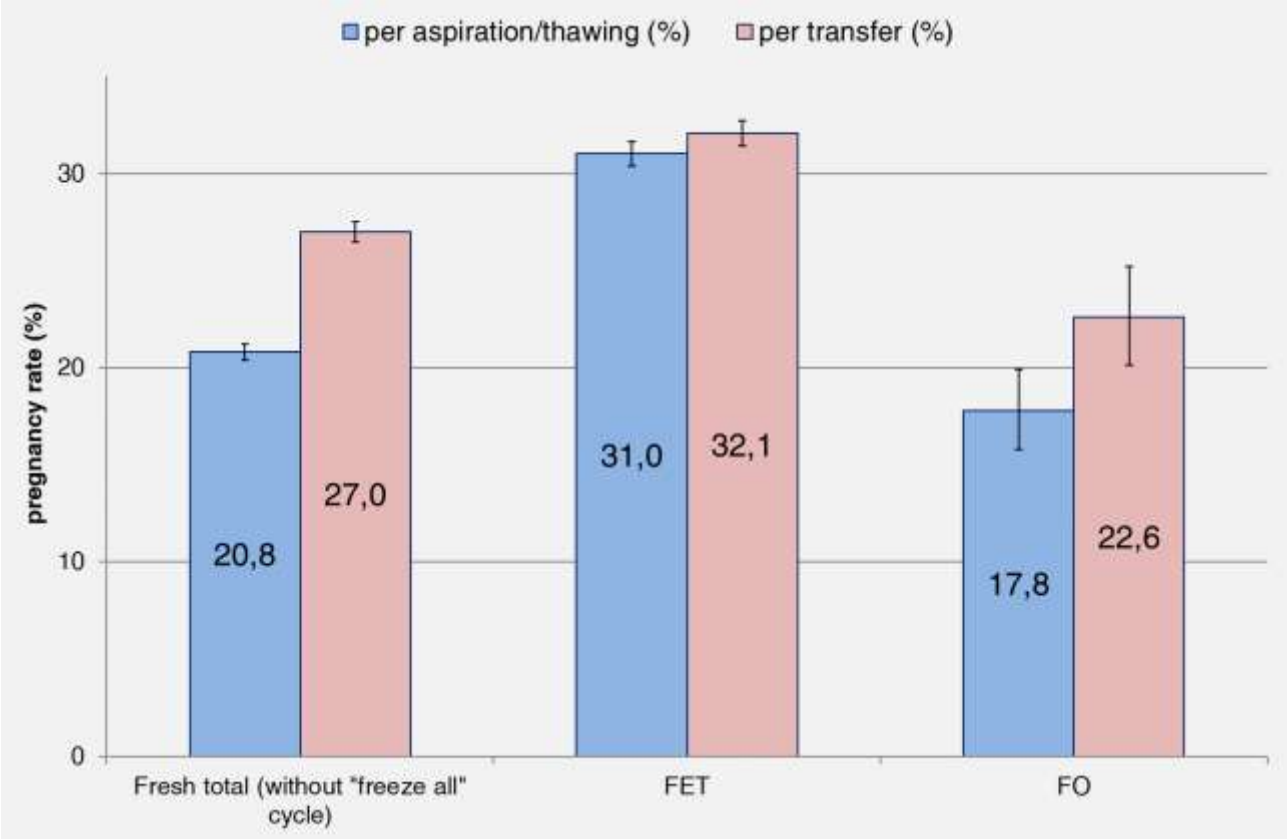


Figure 10. Pregnancy rates per aspiration/thawing and per transfer according to different ART procedures, 2019.

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 coming from one egg retrieval. Individual data instead of summary data collection would be needed to precisely calculate the CPR. 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 like EIM and ICMART, we sum the number of pregnancies obtained from fresh and frozen cycles divided by the number of aspirations, 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.

Figure 11 shows pregnancy rate per fresh cycle and cumulative pregnancy rate by women age groups. Overall, embryo and oocyte cryopreservation increased by 60% the chances of achieving a pregnancy per aspiration. It should be emphasized that as 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 aspiration could be underestimated in each age group.

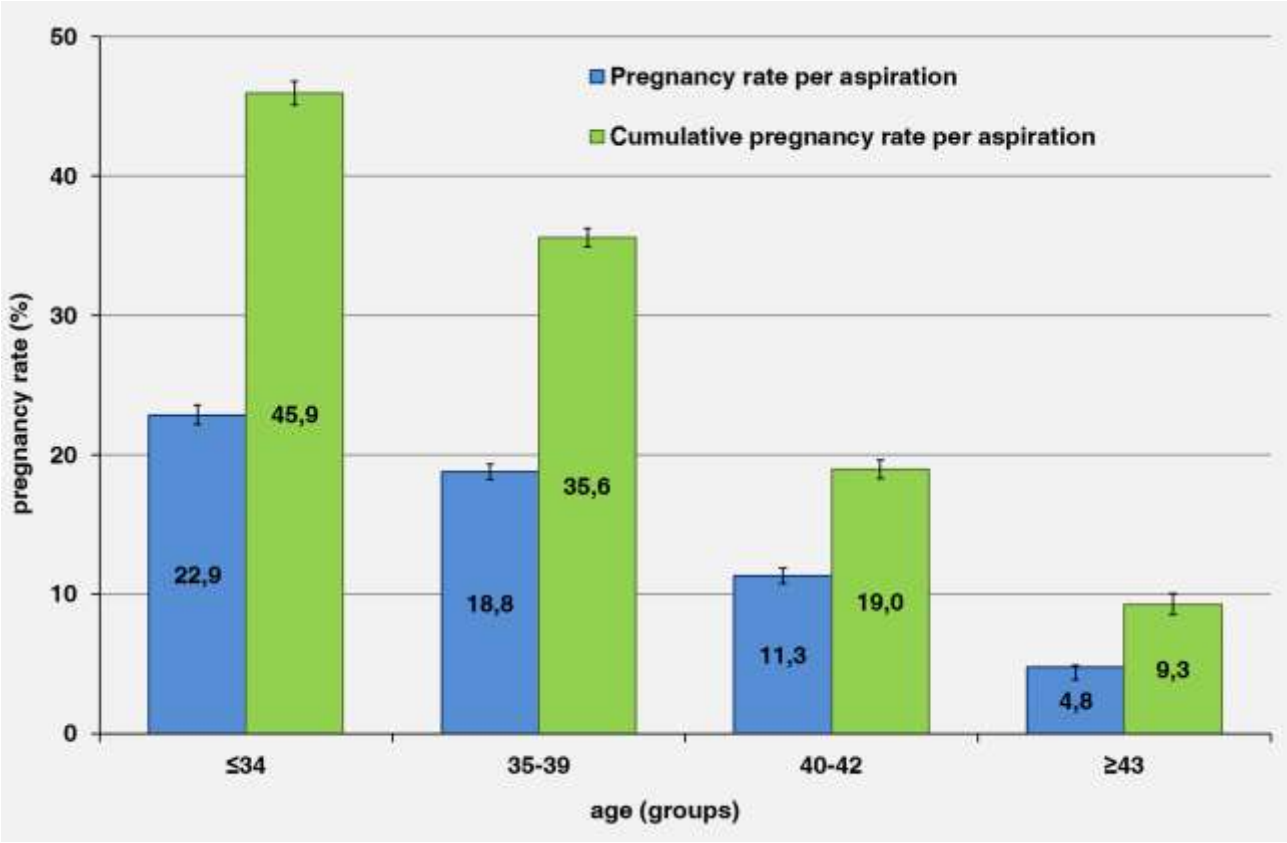


Figure 11. Pregnancy rates per aspiration and cumulative pregnancy rates per aspiration, by female patients’ age groups, 2019.

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 ART performed with partner gametes in Italy in 2019. Of the 6.946 monitored pregnancies issued from fresh cycles 74,2% resulted in a delivery, the 9,4% in multiple deliveries and the 24,3% in a miscarriage. In FET and FO procedures the 72,7 % and 66,5%, respectively, resulted in a delivery. The percentages of multiple deliveries in FET (3,7%) are significantly lower then in fresh cycles, while the percentage of miscarriages are significantly higher both in FET (26,5%) and FOR (32,1%).

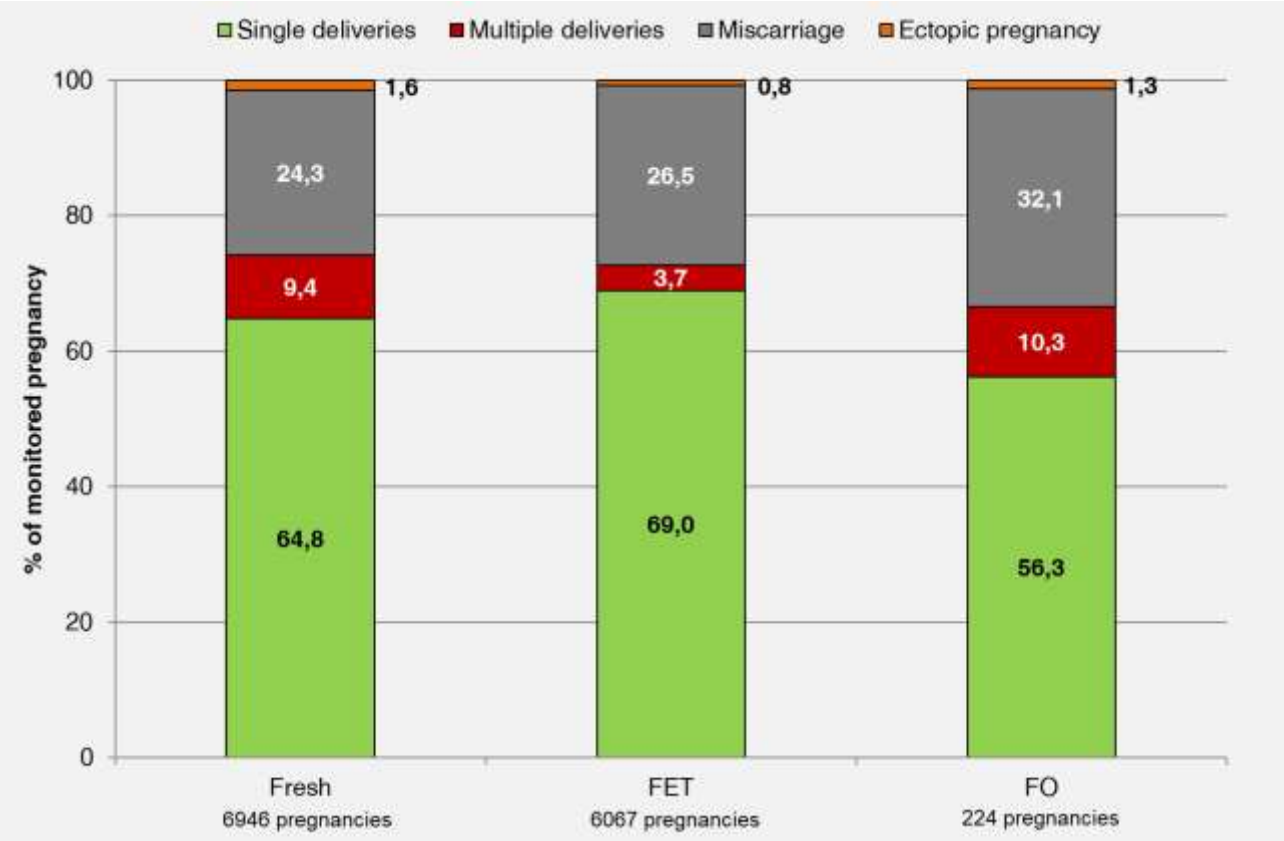
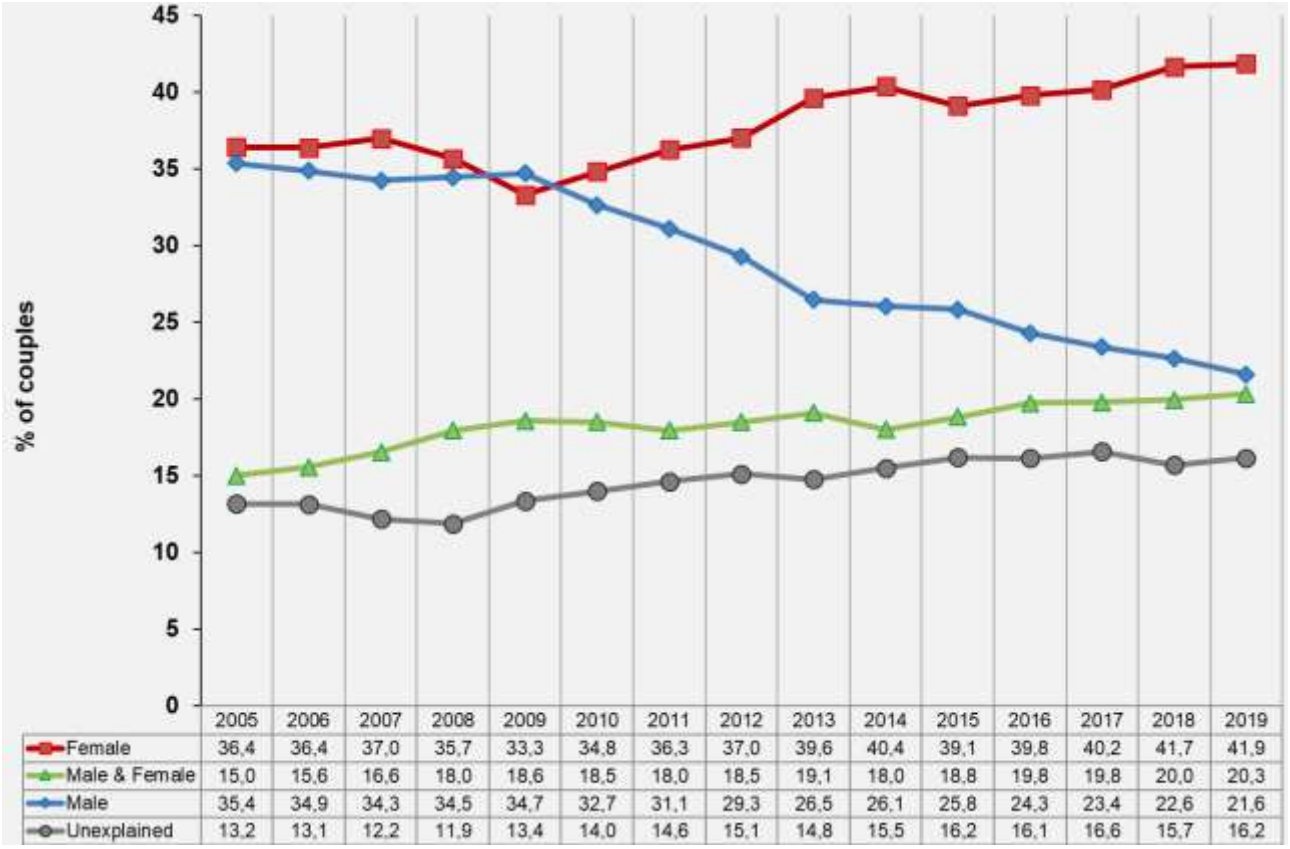


Figure 12. Comparison of the outcomes of monitored clinical pregnancies that resulted from ART non-donor procedures, 2019.

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 2019. 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 have been decreasing since 2009, while the female ones have been increasing since 2015. 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, reaching the maximum values of 62,2% in 2019.



	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Female	36,4	36,4	37,0	35,7	33,3	34,8	36,3	37,0	39,6	40,4	39,1	39,8	40,2	41,7	41,9
Male & Female	15,0	15,6	16,6	18,0	18,6	18,5	18,0	18,5	19,1	18,0	18,8	19,8	19,8	20,0	20,3
Male	35,4	34,9	34,3	34,5	34,7	32,7	31,1	29,3	26,5	26,1	25,8	24,3	23,4	22,6	21,6
Unexplained	13,2	13,1	12,2	11,9	13,4	14,0	14,6	15,1	14,8	15,5	16,2	16,1	16,6	15,7	16,2

Figure 13. Time-trends of gender distributions of infertility causes among patients who had ART using fresh cycle, 2005-2019.

