EXECUTIVE SUMMARY for 2020

IARTR
THE ITALIAN ASSISTED REPRODUCTIVE TECHNOLOGY REGISTER

MONITORING THE ACTIVITY AND OUTCOMES OF ITALIAN ASSISTED REPRODUCTIVE TECHNOLOGY CENTRES 2020

MONITORING THE ACTIVITY AND OUTCOMES OF ITALIAN ART CENTRES IN 2020

AUTHORS

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SUMMARY OF OUTPUTS GENERATED FROM IARTR, 2020

	Patient gametes			Donor gametes		
	Fresh cycles (IVF and ICSI)	**FET**	**FO**	**oocyte donation**	**double donation**	**sperm donation**
n° of patients	32,562	16,029	977	5,887	447	1,341
n° of initiated cycles	38,727	-	-	6,738	513	1,536
n° of aspirations/thawings	34,785	19,314	1,099	-	-	-
n° of transfers	19,431	18,724	817	6,129	483	1,140
with 1 embryo (%)	*47.5*	*79.4*	*47.2*	*76.9*	*75.8*	*62.6*
with 2 embryos (%)	*45.8*	*19.7*	*47.9*	*22.7*	*24.2*	*35.3*
with 3+ embryos (%)	*6.7*	*1.0*	*4.9*	*0.4*	*0.0*	*2.1*
n° of clinical pregnancies*	5,197	6,096	210	2,310	203	446
Pregnancies per initiated cycles (%)	13.4	-	-	34.3	39.6	29.0
Pregnancies per initiated cycles without freeze-all cycles (%)	17.1					
Pregnancies per aspirations/thawings (%)	14.9	31.6	19.1			
Pregnancies per aspirations/thawings without freeze-all cycles (%)	19.6					
Pregnancies per transfers (%)	26.7	32.6	25.7	37.7	42.0	39.1
Cumulative pregnancies per initiated cycles (%)	29.7					
Pregnancies lost to follow-up (%)	12.8	6.8	11.9	12.5	14.8	13.5
Pregnancies loss per monitored pregnancy (%)	26.6	25.9	24.3	24.1	27.2	23.3
n° deliveries	3,327	4,212	140	1,534	126	296
single (%)	*89.6*	*95.6*	*90.0*	*94.4*	*92.1*	*91.6*
twin (%)	*10.3*	*5.5*	*10.0*	*5.6*	*8.6*	*8.4*
triplets or more (%)	*0.1*	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*
Deliveries per aspirations/thawings (%)	9.6	21.8	12.7	22.8	24.6	19.3
Estimated deliveries per aspirations/thawings (%)	11.0	23.4	14.5	26.0	28.8	22.3
Estimated deliveries per aspiration without freeze-all cycles (%)	14.4					
n° live born babies	3,660	4,382	153	1,608	135	320
Live born babies per initiated cycles (%)	9.5	22.7	13.9	23.9	26.3	20.8

*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, 2020

	Intrauterine Insemination		
	patient semen	**donor semen**	**IUI total**
n° of patients	8,088	374	**8,462**
n° of initiated cycles	11,679	492	**12,171**
n° of inseminations	10,496	487	**10,983**
n° of clinical pregnancies*	1,291	109	**1,400**
Pregnancies per initiated cycles (%)	11.1	22.2	**11.5**
Pregnancies per inseminations (%)	12.3	22.4	**12.7**
Pregnancies lost to follow-up (%)	11.6	15.6	**11.9**
Pregnancies loss per monitored pregnancy (%)	21.5	21.7	**21.5**
n° deliveries	896	72	**968**
single (%)	92.6	81.9	**91.8**
twin (%)	7.0	18.1	**7.9**
triplets or more (%)	0.3	0.0	**0.3**
Deliveries per initiated cycles (%)	7.7	14.6	**8.0**
Estimated deliveries per initiated cycles (%)	8.7	17.3	**9.0**
n° live born babies	963	84	**1,047**
Live born babies per initiated cycles (%)	8.2	17.1	**8.6**

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, 3rd December 2005) in implementation of article n° 11 paragraph 1 of Law 40/2004 (G.U. n. 45, 24th February 2004).