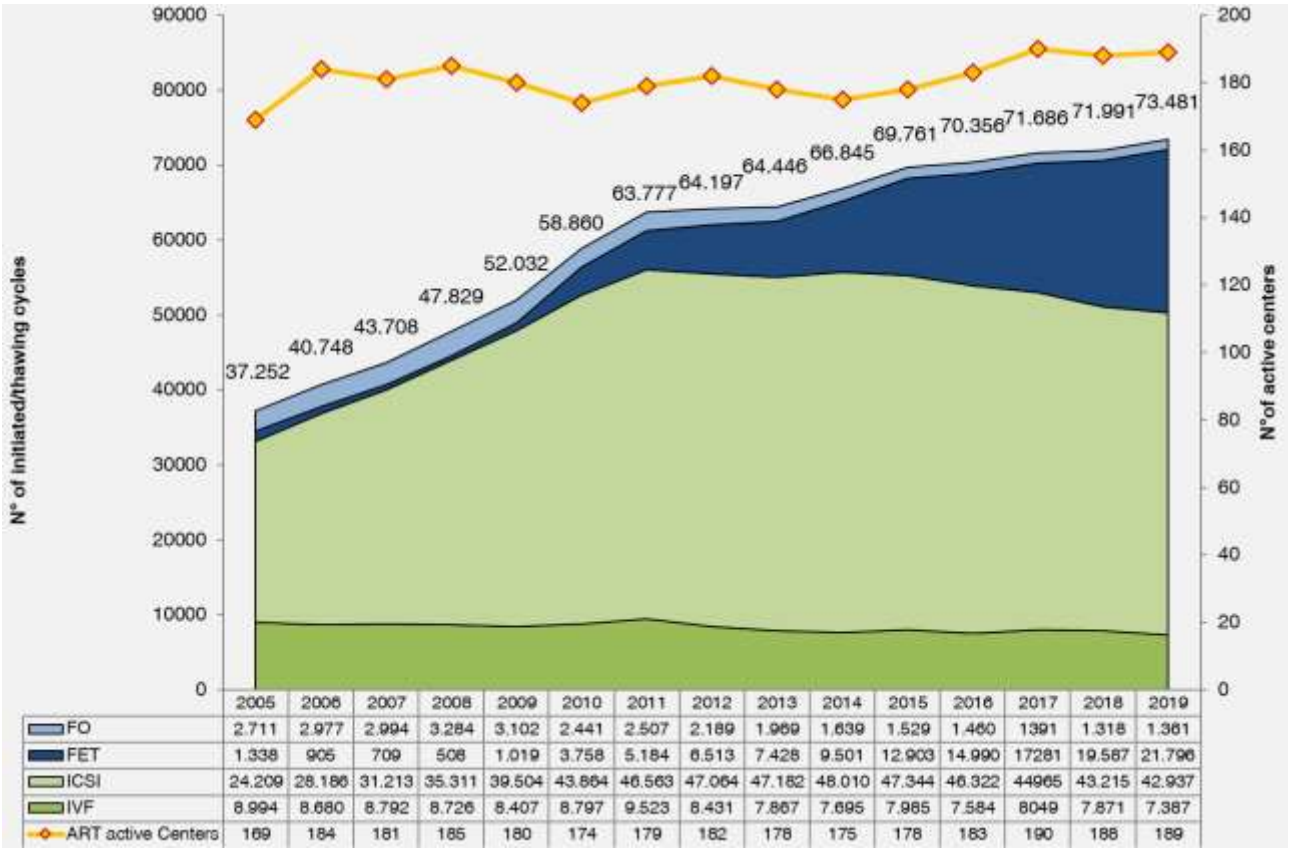
2.2.8. Is the use of ART procedures change over time?

Figure 14 shows the number of ART non-donor initiated/thawing cycle and the number of ART active centres (with at least 1 cycle performed in the year) from 2005 to 2019.

The numbers of initiated cycles almost doubled since 2005 with an average increase of 7% for each year and it seems not to be related to the number of active centres.

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.

The number of ICSI cycles increased from 24.209 in 2005 to 42.937 in 2019, while IVF cycles decreased from 8.994 to 7.387. In addition, FET thawing increased from 1.338 to 21.796, while FO procedures decreased from 2.711 to 1.361.

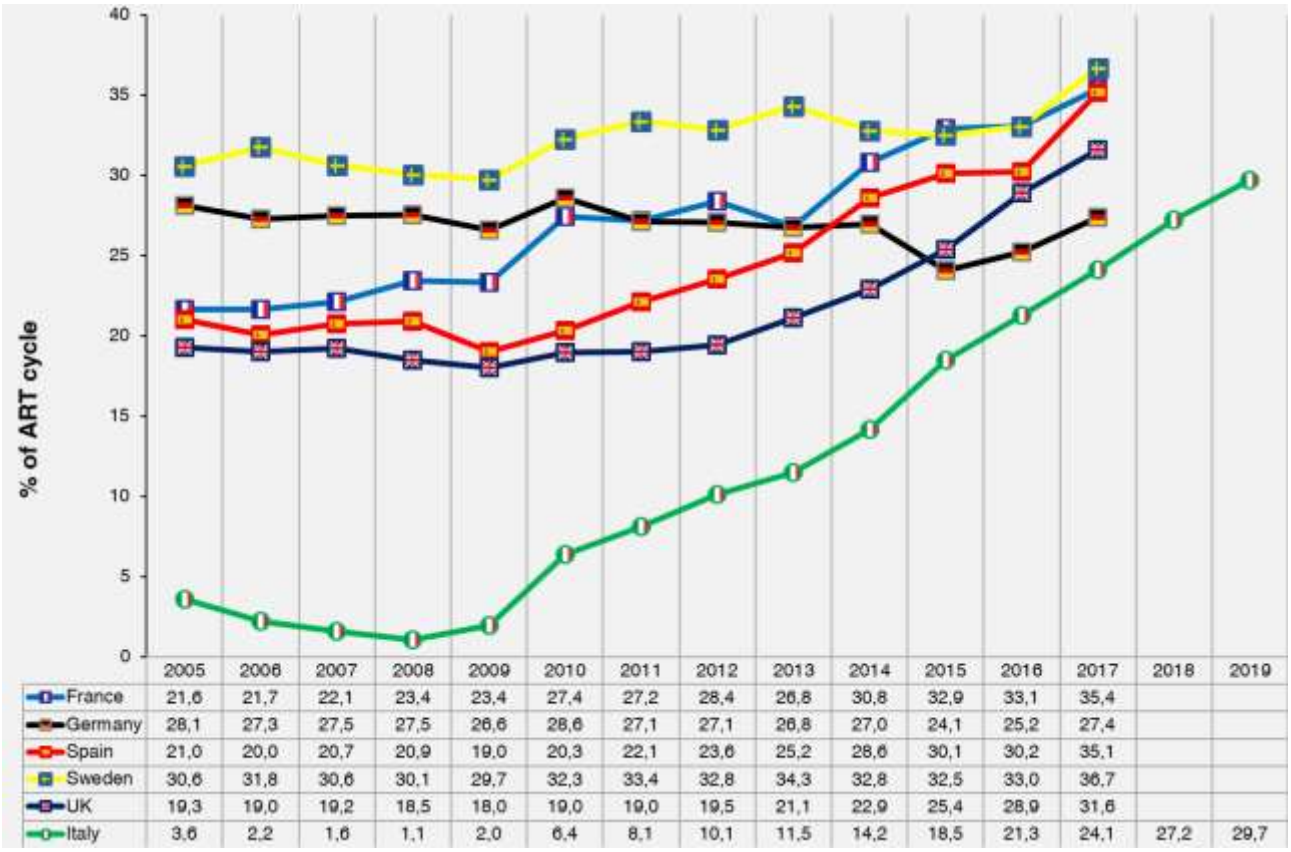


	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
FO	2.711	2.977	2.994	3.284	3.102	2.441	2.507	2.189	1.969	1.639	1.529	1.460	1391	1.318	1.361
FET	1.338	905	709	508	1.019	3.758	5.184	6.513	7.428	9.501	12.903	14.990	17281	19.587	21.796
ICSI	24.209	28.186	31.213	35.311	39.504	43.864	46.563	47.064	47.182	48.010	47.344	46.322	44965	43.215	42.937
IVF	8.994	8.680	8.792	8.726	8.407	8.797	9.523	8.431	7.867	7.695	7.985	7.584	8049	7.871	7.387
ART active Centers	169	184	181	185	180	174	179	182	178	175	178	183	190	188	189

Figure 14. Time-trends of ART non-donor initiated cycles/thawings and number of active ART centres, 2005–2019.

2.2.9. Did the use of FET (Frozen Embryo Transfer) procedures differ in Italy compared to the 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 14**). As shown in **Figure 15** percentage of FET cycles performed highly increased from 3,6% in 2005 to 29.7% in 2019. In comparison with some European countries[1], such as France, Germany and Sweden, for 2017 last European data available, Italy still shows the lowest number of FET cycles performed, but they are steadily increasing.



	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
France	21,6	21,7	22,1	23,4	23,4	27,4	27,2	28,4	26,8	30,8	32,9	33,1	35,4		
Germany	28,1	27,3	27,5	27,5	26,6	28,6	27,1	27,1	26,8	27,0	24,1	25,2	27,4		
Spain	21,0	20,0	20,7	20,9	19,0	20,3	22,1	23,6	25,2	28,6	30,1	30,2	35,1		
Sweden	30,6	31,8	30,6	30,1	29,7	32,3	33,4	32,8	34,3	32,8	32,5	33,0	36,7		
UK	19,3	19,0	19,2	18,5	18,0	19,0	19,0	19,5	21,1	22,9	25,4	28,9	31,6		
Italy	3,6	2,2	1,6	1,1	2,0	6,4	8,1	10,1	11,5	14,2	18,5	21,3	24,1	27,2	29,7

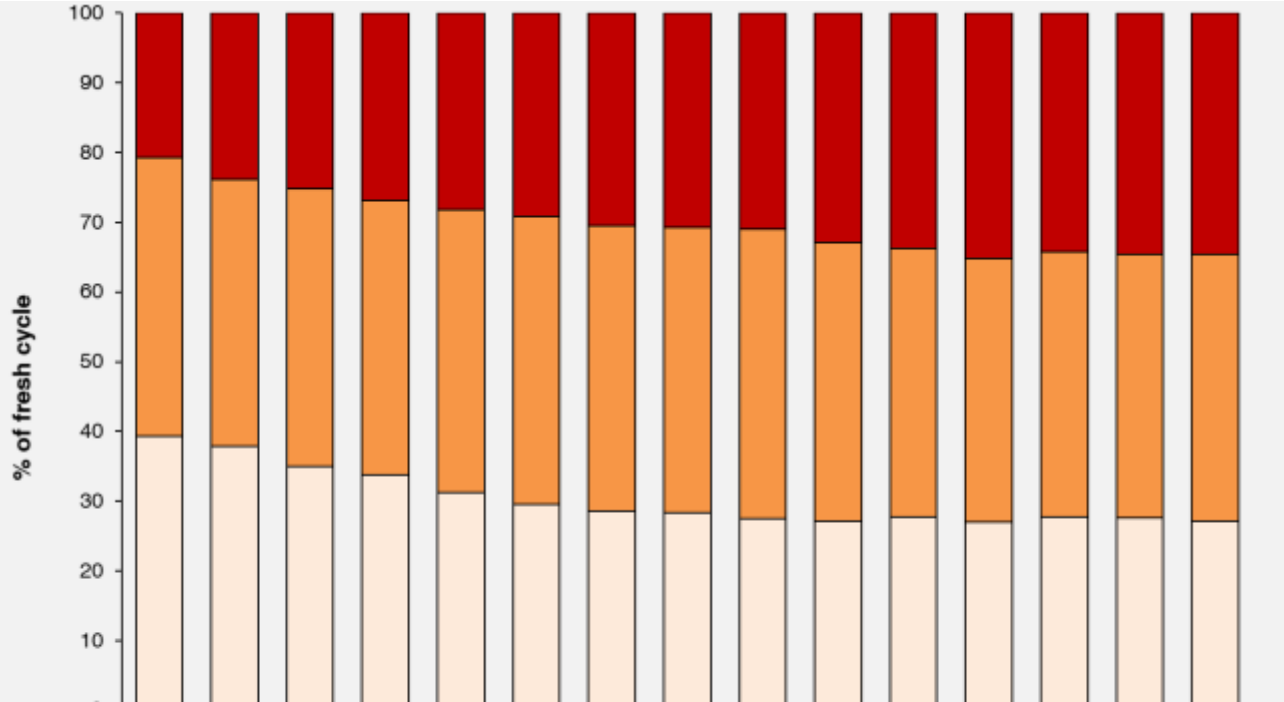
Figure 15. Time-trends of percentages of FER thawing on total ART non-donor initiated cycles in selected European countries (2005-2017)* and Italy (2005-2019).

*Elaboration of number of ART treatment cycles: source ESHRE reports on ART.

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

Figure 16 shows the distribution of fresh cycles by age groups of women, from 2005 to 2019.

For women older than 40 the percentage of fresh cycles performed increased from 20,7% in 2005 to 34,6% in 2018 and 2019, while the percentage of fresh cycles performed in women ≤34 years old decreased from 39,3% in 2005 to 27,1% in 2019. Overall, the mean age of women who had fresh cycles increase over time from 35,3 to 36,8 years.

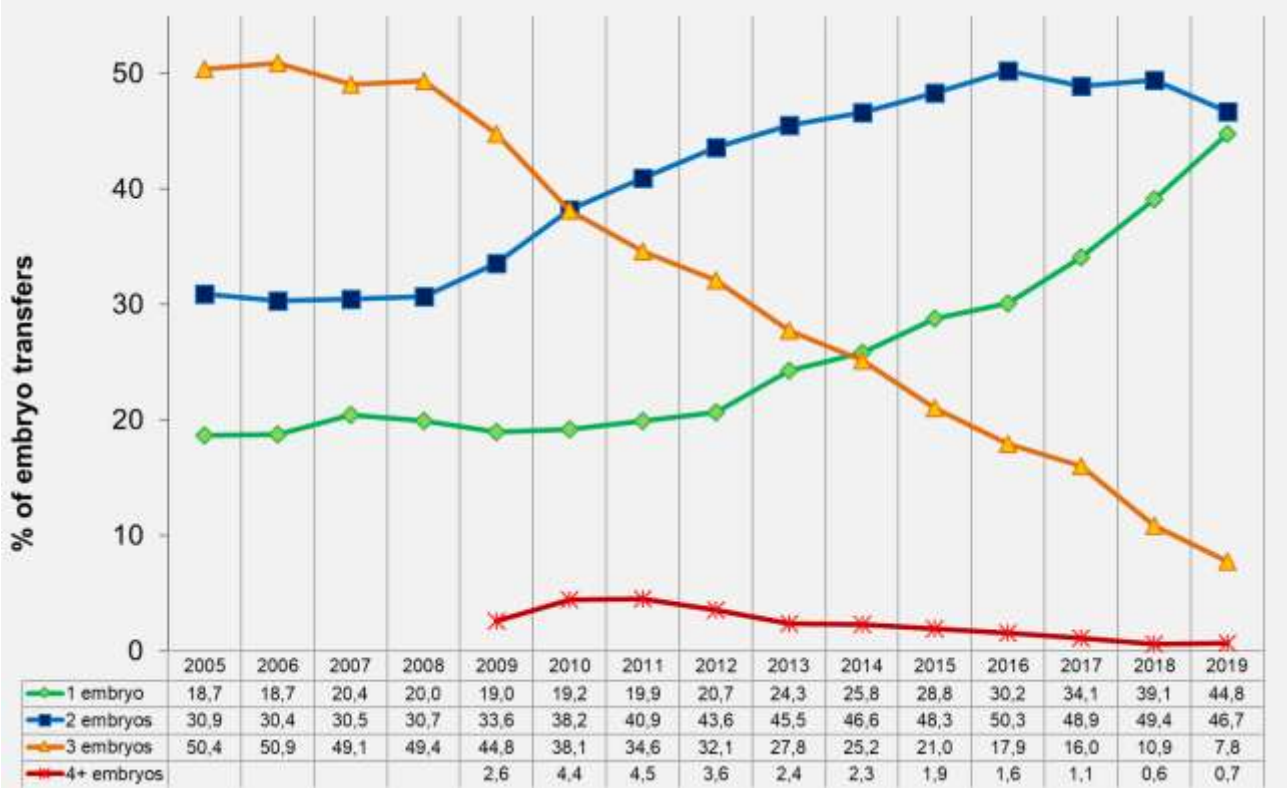


	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
mean age	35,3	35,5	35,8	35,9	36,2	36,3	36,5	36,5	36,6	36,7	36,7	36,8	36,7	36,7	36,8
≥40	20,7	23,8	25,2	26,8	28,2	29,2	30,5	30,7	31,0	32,9	33,7	35,2	34,3	34,6	34,6
35-39	40,0	38,3	39,8	39,4	40,5	41,2	40,9	41,0	41,5	40,0	38,5	37,8	38,0	37,8	38,3
≤34	39,3	37,9	35,0	33,8	31,3	29,6	28,6	28,3	27,5	27,1	27,8	27,0	27,8	27,6	27,1

Figure 16. Time-trends of fresh initiated cycle's distributions by age classes of female patients, 2005-2019.

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

Figure 17 shows trends with the percentage of the number of embryos transferred in fresh cycles. From 2005 to 2019, the single embryo transfers increased from 18,7% to 44,8% reaching the proportion of the double embryo transfers. On the other hand, transfers with three embryos dramatically decreased from 50,4%, first to 38,1% in 2010 to reach 7,8% in 2019. As shown in the figure**,** this trend began from the end of 2009 when Law 40/2004 was changed, by the Parliament, and the limit to transfer all the embryos created for a maximum of three removed. Values of transfers with four or more embryos decreased to 0,7% in 2019, after having been quite stable during time. The average number of embryos transferred decreased from 2,3 embryos per transfer in 2005 to 1,7 in 2019. This trend is similar in most European countries[1].



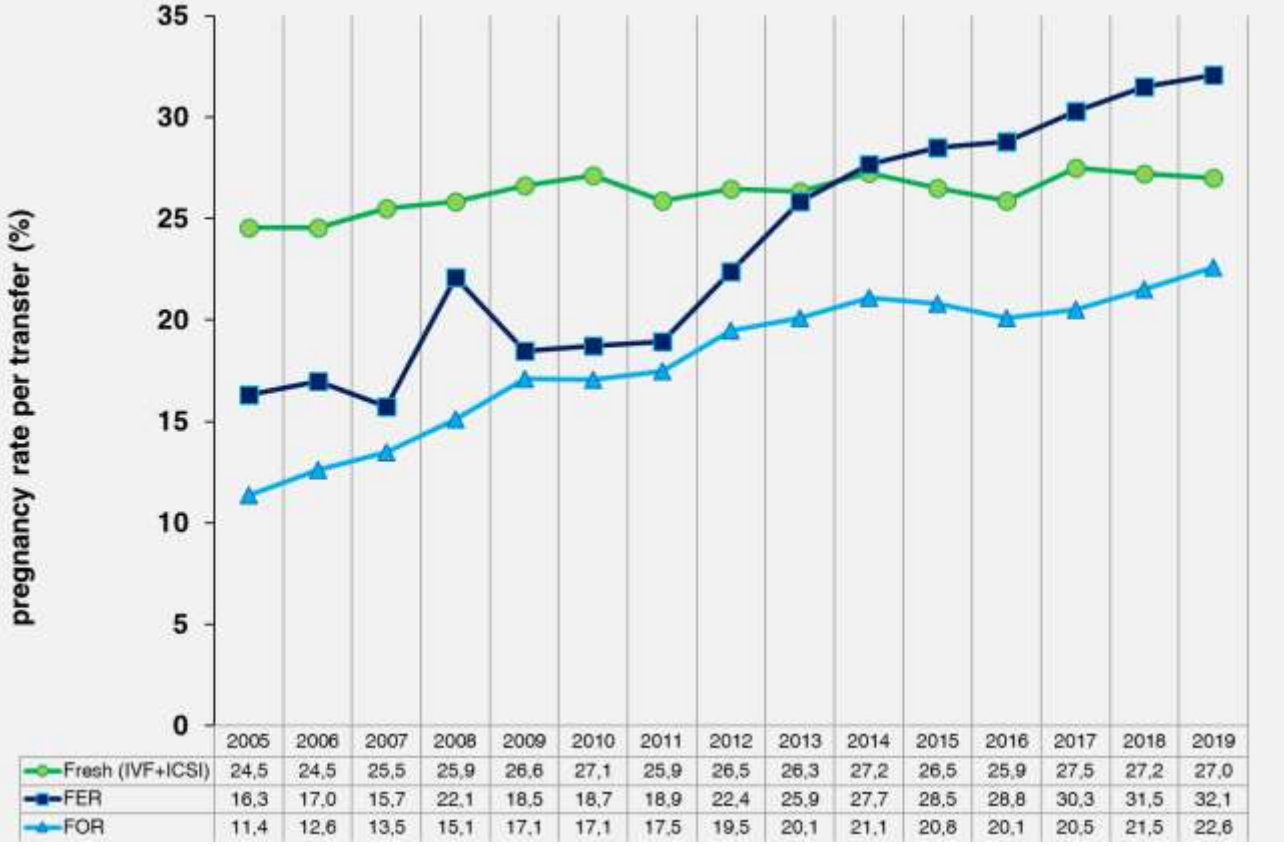
	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
1 embryo	18,7	18,7	20,4	20,0	19,0	19,2	19,9	20,7	24,3	25,8	28,8	30,2	34,1	39,1	44,8
2 embryos	30,9	30,4	30,5	30,7	33,6	38,2	40,9	43,6	45,5	46,6	48,3	50,3	48,9	49,4	46,7
3 embryos	50,4	50,9	49,1	49,4	44,8	38,1	34,6	32,1	27,8	25,2	21,0	17,9	16,0	10,9	7,8
4+ embryos					2,6	4,4	4,5	3,6	2,4	2,3	1,9	1,6	1,1	0,6	0,7

Figure 17. Time-trends of transfer by number of embryos transferred, 2005-2019.

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

Figure 18 shows pregnancy rates per transfer in order to compare cycles with fresh oocytes and embryos 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 32,1% in 2019: those with fresh oocytes slightly increased from 24,5% to 27%, and those with frozen oocytes from 11,4% to 22,6%. Since 2014, FET pregnancy rates have been higher than the fresh ones. The consolidation of the probability of obtaining a pregnancy for the fresh techniques and the increase for those of thawing takes place despite the fact that the number of embryos transferred has decreased over the years.

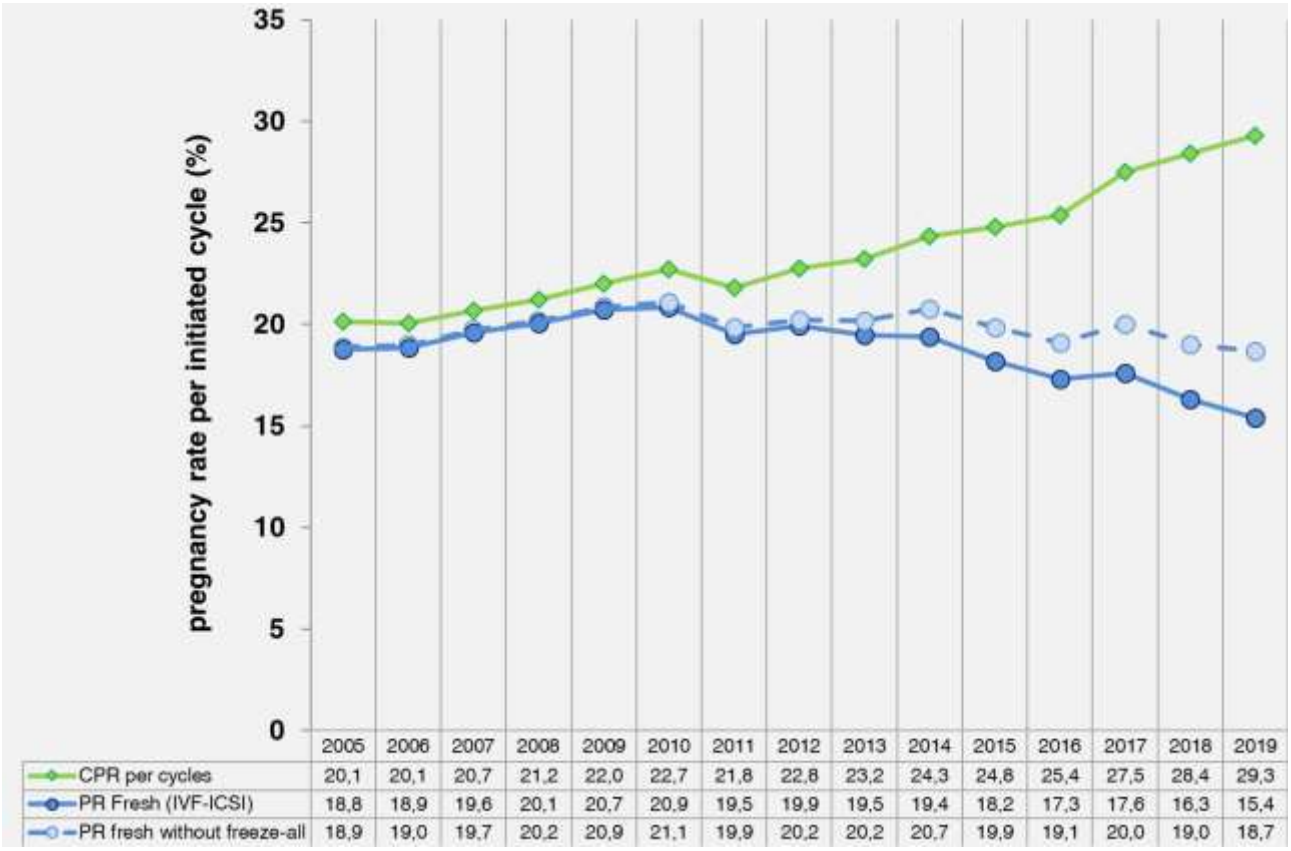


	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Fresh (IVF+ICSI)	24,5	24,5	25,5	25,9	26,6	27,1	25,9	26,5	26,3	27,2	26,5	25,9	27,5	27,2	27,0
FER	16,3	17,0	15,7	22,1	18,5	18,7	18,9	22,4	25,9	27,7	28,5	28,8	30,3	31,5	32,1
FOR	11,4	12,6	13,5	15,1	17,1	17,1	17,5	19,5	20,1	21,1	20,8	20,1	20,5	21,5	22,6

Figure 18. Time-trends of pregnancy rate per transfer for fresh, thawed embryos (FET) and thawed/warmed oocytes cycles (FO), 2005-2019.

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

Figure 19 compares the percentage of pregnancies obtained on fresh initiated cycles with the Cumulative Pregnancy Rate (CPR) over time. As described in **Chapter 2.2.5**, CPR is presented as the sum of pregnancies obtained from fresh cycles and 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 obtaining 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 benefit of embryo and oocyte cryopreservation. As the figure shows, this value is constantly growing from +6,6% in 2005 to a +56,7% in 2019. The trend of the pregnancy rate, calculated by excluding the "freeze-all cycles" from the count of the fresh ones, shows the impact on the outcomes of the fresh techniques of this new and increasingly widespread procedure.



	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
CPR per cycles	20,1	20,1	20,7	21,2	22,0	22,7	21,8	22,8	23,2	24,3	24,8	25,4	27,5	28,4	29,3
PR Fresh (IVF-ICSI)	18,8	18,9	19,6	20,1	20,7	20,9	19,5	19,9	19,5	19,4	18,2	17,3	17,6	16,3	15,4
PR fresh without freeze-all	18,9	19,0	19,7	20,2	20,9	21,1	19,9	20,2	20,2	20,7	19,9	19,1	20,0	19,0	18,7

Figure 19. Time-trends of pregnancy rate per initiated cycle for fresh and cumulative pregnancy rate per initiated cycle, 2005-2019.

2.2.14. 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 shown in **figure 20** pregnancy loss rates were much higher in older age groups. Rates increased from 53,7% in 2017 to 60,1% in 2019 for women older than 43, while they are quite stable in the remaining age groups.

	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
≥43	65,2	51,0	55,2	61,5	60,8	48,5	53,3	53,6	53,7	57,8	60,1
40-42	42,5	37,6	37,8	39,9	39,0	35,1	39,6	38,8	37,8	40,9	39,3
35-39	22,9	23,8	25,8	26,1	26,9	23,9	25,1	25,1	24,4	24,9	26,1
≤34	19,4	18,7	19,4	19,7	18,6	18,4	19,1	18,2	19,5	20,4	20,4

Figure 20. Time-trends of percentages of total pregnancy loss using ART non-donor cycles by female age groups, 2009-2019.

2.3. ART donor cycles

In April 2014 Italian Constitutional Court removed the prohibition (set out in the Law 40/2004), regarding the practice of ART techniques using donor gametes. Currently oocyte donation, semen donation and double donation are allowed.

See the Summary table (see page 55) for more detailed data on activity and outcomes regarding ART donor cycles in 2019.

2.3.1. Which gametes were used in ART donor cycles in 2019?

Figure 21 shows the distribution of the types of the 8995 ART cycles using donor gametes applied in Italy in 2019 and the origin of the donated frozen oocytes. In about 82,3% of ART donor cycles, fresh or frozen donated eggs were used, in 17,7% of cycles there is a donation of male gametes only. In the oocyte donation cycles, almost all cycles (97,8%) were performed with oocytes obtained from a foreign bank.

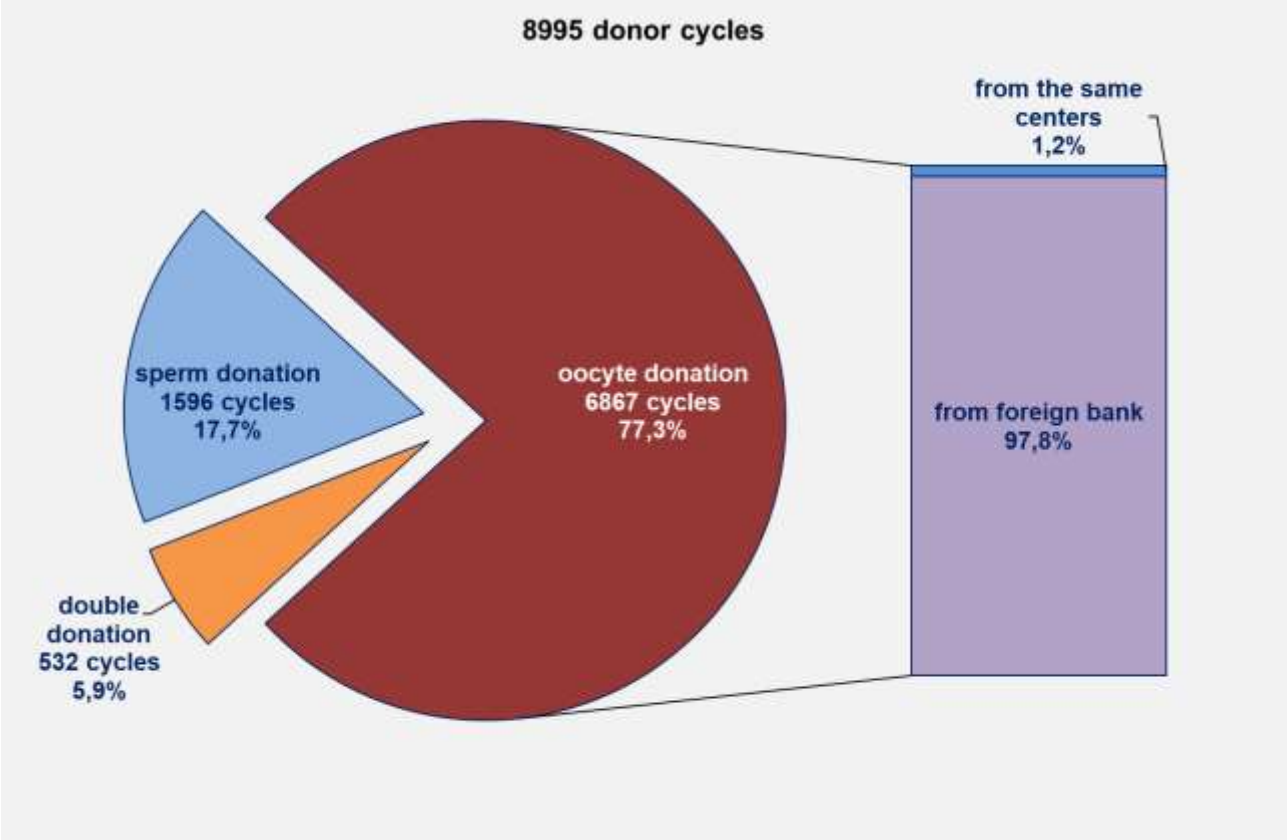


Figure 21. Distribution of all ART cycles using donor gametes and origin of the oocytes for the donor oocyte cycles, 2019. Total cycles = 8.995.

2.3.2. How did the types of donated gametes change among the recipient women of different ages classes?

Figure 22 shows the distribution of performed transfers according to the recipient female age group at the start of a donation cycle. The different types of gametes utilised in the different age distribution reflects the treatment indication. Meanwhile in the youngest women is more frequent a sperm donation (61,0%): the using of donated oocyte growing considerably with the age of the recipient women.