The Register collects descriptive, technical, structural and organizational information of Assisted Reproductive Techniques (ART) centres 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), different techniques performed, activity, availability, efficacy and safety of performed techniques;
- PROMOTE research and study on couple infertility causes, long-term evaluation of the children born after ART procedures; research on gametes characteristics and new cryopreservation procedures;
- MONITORE time trends in ART applications to compare different attitudes with other countries.

The Register prepares an annual epidemiological report on the ART centres' activity for the Minister of Health to illustrate to the Italian Parliament the situation of ART application.

The IARTR is linked to the European IVF Monitoring (EIM – European *In-vitro* fertilization Monitoring) Consortium, which collects data on ART from 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 till 2018.

HOW DOES IARTR WORK?

Dr Giulia Scaravelli, MD-Gynaecologist and PhD-Obstetrics and Gynaecology, is the chief manager of the IARTR. In the staff, there are many researcher with different skills: statistics, epidemiology, gynaecology, biology, psychology and informatics.

Data on efficacy, safety and outcomes of reproductive techniques, including IUI, are collected on a website in 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 time frames:

- The first phase of the collection is related to the activity conducted till pregnancies obtained in 2020 and it was carried out from May to June 2021;
- The second phase of the collection is related to the outcomes of pregnancies obtained from ART treatments started in 2020 and it was carried out from October to December 2021.

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 eventually occurred during treatments.

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.

The website represent:

- 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 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 are 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 some KPIs (Key Performance Indicators) on clinical and laboratory activity to check how they perform in respect with the national values and with the other centres of their region.
- A service for all 20 Italian Regional Authorities: they can see all the data relating to the centres operating on their territory and all the KPIs related to each centres to monitor and elaborate data on their specific activity.

The Registry's website was visited last year by approximately 85,000 users, with a daily average of about 230 hits, and is the second most visited site in the National Institute of Health Portal.

Impact of COVID-19 on ART activity in Italy 2020

Italy was the first European country in which Sars-CoV-2 infection occurred. The first case of evident transmission of Sars-CoV-2 was recorded February 20th, 2020 in Codogno (Lombardia). Since that date, the number of diagnosed cases of Covid-19 increased exponentially and Lombardia became the area most affected by the pandemic. Following the increase in numbers and in territorial distribution of the cases detected, a national lockdown was imposed in March 11th with a Decree of the Presidency of the Council of Ministers. This Decree and the subsequent" Guidelines for the remodulation of deferrable programmed activity during Covid-19 emergencies" issued by the Ministry of Health on March 16th have suspended "deferrable" and "non-urgent" hospitalizations. Also the treatments of Assisted Reproductive Technology (ART) and outpatient services were suspended. On March 17th the Italian ART National Registry, in collaboration with the National Transplant Centre, issued a technical note addressed to the ART centres, regarding the "measures to prevent the transmission of Sars-CoV-2 infection in Italy for reproductive cells and in vitro fertilization treatments". Recommendations referred to suspending new treatments, including induction of ovulation, intrauterine insemination (IUI) and in vitro fertilization, as well as cryopreservation of gametes, cancellation of embryo transfers, both in fresh cycles and in those from thawing. It also was recommended that gamete donations were temporarily suspended. The only exceptions concerned patients who were currently "in treatment" or requiring fertility preservation treatment before starting gonadotoxic therapies. Beyond these suspensions, which took place between March and May 2020, there were further slowdowns in ART activities due to the subsequent pandemic waves that occurred between October and December 2020. The measures adopted to contain the spread of the virus were aimed at limiting movements and interactions of the population, access not strictly necessary to health facilities and above all to shift health personnel to Covid-19 assistance. Consequentially ART cycles treatment in 2020 recorded a decrease of 17.6% compared to those carried out in 2019. As expected, the decrease was higher (-25.6%) for the cycles carried out by the National Health System (NHS) and for the treatments carried out in the centres that were located in the regions most affected by the virus, such as Lombardy (-32.2%). The ART activity reduction was less than expected, because the Italian centres shown great ability in adapting promptly to new needs by efficiently reorganizing the care activities as well as the clinical and laboratory management.