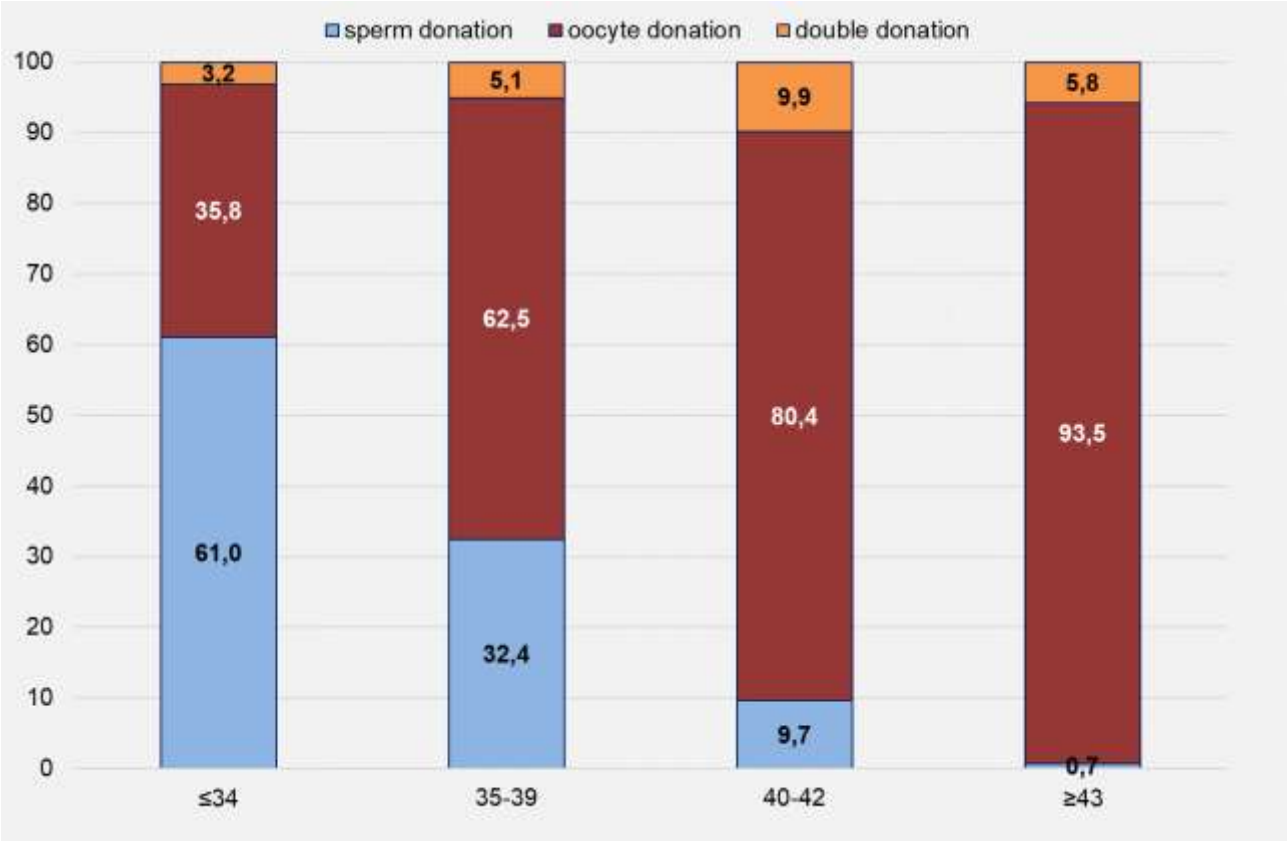


Figure 22. Distribution of donated gametes by recipient female age groups, 2019.

2.3.3. What was the percentage of transfers that result in pregnancies in ART donor cycles in 2019?

Figure 23 shows the pregnancy rate per transfer in ART donor techniques.

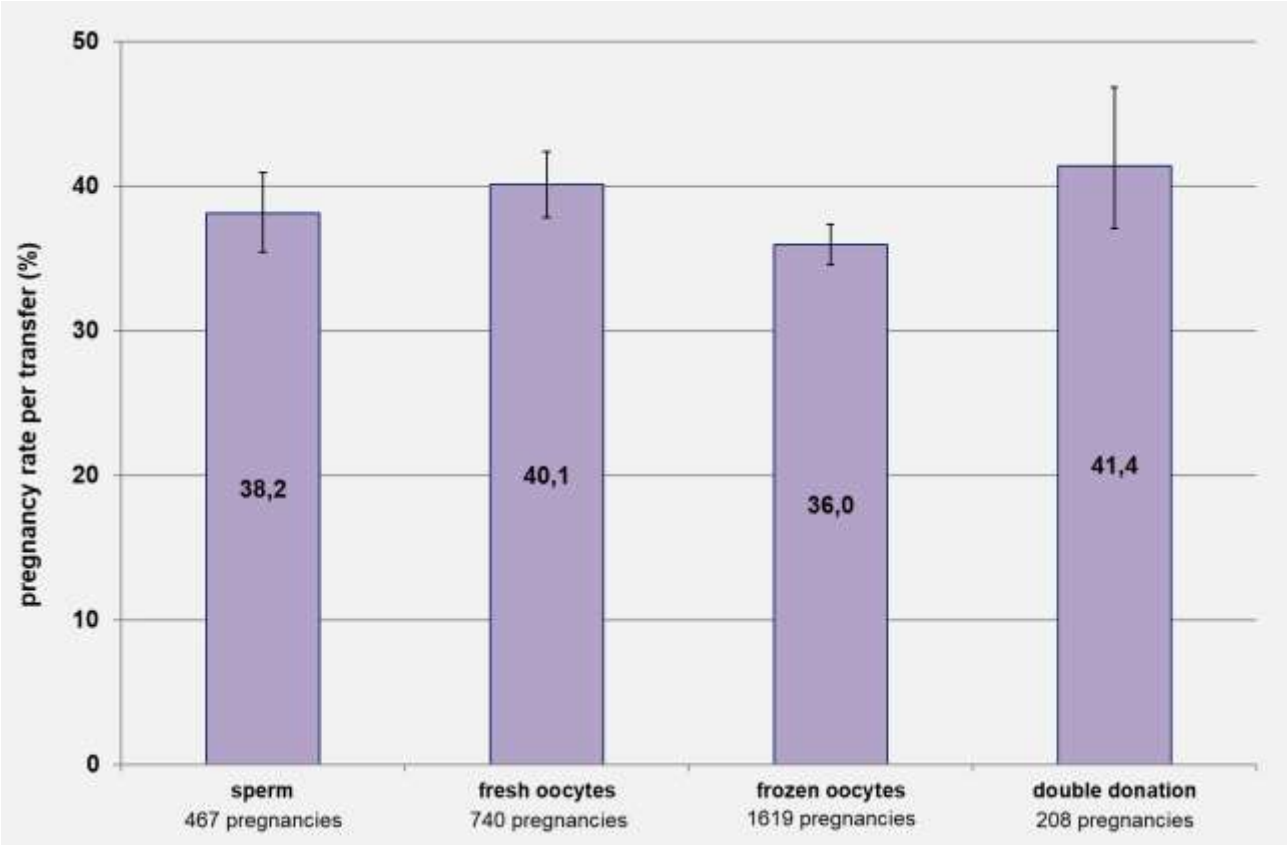


Figure 23. Distribution of pregnancy rate per transfer using donor gametes, 2019.

2.3.3. What were the outcomes of pregnancies obtained in ART donor cycles in 2019?

Figure 24 shows the outcomes of the 2.667 monitored clinical pregnancies obtained from the application of ART donor procedures in Italy in 2019. Of the 467 monitored pregnancies obtained from sperm donation 6,3% resulted in multiple deliveries and 24,1% in an abortion. In frozen donor oocyte cycles the multiple deliveries rate was higher (6,4%) than in fresh donor oocyte ones (4%), while there were no differences for the percentage of abortion, 23,8% and 21,2%, respectively. The percentage of abortions seems to be higher when both donated gametes are used rather than just one, but the low number of pregnancies obtained with a double donation does not allow speculation.

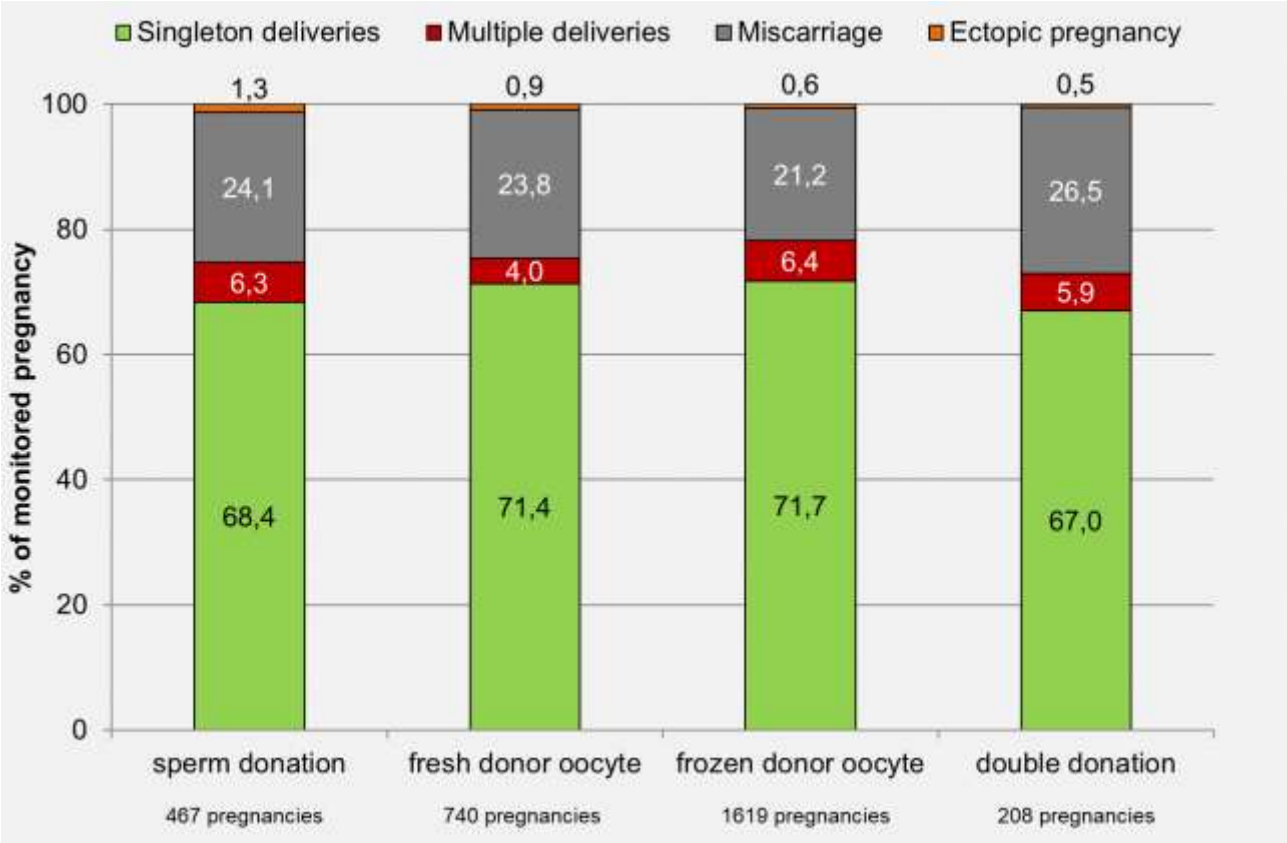


Figure 24. Comparison of the outcomes of monitored clinical pregnancies that resulted from ART donor cycles, 2019.

2.4. PGT (Pre-Implantation Genetic Testing) activity

During an ART treatment, some investigation could be performed to analyse the DNA from embryos (at cleavage stage or blastocyst) for HLA-typing or for determining genetic abnormalities. These investigations include:

- **PGT-A -** test for the detection of aneuploidies;
- **PGT-M** – test for monogenic/single defects;
- **PGT-SR** – tests for chromosomal structural rearrangements.

2.4.1. Which types of genetic tests were performed in ART cycles in 2019?

PGT activity, recorded from 55 centres, involved 3.314 tests (3.171 in fresh cycles and 143 in thawing ones). They result in 2.060 fresh and 99 frozen embryo transfers. **Figure 25** shows the distribution of the application of PGT (Preimplantation Genetic Testing) cycles in Italy. A total of 975 pregnancies (47,3% per transfer) and 646 deliveries (31,4% per transfer) resulted from fresh cycles, while 35 pregnancies (35,4% per transfer) and 19 deliveries (19,2% per transfer) resulted from frozen embryo cycles. Please check on summary table (see page 54) for more detailed data on activity and outcomes regarding PGT cycles in 2019.

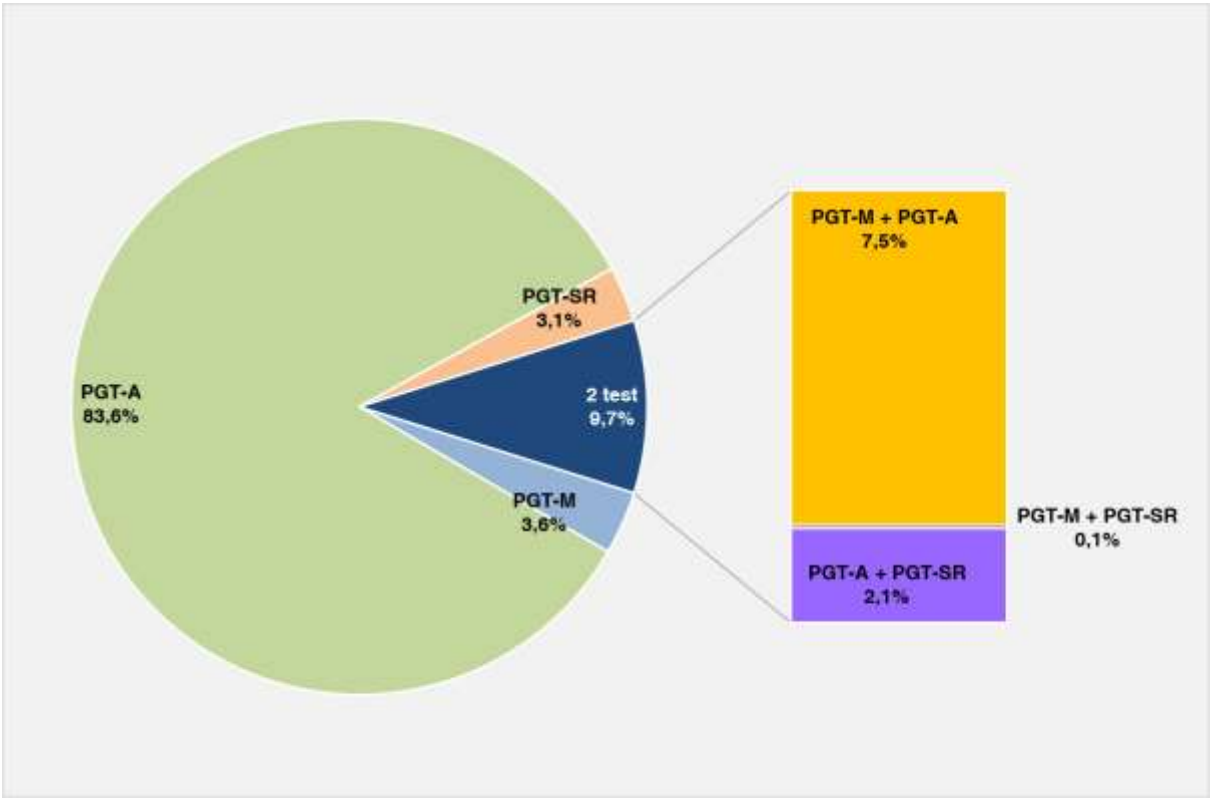
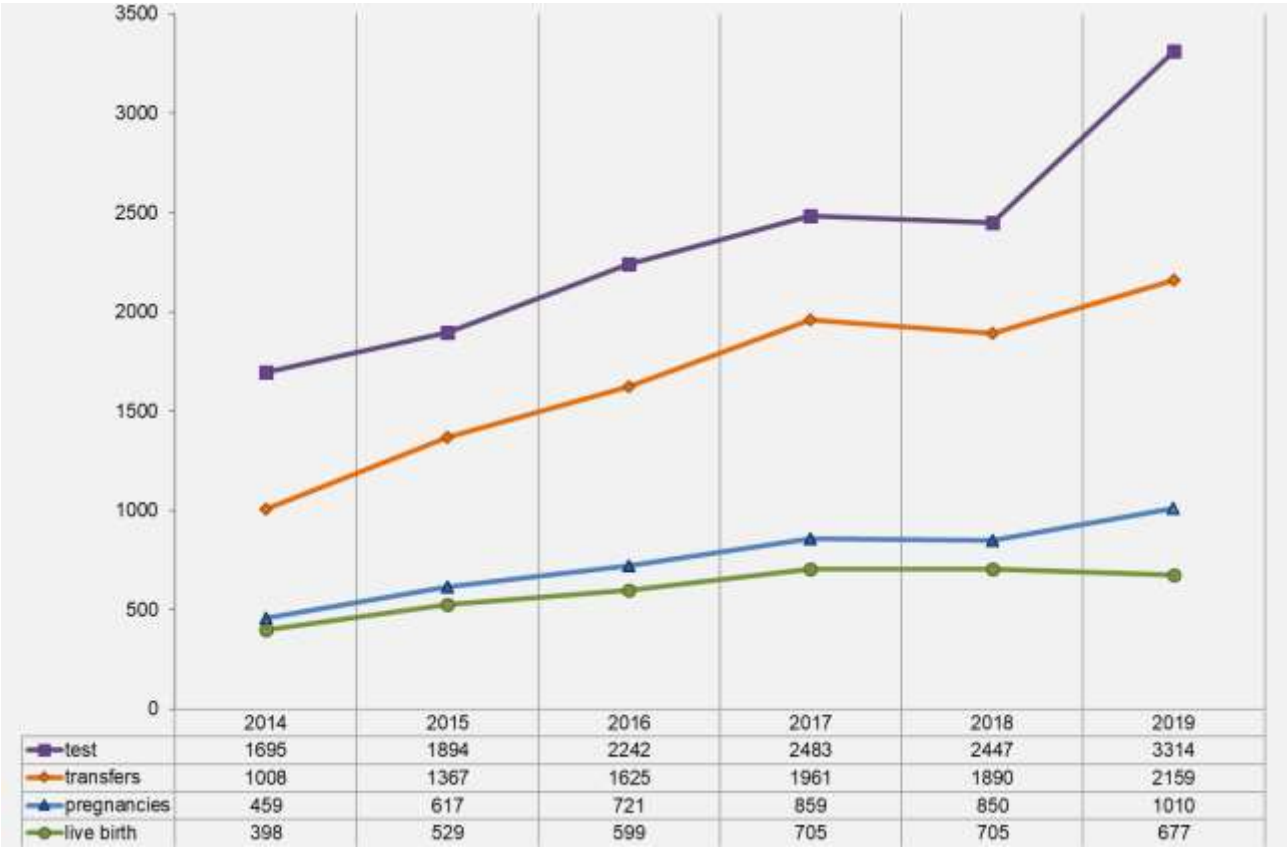


Figure 25. Distribution of PGD/PGS tests, 2019.

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

Figure 22 shows the progress of the application of the preimplantation genetic tests in the different phases that occur in a complete cycle of ART. Since the first data collection on PGT cycles performed on 2014 activity, the number of centres performing at least one cycle increased from 22 in 2014 to 55 in 2019. At the same time, the number of analysis performed increased from 1.695 cycles in 2014 to 3.314 cycles in 2019. Since 2014, the Registry has been collected information on a total of 14.075 cycles in which genetic tests were carried out, 10.010 transfers, 4.516 pregnancies obtained and 3.613 children born alive. The children born alive with the application of techniques that involved carrying out PGT have increased, from 398 children in 2014 to 677 in 2019.



	2014	2015	2016	2017	2018	2019
test	1695	1894	2242	2483	2447	3314
transfers	1008	1367	1625	1961	1890	2159
pregnancies	459	617	721	859	850	1010
live birth	398	529	599	705	705	677

Figure 26. Time-trend of number of test, transfer pregnancies and live birth after a PGT test, 2014-2019.

3. ART SAFETY INDICATORS

3.1. Safety in ART procedures

Although ART techniques are considered a safe medical procedure, in few cases some complications could arise during the treatment. These complications could arise at the moment of the ovarian stimulation or during pick-up procedure. Both could affect women's health. Another kind of complication for mother and child it is strictly related to embryo transfer policies. The transfer of more than one embryo could determine multiple pregnancies, therefore multiple deliveries and multiple births that could determine prematurity, morbidity and perinatal mortality of the babies.

3.1.1. Did the numbers of complications for ART cycles change over time?

Complications in an ART treatment are considered:

- **Ovarian Hyper Stimulation Syndrome (OHSS)**: An exaggerated systemic response to ovarian stimulation characterized by a wide spectrum of clinical and laboratory manifestations. It may be classified as mild, moderate or severe according to the degree of complications[3]. It is registered as a complication in the ART Register when it is diagnosed as "severe" (at least grade 3).
- **Bleeding**: Significant bleeding, internal or external, after oocyte aspiration retrieval requiring hospitalization for blood transfusion, surgical intervention, clinical observation or other medical procedure[3].
- **Infection**: The presence of a bacterial or viral infection that can occur during any surgical procedure.

Cases of bleedings and infections are decreasing during time, while the number of OHSS is quite stable.

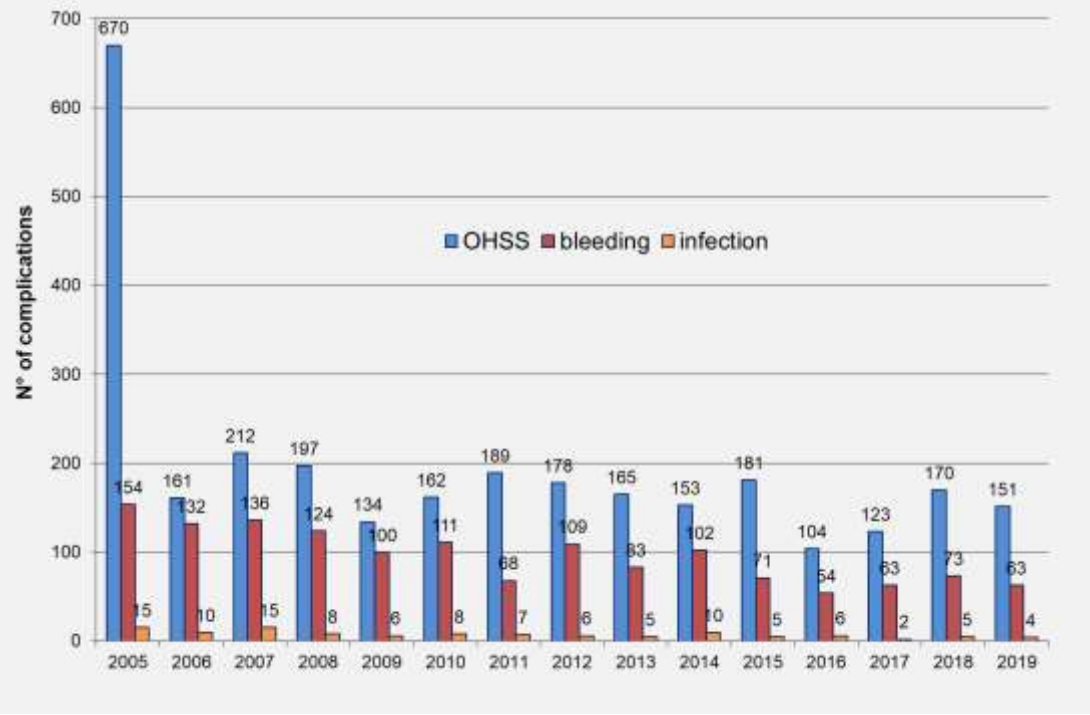
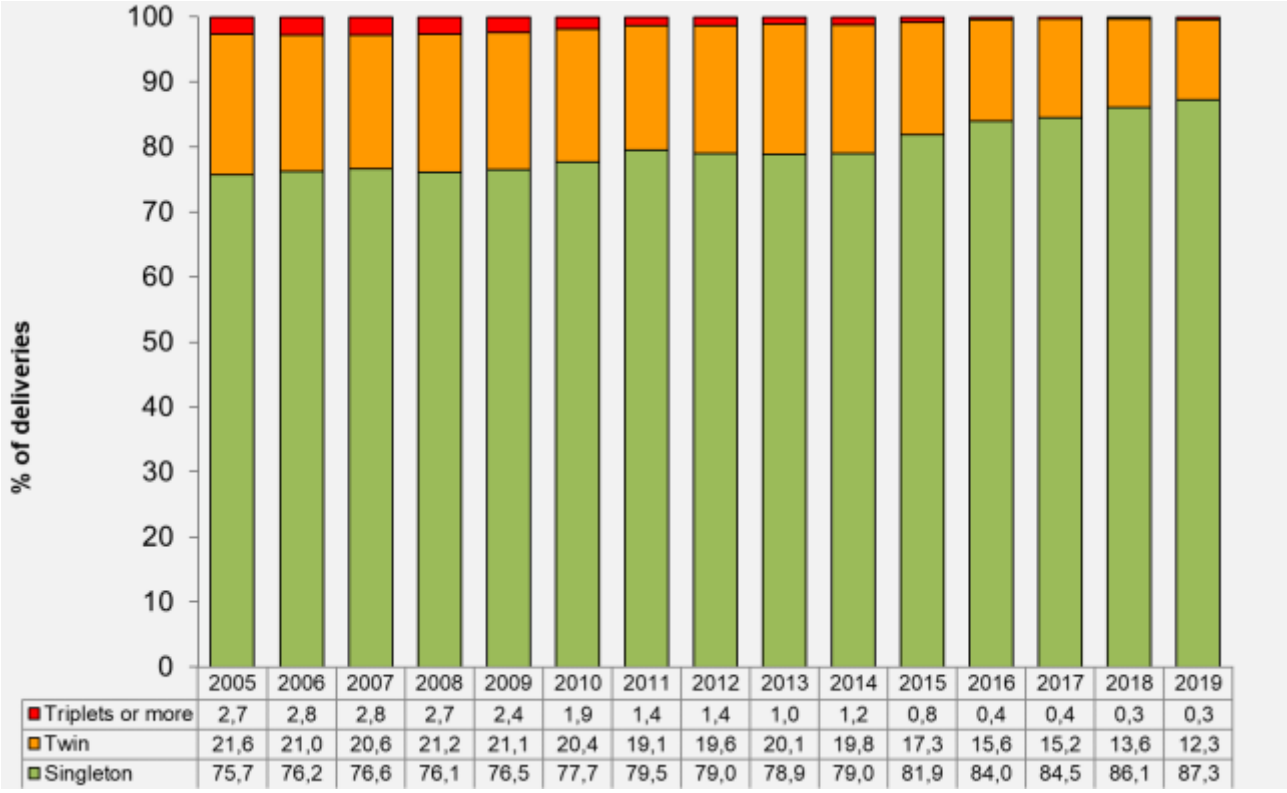


Figure 27. Time-trends of complications in fresh non-donor ART treatments, 2005-2019.

3.1.2. Did the percentages of multiple deliveries for ART non-donor cycles change over time?

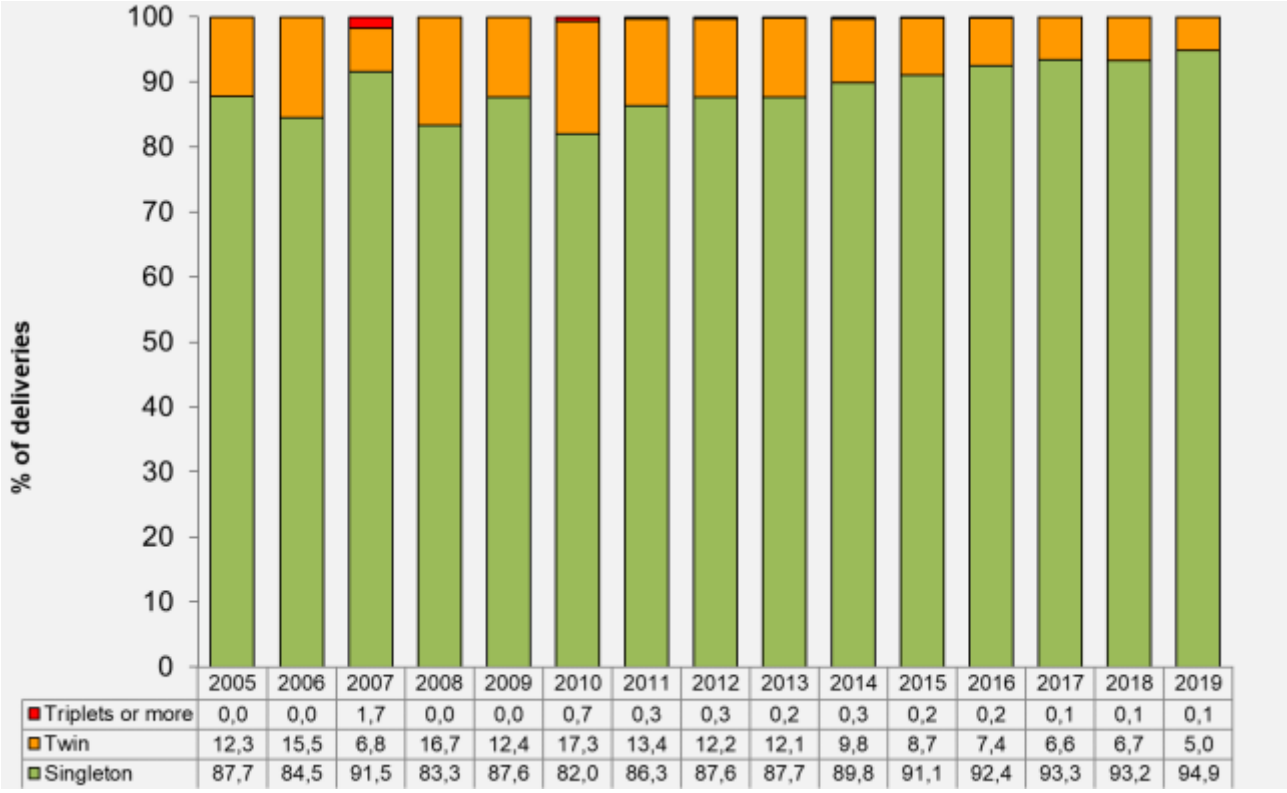
Figure 28 shows trends for multiple deliveries in fresh cycles. From 2005 to 2019, twin delivery percentage decreased from 21,6% to 12,3% while percentages of triplets and more deliveries decreased from 2,7% to 0,3%. This values are similar to the average European values of respectively 14,2% and 0,3% reported in 2017 EIM data1. We should remember that from 2004 till 2009 the Law obliged to transfer at once, all the embryos created for a maximum of three.



	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Triplets or more	2,7	2,8	2,8	2,7	2,4	1,9	1,4	1,4	1,0	1,2	0,8	0,4	0,4	0,3	0,3
Twin	21,6	21,0	20,6	21,2	21,1	20,4	19,1	19,6	20,1	19,8	17,3	15,6	15,2	13,6	12,3
Singleton	75,7	76,2	76,6	76,1	76,5	77,7	79,5	79,0	78,9	79,0	81,9	84,0	84,5	86,1	87,3

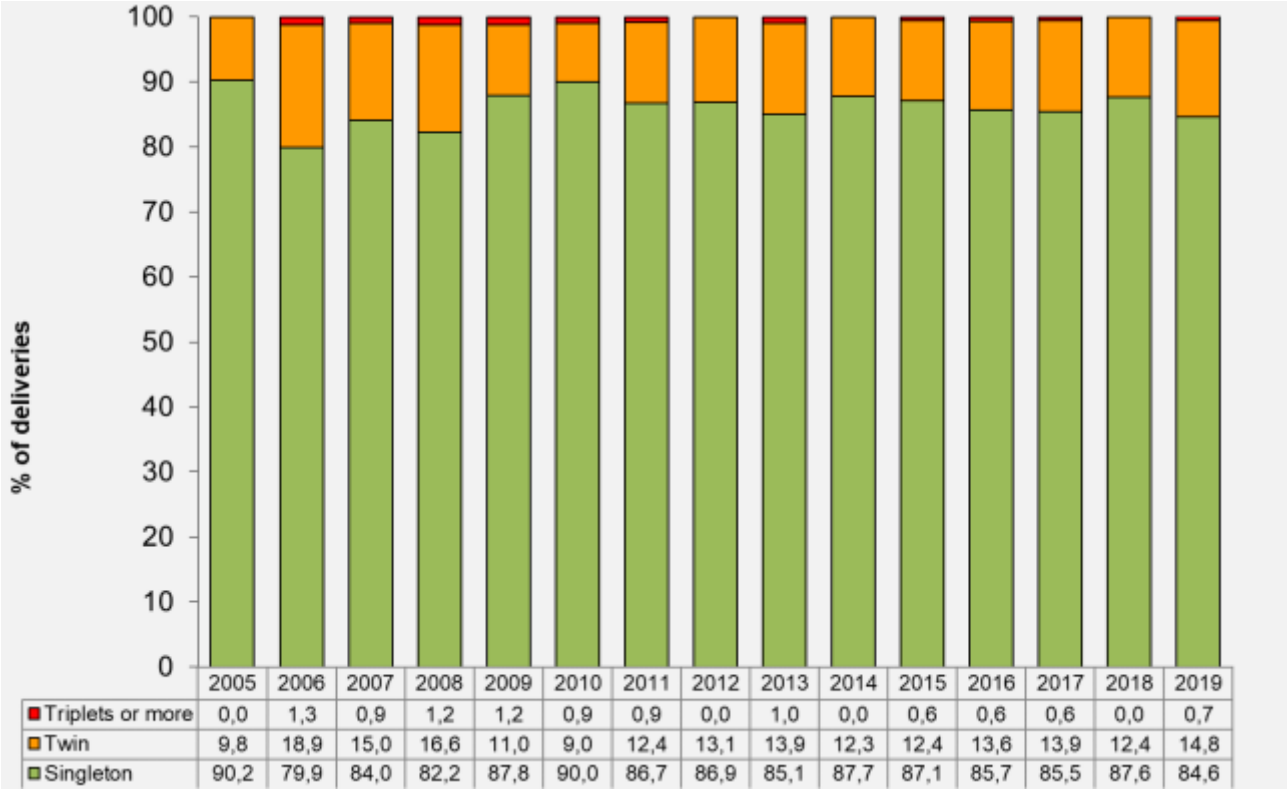
Figure 28. Time-trends of deliveries from fresh cycles according to gestational order, 2005-2019.