ART procedures (II-III level treatments) decreased by 17.6% from 2019 to 2020.

In 2020, almost 68,000 ART total cycles (II-III level techniques) were recorded. Treatments decreased overall by 17.6% from 2019 to 2020 (-14,548 cycles). The greatest decrease of 23% of cycles was found in cycles with fresh embryo transfer. The ART cycles that utilized thawed embryos

decreased by 11.4%, while the cycles that involved the use of donated gametes decreased only by 2.3%. A decrease in activities in 2020 was also recorded in cryopreservation cycles (-14.8%), with a lower impact in embryo cryopreservation (-12.9%) respect to oocyte cryopreservation (-30.8%). Intrauterine Insemination (IUI) treatment underwent a total reduction of 26.6%, showing no difference in percentage of cycles performed with or without donation (**Table I**).

Table I. Number of initiated cycles according to the type of technique used, 2019 and 2020

	2019	2020	difference (%)
ART technique			
Fresh cycle (IVF-ICSI)	50,324	38,728	-23.0
Frozen/thawed Embryo Transfer (FET)	21,796	19,314	-11.4
Frozen/thawed Oocyte (FO)	1,361	1,099	-19.3
Donor gametes	8,995	8,787	-2.3
oocytes	*6,867*	*6,738*	*-1.9*
semen	*1,596*	*1,536*	*-3.8*
oocytes and semen	*532*	*513*	*-3.6*
ART Total	**82,476**	**67,928**	**-17.6**
Cryopreserved embryos cycles	17,713	15,434	-12.9
Cryopreserved oocytes cycles	2,088	1,445	-30.8
Cryopreserved cycles total	**19,801**	**16,879**	**-14.8**
IUI			
IUI-H (husband semen)	15,895	11,679	-26.5
IUI-D (donor semen)	691	492	-28.8
IUI Total	**16,586**	**12,171**	**-26.6**

Greatest reduction in activity recorded in public centres and private accredited by NHS centres.

ART treatments performed by the NHS showed a reduction equals to 25.6% (from 51,974 cycles in 2019 to 38,669 cycles in 2020) compared to the decrease of only 4.1% for treatments performed in private centres (**Table II**). The large reduction observed in the treatments carried out by the NHS could be explained both by the impact that the pandemic had on the entire NHS, and by the slower resumption of activities that occurred in public facilities. In addition, in these structures, generally, there has been a greater utilization of all the doctors for Covid-19 assistance and a greater limitation of access to the structures.

Table II. Number of cycles initiated with ART techniques according to centres setting, 2019 and 2020

centres setting	2019	2020	difference (%)
public and private accreditate by the NHS	51,974	38,669	-25.6
private	30,502	29,259	-4.1
ART total	**82,476**	**67,928**	**-17.6**

Since 2006, ART cycles performed by the NHS have always been the majority, and up to 2019 these cycles represented 64% of all cycles carried out in Italy, while in 2020 this percentage dropped to 57% (**Figure A**).