The same trends in percentage of the multiple deliveries are founds in FER (**Figure 29**). On the other hand, the FO technique shows an increase in twin deliveries which go from 9.8% in 2005 to 14.8% in 2019 (**Figure 30**).



	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Triplets or more	0,0	0,0	1,7	0,0	0,0	0,7	0,3	0,3	0,2	0,3	0,2	0,2	0,1	0,1	0,1
Twin	12,3	15,5	6,8	16,7	12,4	17,3	13,4	12,2	12,1	9,8	8,7	7,4	6,6	6,7	5,0
Singleton	87,7	84,5	91,5	83,3	87,6	82,0	86,3	87,6	87,7	89,8	91,1	92,4	93,3	93,2	94,9

Figure 29. Time-trends of deliveries from FER thawing according to gestational order, 2005-2019



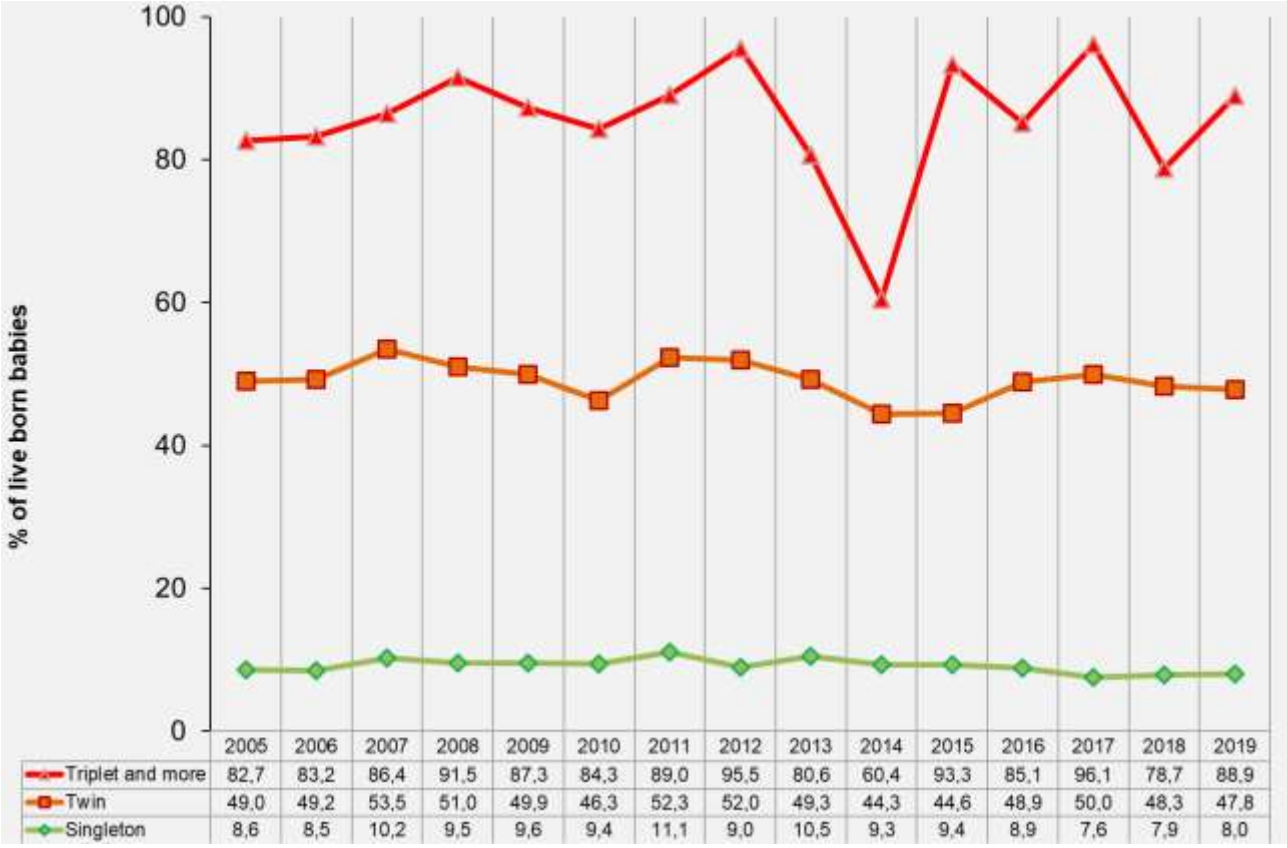
	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Triplets or more	0,0	1,3	0,9	1,2	1,2	0,9	0,9	0,0	1,0	0,0	0,6	0,6	0,6	0,0	0,7
Twin	9,8	18,9	15,0	16,6	11,0	9,0	12,4	13,1	13,9	12,3	12,4	13,6	13,9	12,4	14,8
Singleton	90,2	79,9	84,0	82,2	87,8	90,0	86,7	86,9	85,1	87,7	87,1	85,7	85,5	87,6	84,6

Figure 30. Time-trends of deliveries from FO thawing according to gestational order, 2005-2019

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 triplet deliveries, there is a variability from year to year, but overall the trend is upwards from 82,7% in 2005 to 88,9% in 2019 while it is stable or slightly lower in singletons.



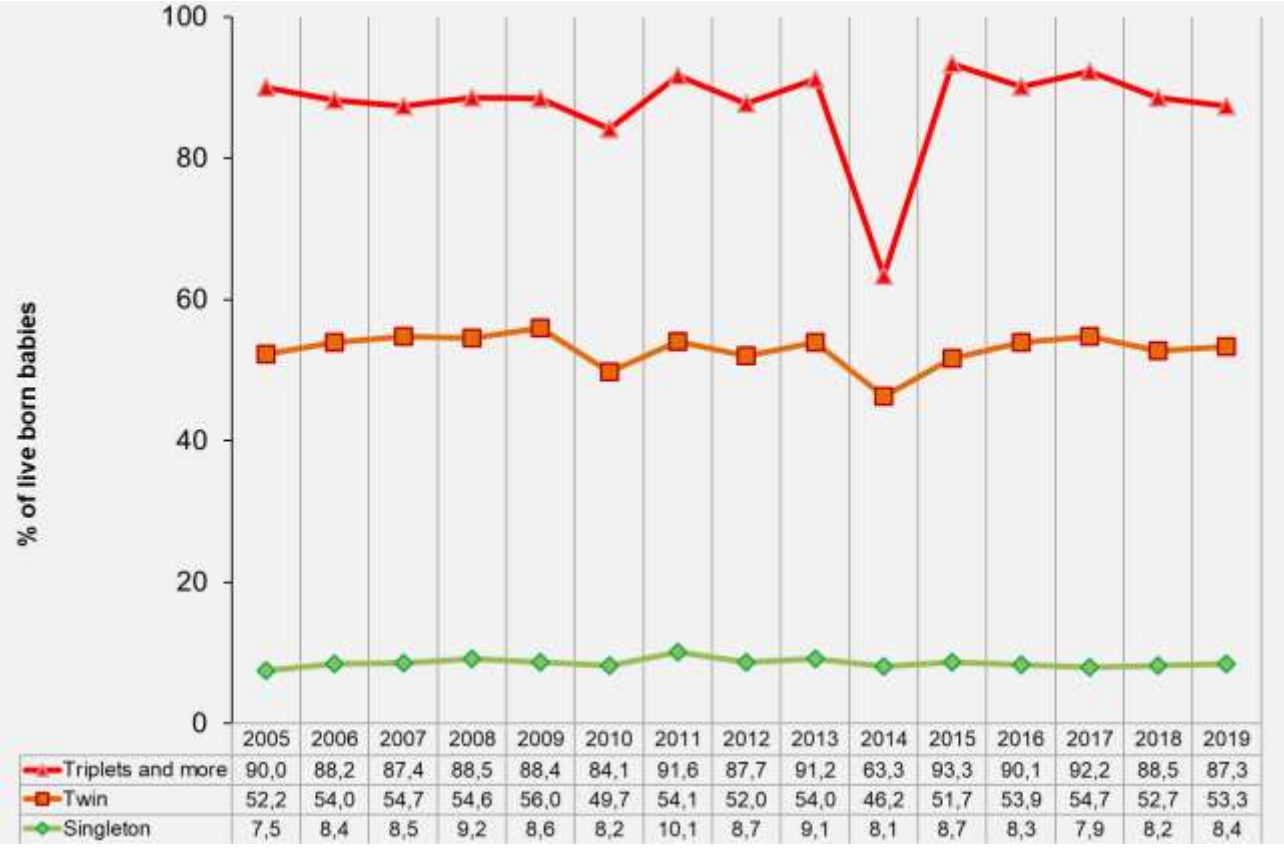
	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Triplet and more	82,7	83,2	86,4	91,5	87,3	84,3	89,0	95,5	80,6	60,4	93,3	85,1	96,1	78,7	88,9
Twin	49,0	49,2	53,5	51,0	49,9	46,3	52,3	52,0	49,3	44,3	44,6	48,9	50,0	48,3	47,8
Singleton	8,6	8,5	10,2	9,5	9,6	9,4	11,1	9,0	10,5	9,3	9,4	8,9	7,6	7,9	8,0

Figure 31. Time-trends of percentage of preterm ART live born babies (<37 week of gestation) by gestational order, 2005-2019.

3.1.4. 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 triplet and more deliveries from 90% in 2005 to 87,3% in 2019 with a minimum value of 63.3% in 2014 due to variability of the small number.



	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Triplets and more	90,0	88,2	87,4	88,5	88,4	84,1	91,6	87,7	91,2	63,3	93,3	90,1	92,2	88,5	87,3
Twin	52,2	54,0	54,7	54,6	56,0	49,7	54,1	52,0	54,0	46,2	51,7	53,9	54,7	52,7	53,3
Singleton	7,5	8,4	8,5	9,2	8,6	8,2	10,1	8,7	9,1	8,1	8,7	8,3	7,9	8,2	8,4

Figure 32. Time-trends of percentage of ART live born babies underweight (<2,500 gr) by gestational order, 2005-2019.

4. INTRA-UTERINE INSEMINATION PROCEDURES

4.1. Access to Intra-Uterine Insemination service

Figure 33 shows the regional distribution of the 346 Intra-Uterine Insemination (IUI) authorized centers in 2019, but only 299 performed at least one homologous IUI cycle.

The majority of centres is concentrated in northern Italy (157, 45,4% of the total) and then in the south (121 centers, 35% of the total), irrespective of the amount of activity they performed . Even with some differences the access is almost good in all the regions.

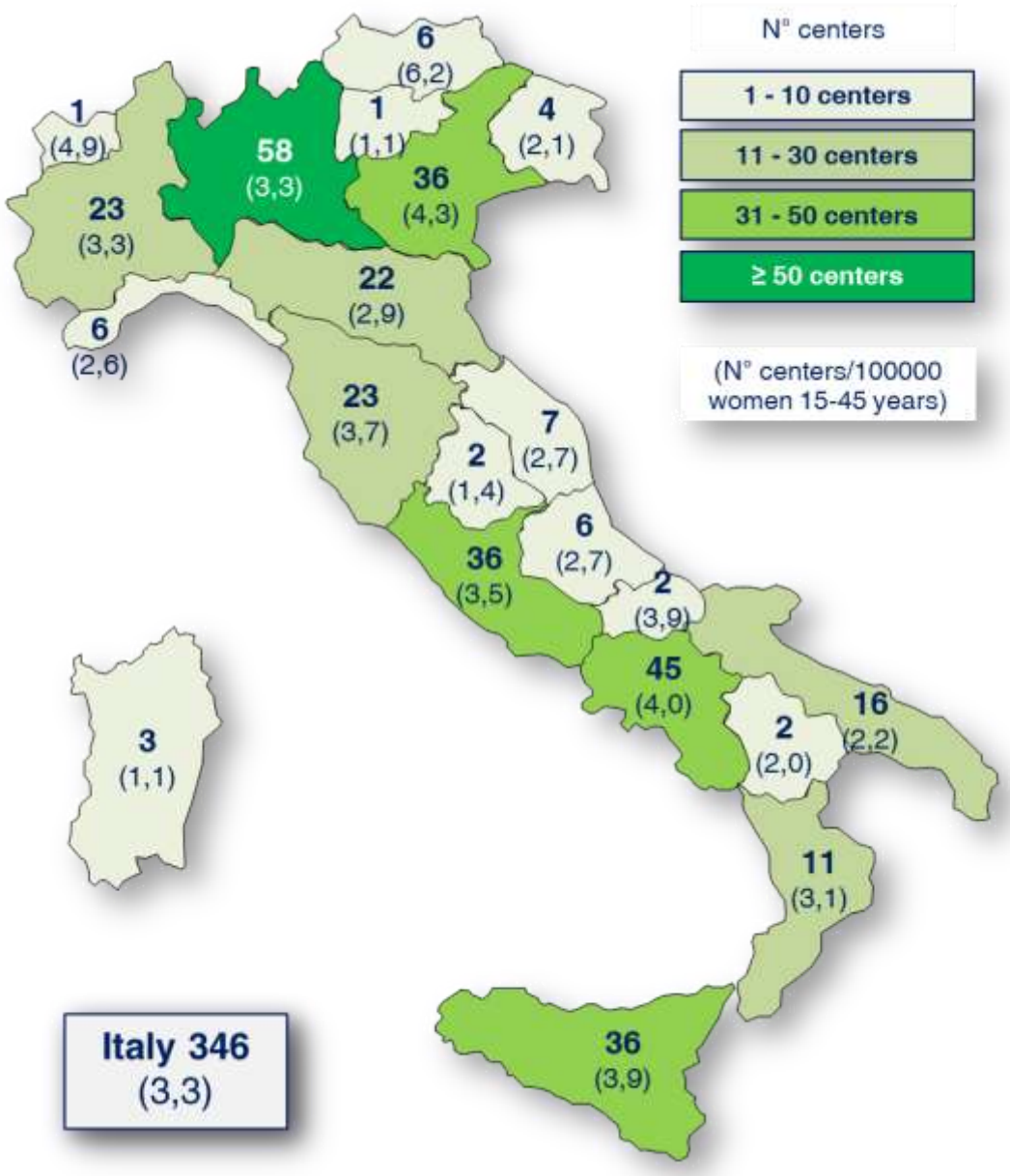


Figure 33. Regional distribution of IUI + ART authorized centres and in brackets the number of centres per 100000 women of reproductive age (15-45 years)*, 2019.

*Average resident population in Italy in 2019: Source ISTAT.

As shown in **Table 3**, in 2019 there were 346 authorized centers that perform IUI of which only 126 operating within the National Health System (public and private 36,4%) and 220 providing private service (63,6%). Most of public centres that could perform IUI in Italy were in the north: 60 out of 106 centres (56,6%).

Table 3. IUI authorized centres distribution by region and type of service, 2019

Region and geographical area	Total	Type of service					
		public		private covered by NHS		private	
		N	%	N	%	N	%
Piemonte	23	7	30,4	1	4,3	15	65,2
Valle d'Aosta	1	1	100,0	0	0,0	0	0,0
Lombardia	58	17	29,3	10	17,2	31	53,4
Liguria	6	4	66,7	0	0,0	2	33,3
North west	**88**	**29**	**33,0**	**11**	**12,5**	**48**	**54,5**
P.A. Bolzano	6	4	66,7	0	0,0	2	33,3
P.A. Trento	1	1	100,0	0	0,0	0	0,0
Veneto	36	13	36,1	2	5,6	21	58,3
Friuli Venezia Giulia	4	3	75,0	1	25,0	0	0,0
Emilia Romagna	22	10	45,5	0	0,0	12	54,5
North east	**69**	**31**	**44,9**	**3**	**4,3**	**35**	**50,7**
Toscana	23	8	34,8	5	21,7	10	43,5
Umbria	2	1	50,0	0	0,0	1	50,0
Marche	7	2	28,6	0	0,0	5	71,4
Lazio	36	6	16,7	1	2,8	29	80,6
Central	**68**	**17**	**25,0**	**6**	**8,8**	**45**	**66,2**
Abruzzo	6	3	50,0	0	0,0	3	50,0
Molise	2	0	0,0	0	0,0	2	100,0
Campania	45	10	22,2	0	0,0	35	77,8
Puglia	16	4	25,0	0	0,0	12	75,0
Basilicata	2	2	100,0	0	0,0	0	0,0
Calabria	11	2	18,2	0	0,0	9	81,8
Sicilia	36	5	13,9	0	0,0	31	86,1
Sardegna	3	3	100,0	0	0,0	0	0,0
South and islands	**121**	**29**	**24,0**	**0**	**0,0**	**92**	**76,0**
Italy	**346**	**106**	**30,6**	**20**	**5,8**	**220**	**63,6**

4.2. Efficacy safety and trends of IUI

4.2.1. Is the use of IUI-H increasing?

Intra-Uterine Insemination (IUI) is a medical procedure in which a laboratory processed sperm is placed into the women's uterus to attempt a pregnancy[3]. 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 (see page 31) the IUI-D procedures have been permitted only after the Italian Constitutional Court sentence in April 2014. For the activity of IUI-D in 2019, please check on Summary table for 2019 (see page 55) for more detailed data.

Figure 34 shows the use of IUI-H from 2005 to 2019. The number of IUI-H cycles decreased from 26.292 to 15.895 after having reached his maximum of 33.335 cycles in 2009. There were no changes in pregnancy rate from 10,7% in 2005 to 10,3% in 2019. The average age of women fluctuates over time around 35 years of age: in 2019 it was 34.8 years.

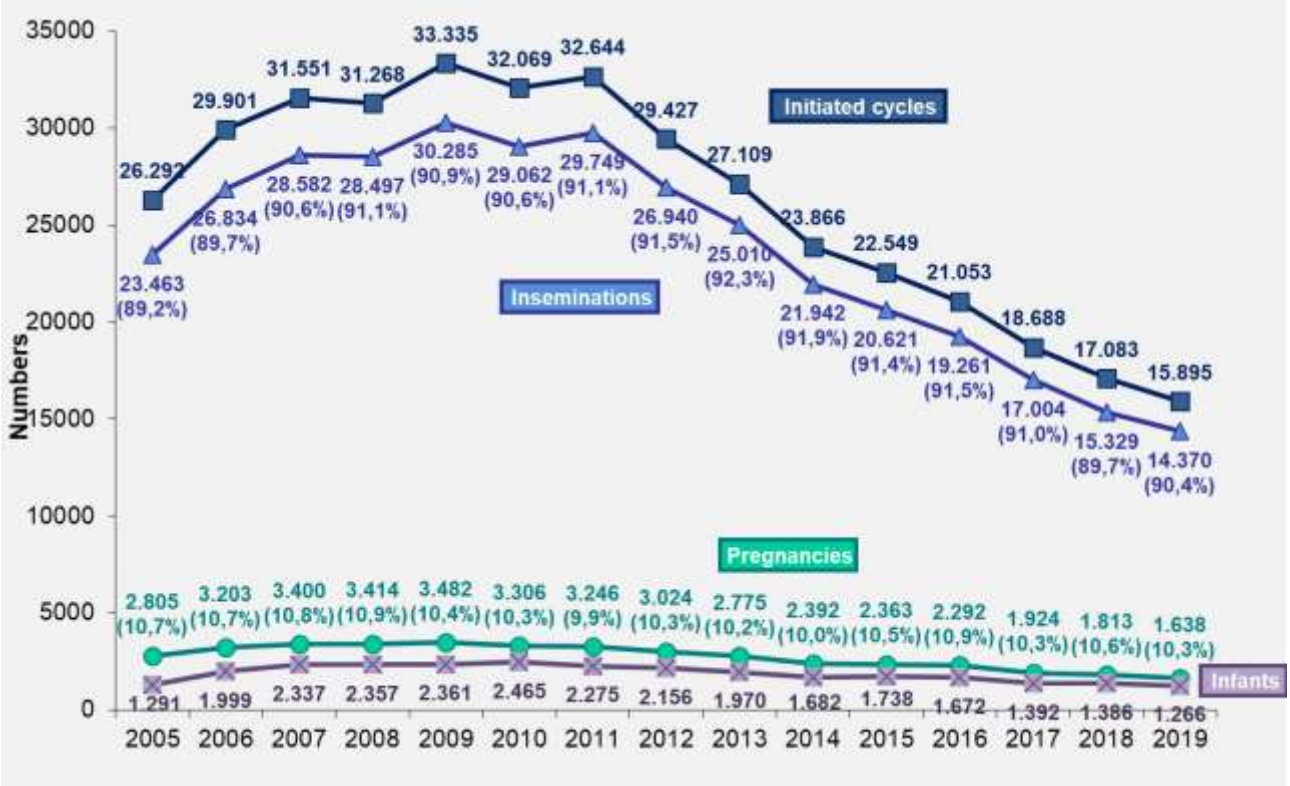


Figure 34. Time-trends of outcomes of IUI-H cycles, 2005-2019.

4.2.2. Do percentages of IUI-H cycles resulting in pregnancies 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. The percentage in older women are very low: 3,7% for pregnancy and 1,4% for delivery in over 43.

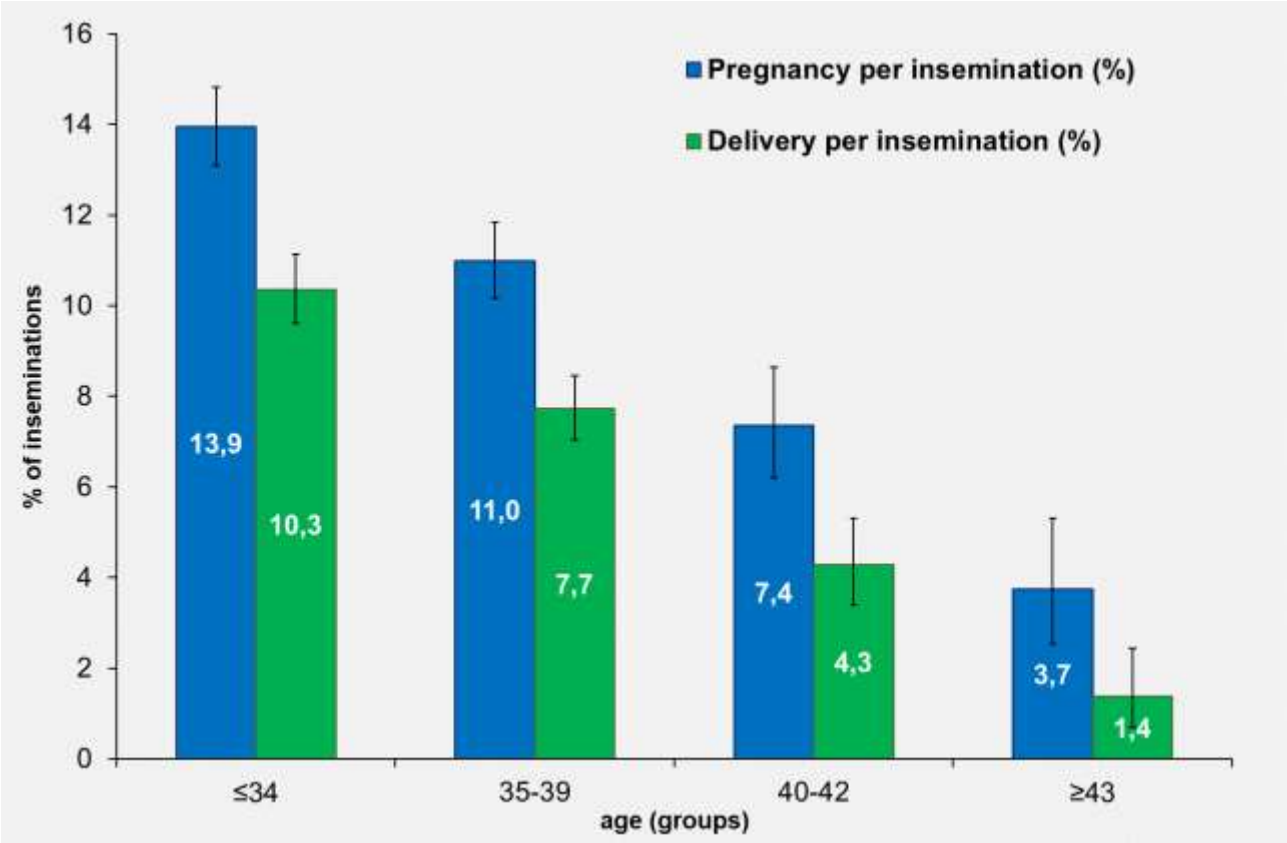


Figure 35. Pregnancy rates and delivery rates per insemination for IUI-H cycles by age groups of female patients, 2019.

4.2.3. What were the outcomes of pregnancies obtained in IUI-H cycles in 2019?

Figure 36 shows the outcomes of the monitored clinical pregnancies obtained from the application of the homologous IUI in Italy in 2019. Of the 1.456 monitored pregnancies in homoulogous IUI cycles 6,9% resulted in multiple deliveries and 18,9% had a miscarriage.

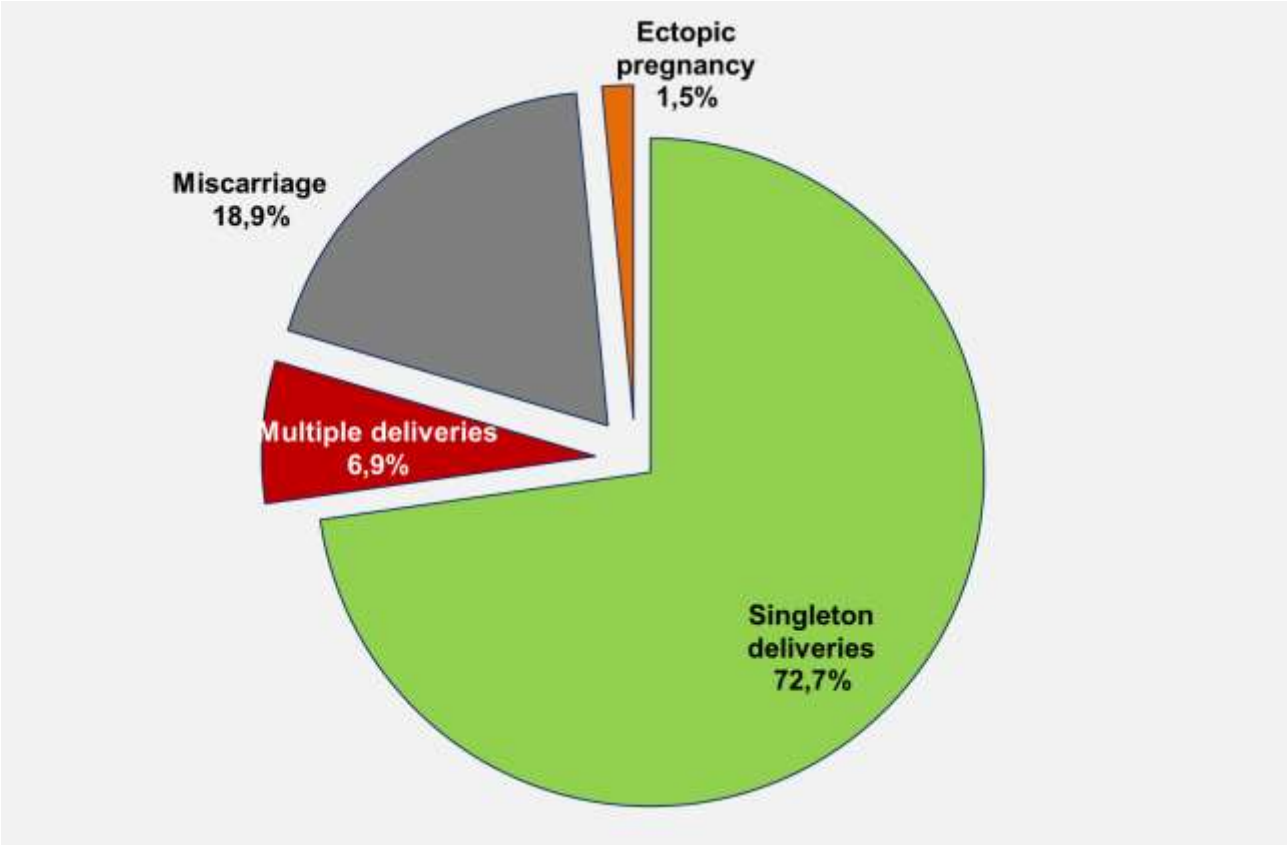


Figure 36. Outcomes of clinical pregnancies that resulted from H-IUI cycles, 2019.

4.2.4. Did the numbers of complications for H-IUI cycles change over time?

Figure 37 shows that complications for OHSS have been decreasing continuously since 2008, going from 42 (0.15% of the inseminations) to 6 (0.04%). Complications for "other causes" also continue to decrease to 9 (0.06%) but only after reaching their maximum value of 61 (0.21%) in 2011.

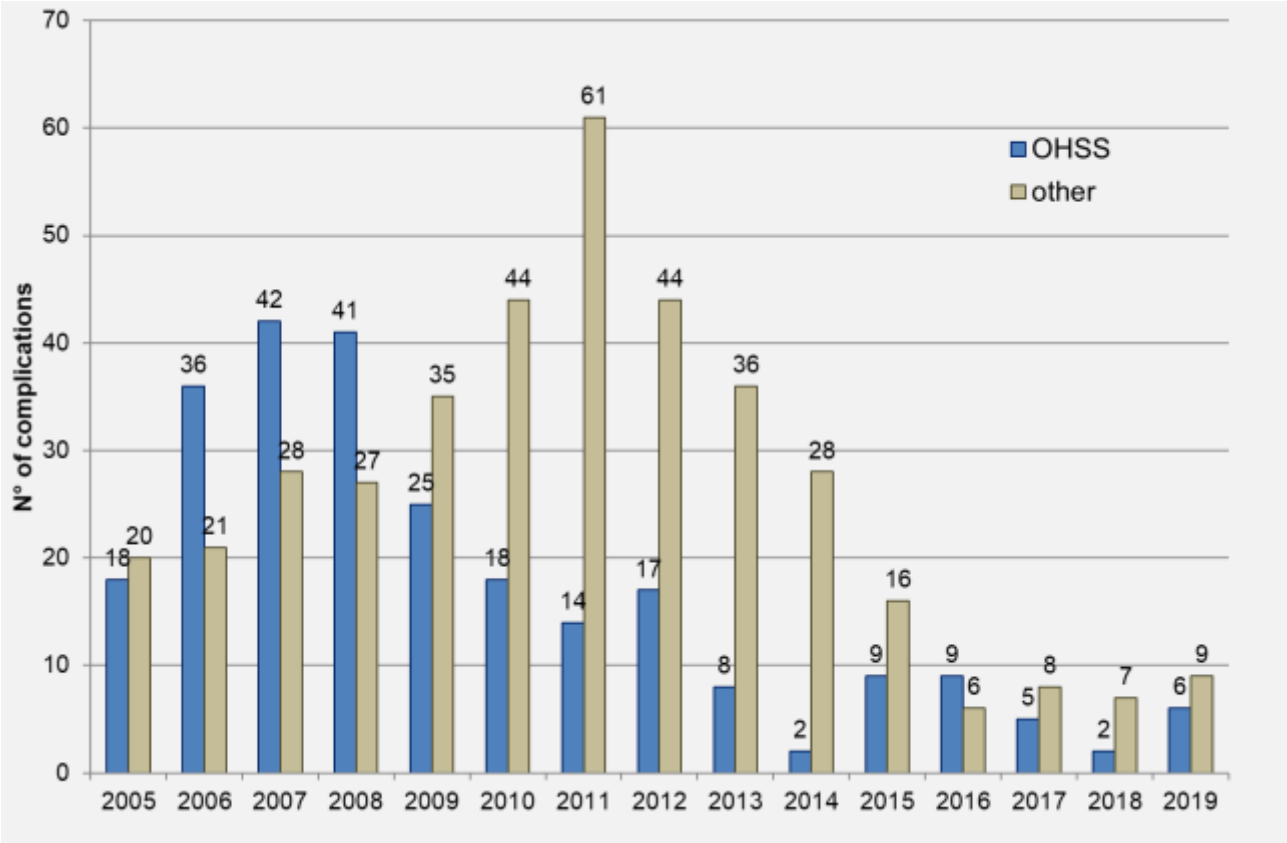
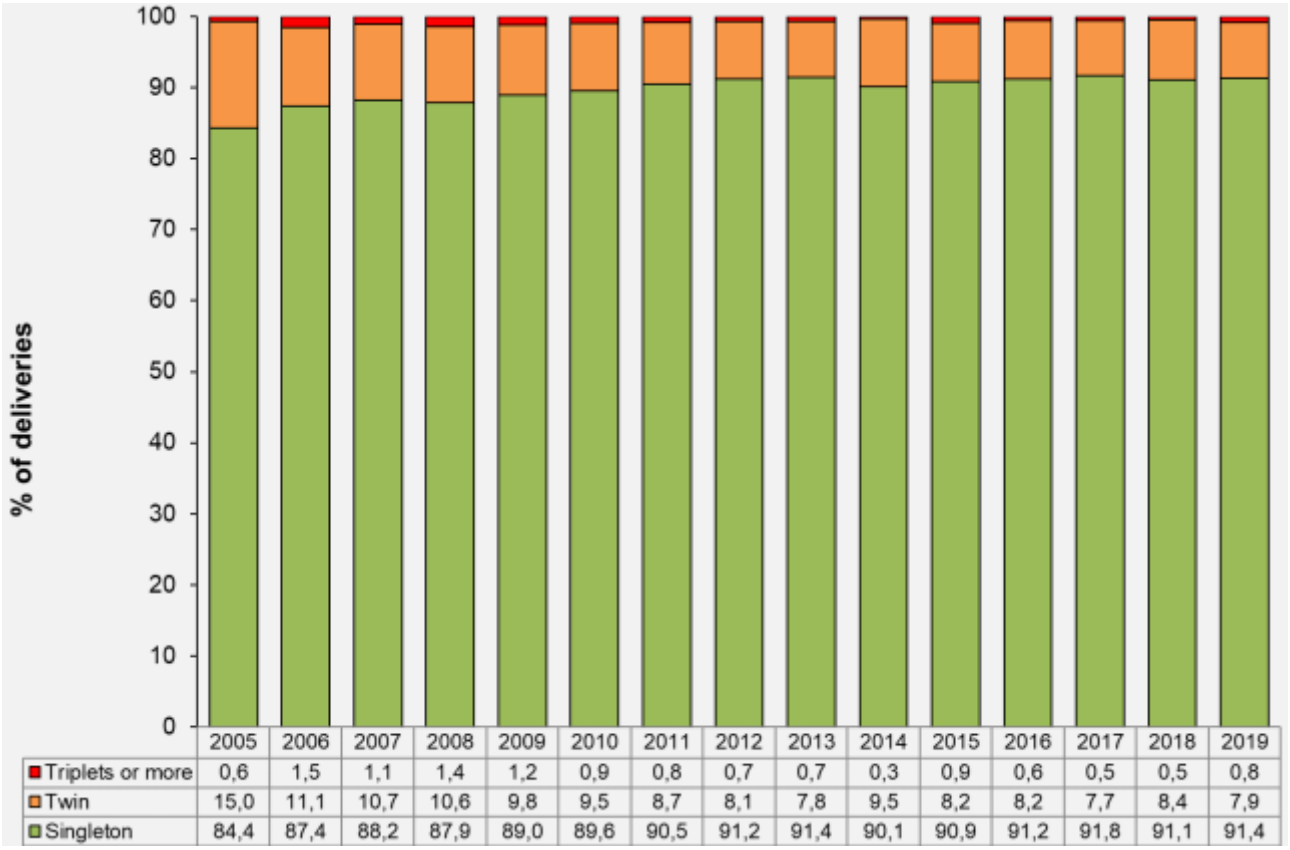


Figure 37. Time-trends of complications in homologous-IUI treatments, 2005-2019.

4.2.5. Did the percentages of multiple deliveries change over time for homologous intrauterine insemination cycles?

Figure 38 shows time trends for multiplicity of deliveries in IUI-H cycles. From 2005 to 2019 twin deliveries rates decreased from 15% to 7,9% while percentage of triplets and more deliveries are quite stable. Since 2007, 9 deliveries out of 10 are singleton.



	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Triplets or more	0,6	1,5	1,1	1,4	1,2	0,9	0,8	0,7	0,7	0,3	0,9	0,6	0,5	0,5	0,8
Twin	15,0	11,1	10,7	10,6	9,8	9,5	8,7	8,1	7,8	9,5	8,2	8,2	7,7	8,4	7,9
Singleton	84,4	87,4	88,2	87,9	89,0	89,6	90,5	91,2	91,4	90,1	90,9	91,2	91,8	91,1	91,4

Figure 38. Time-trends of deliveries from IUI-H cycles according to gestational order, 2005-2019.

4.3. IUI donor cycles

4.3.1. What was the outcome in IUI donor cycles in 2019?

In total 691 initiated cycles using donor sperm in IUI cycle started in 2019, 20,1% resulted in a clinical pregnancy and 13,0% resulted in a delivery. However, most of these cycles (about 81,3%) did not produce a pregnancy while a small proportion (3,3%) resulted in a pregnancy loss (i.e. ectopic pregnancy or miscarriage).

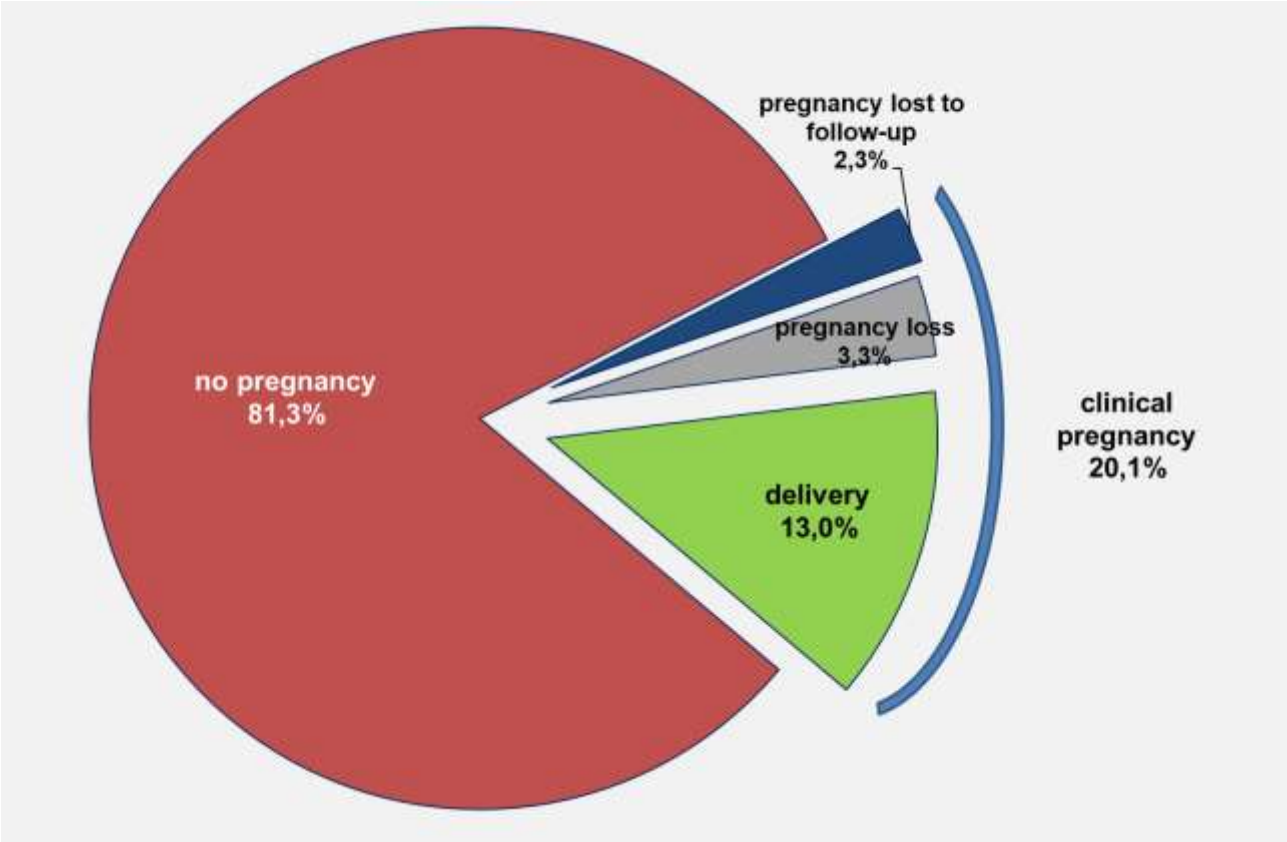


Figure 39. Outcome of IUI-D cycles, 2019 (691 initiated cycles).

APPENDIX

SUMMARY TABLE OF ACTIVITY AND OUTCOME OF ART PROCEDURES YEARS 2011-2019

Summary table of activity and outcome of all ART procedures, 2011-2019

	2014	2015	2016	2017	2018	2019
N° Clinics	362	366	360	366	345	346
% of clinics reporting data to ISS	100	100	100	100	100	100
ALL PROCEDURES (IUI-H, IUI-D, ART Non donor and Donor)						
N° Patients	70.826	74.292	77.522	78.366	77.509	78.618
N° Initiated cycles	90.957	95.110	97.656	97.888	97.149	99.062
N° Live born	12.720	12.836	13.582	13.973	14.139	14.162
ART activity (Fresh non donor, Thawing non donor, donor)						
N° Patients	55.859	59.747	63.724	65.943	66.083	67.633
N° Initiated cycles	67.054	72.048	75.889	78.457	79.735	82.476
N° Pregnancies	13.642	14.391	15.405	16.793	17.402	17.787
Cumulative Pregnancy Rate per fresh initiated cycle	24,3	24,8	25,4	27,5	28,4	29,3
% Pregnancies lost to follow-up	10,8	11,3	10,2	11,9	9,7	10,6
N° Deliveries	9.252	9.512	10.386	11.094	11.428	11.754
N° Live born	11.037	11.029	11.791	12.454	12.646	12.797
ART SERVICES AVAILABILITY INDICATORS						
ART Initiated cycles per 1 million women aged 15 and 45	5.860	6.341	6.781	7.106	7.341	7.697
ART Initiated cycles per 1 million inhabitants	1.103	1.175	1.237	1.275	1.297	1.341
IUI-H and IUI-D activity						
N° Patients	14.967	14.545	13.798	12.423	11.426	10.985
N° Initiated cycles	23.903	23.062	21.767	19.431	17.774	16.586
N° Pregnancies	2.399	2.466	2.429	2.078	1.952	1.767
% Pregnancy Rate per cycle	10,0	10,7	11,2	10,7	11,0	10,7
% Pregnancies lost to follow-up	18,2	16,8	15,0	13,9	11,7	11,2
N° Deliveries	1.530	1.649	1.629	1.396	1.369	1.249
N° Live born	1.683	1.807	1.791	1.519	1.493	1.365

Summary table of activity and outcome of ART non donor procedures, 2011-2019

	2014	2015	2016	2017	2018	2019
FRESH CYCLES (Non Donor)						
N° Patients	45.985	45.689	44.965	44.279	42.090	41.149
Average age calculated	36,68	36,68	36,80	36,70	36,74	36,79
N° Initiated cycles	55.705	55.329	53.906	53.014	51.087	50.324
N° aspirations	50.794	50.214	48.756	47.911	46.387	46.090
N° transfers	39.768	37.975	36.038	33.832	30.584	28.731
N° Pregnancies	10.834	10.081	9.326	9.310	8.307	7.753
% Pregnancies rate per cycles	19,4	18,2	17,3	17,6	16,3	15,4
% Pregnancies rate per cycles without freeze-all strategy	20,7	19,9	19,1	20,0	19,0	18,7
% Pregnancies rate per aspirations	21,3	20,1	19,1	19,4	17,9	16,8
% Pregnancies rate per transfers	27,2	26,5	25,9	27,5	27,2	27,0
% Twin Pregnancies	19,5	17,0	15,6	15,0	13,1	12,3
% Triplet or more Pregnancies	1,4	0,9	0,6	0,5	0,4	0,5
% Pregnancies lost to follow-up	11,9	13,1	11,2	13,4	10,9	10,4
N° Deliveries	7.277	6.498	6.196	6.029	5.458	5.151
N° Live born	8.848	7.695	7.172	6.951	6.186	5.797
FROZEN/THAWED EMBRYOS (FER)						
N° Patients	8.139	10.557	12.485	14.441	16.067	17.562
Average age calculated	35,4	35,2	35,3	35,3	35,2	35,3
N° thawing cycles	9.501	12.903	14.990	17.281	19.587	21.796
N° transfers	8.851	11.849	14.328	16.673	19.016	21.078
N° Pregnancies	2.448	3.379	4.128	5.059	5.995	6.758
% Pregnancies rate per thawings	25,8	26,2	27,5	29,3	30,6	31,0
% Pregnancies rate per transfers	27,7	28,5	28,8	30,3	31,5	32,1
% Twin Pregnancies	11,2	9,8	9,1	7,7	7,0	5,0
% Triplet or more Pregnancies	0,4	0,4	0,3	0,1	0,1	0,1
% Pregnancies lost to follow-up	5,5	5,6	6,7	7,9	6,6	10,2
N° Deliveries	1.747	2.403	2.890	3.486	4.127	4.412
N° Live born	1.929	2.609	3.104	3.703	4.393	4.637
FROZEN/THAWED OOCYTES (FO)						
N° Patients	1.530	1.418	1.341	1.281	1.201	1.248
Average age calculated	35,1	35,2	35,1	35,2	35,4	35,3
N° thawing cycles	1.639	1.529	1.460	1.391	1.318	1.361
N° transfers	1.295	1.221	1.187	1.146	1.036	1.071
N° Pregnancies	273	254	238	235	223	242
% Pregnancies rate per thawings	16,7	16,6	16,3	16,9	16,9	17,8
% Pregnancies rate per transfers	21,1	20,8	20,1	20,5	21,5	22,6
% Twin Pregnancies	12,5	10,6	12,2	12,8	9,9	11,2
% Triplet or more Pregnancies	0,8	0,4	1,3	0,4	0,0	0,4
% Pregnancies lost to follow-up	7,0	5,9	4,6	4,7	6,7	7,4
N° Deliveries	179	170	154	165	153	149
N° Live born	199	193	177	190	172	173

Summary table of activity and outcome of ART with PGT analysis, 2014-2019

	2014	2015	2016	2017	2018	2019
PGT activity						
N° clinics reporting data (with at least 1 patient treated)	22	33	35	42	46	55
N° Patients	1.596	1.799	2.247	2.459	2.653	3.625
N° Tests performed	1.695	1.894	2.242	2.483	2.447	3.314
Patient average age	36,1	36,2	36,0	36,0	36,2	36,3
N° Pregnancies	459	617	721	859	850	1.010
% Pregnancies rate per transfer	45,5	45,1	44,4	43,8	45,0	46,8
% Pregnancies lost to follow-up	1,5	1,5	2,5	3,3	1,9	18,6
N° Deliveries	383	514	582	693	694	665
N° Live born	398	529	599	705	705	677

Summary table of activity and outcome of ART procedures with gamete donation, 2014-2019

	2014	2015	2016	2017	2018	2019
ART-Donor activity						
N° clinics reporting data (with at least 1 patient treated)	17	69	83	91	101	96
N° Patients	205	2.083	4.933	5.941	6.725	7.674
N° Initiated cycles	209	2.287	5.533	6.771	7.743	8.995
N° Pregnancies	87	677	1.713	2.189	2.517	3.034
% Pregnancies lost to follow-up	26,4	15,7	13,9	15,5	13,7	12,1
N° Deliveries	49	441	1.146	1.414	1.690	2.042
N° Live born	61	532	1.338	1.610	1.895	2.190
IUI-D activity (sperm donation)						
N° clinics reporting data (with at least 1 patient treated)	13	52	65	62	73	76
N° Patients	32	379	517	487	488	514
N° Initiated cycles	37	513	714	743	691	691
N° Pregnancies	7	103	137	154	139	129
% Pregnancies rate per cycles	18,9	20,1	19,2	20,7	20,1	18,7
% Pregnancies lost to follow-up	85,7	30,1	16,8	16,9	16,5	12,4
N° Deliveries	1	61	98	110	93	90
N° Live born	1	69	119	127	107	99

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