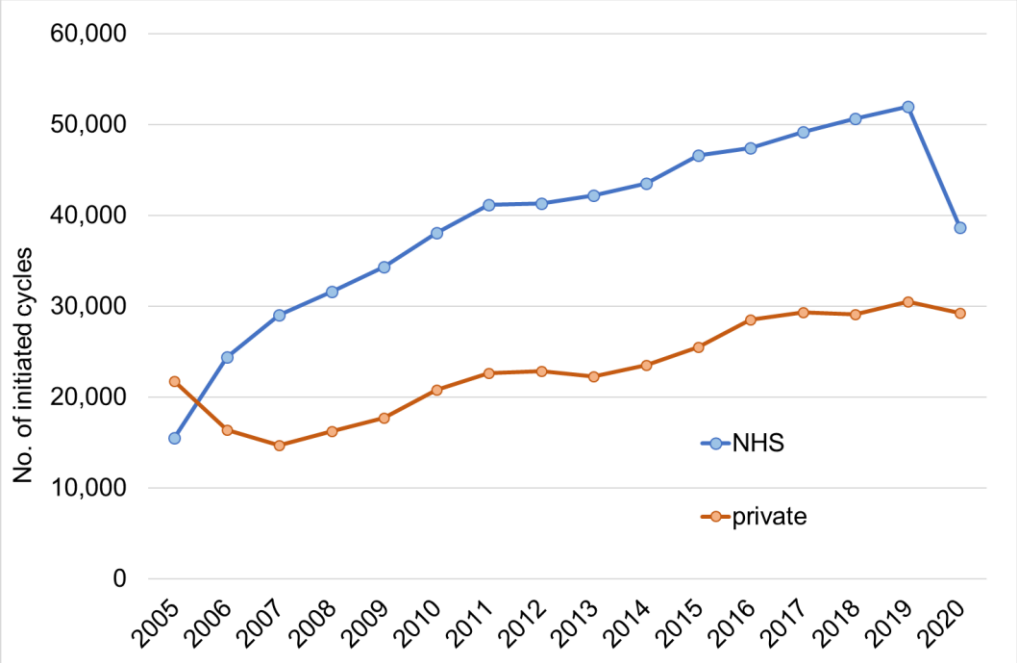


Figure A. Number of ART initiated cycles according to the centres setting, 2005-2020

Greater reduction of ART cycles in patients less than 40 years old

Following the recommendations made in 2020 there was a greater reduction in ART activities among patients less than 40 years old (-20.3%) compared to those over 40 years old (-17.3%). In particular, there was the greatest reduction (-21.6%) in patients aged between 35 and 39 years, and the least reduction (-12.1%) in patients older than 42 years (**Table III**).

Table III. Number of ART initiated cycles using own gametes, according to the age groups of the patients, 2019 and 2020

Female age group in non-donor ART treatment	2019	2020	difference (%)
≤ 34	22,511	18,333	-18.6
35-39	28,788	22,562	-21.6
40-42	16,016	12,824	-19.9
≥ 43	6,166	5,421	-12.1
Non-donor ART total	**73,481**	**59,140**	**-19.5**

Looking at the reductions by age and centres setting, we observe a greater reduction in activities for all age groups for treatments charged to the NHS compared to those carried out privately (**Table IV**). The cycles offered privately on younger patients in 2020 increased about 1%, showing that in this age group a part of the demand not provided by public centres was accepted by private ones.

Table IV. Difference in activities (2019-2020) of ART treatments with own gametes according to the age groups of the patients and centres settings.

	difference (%)	
Female age group in non-donor ART treatment	Public and private accreditate by the NHS centres	Private centres
≤ 34	-27.8	+0.9
35-39	-27.8	-8.0
40-42	-27.7	-1.7
≥ 43	-19.7	-2.9
Non-donor ART total	**-27.2**	**-3.4**

Impact of Covid-19 on ART activities changed at regional level.

The impact of Covid-19 on ART activities in Italy in 2020 compared to 2019 varies greatly depending on Italian regions and geographical areas. As expected, the greatest decrease in activities was observed in the centres located in the North-West regions (-30.0%), followed by those located in the North-East regions (-15.0%), i.e. the areas which were most affected by the spread of the virus. The region with the greatest reduction in activities was Lombardia, whose centres performed 7,337 fewer cycles than in 2019, equal to a 32.2% reduction in activities (**Table V**).

Table V. Number of ART initiated cycles according to the region and geographical area in which the centres reside, 2019 and 2020

Regions and geographic area	2019	2020	difference (%)
Piemonte	4,750	3,843	-19.1
Valle d'Aosta	458	316	-31.0
Lombardia	22,758	15,421	-32.2
Liguria	974	691	-29.1
North West	***28,940***	***20,271***	**-30.0**
P.A. Bolzano	2,010	1,517	-24.5
P.A. Trento	796	611	-23.2
Veneto	4,722	4,328	-8.3
Friuli Venezia Giulia	1,557	1,450	-6.9
Emilia Romagna	6,963	5,741	-17.5
North East	***16,048***	***13,647***	**-15.0**
Toscana	9,826	9,273	-5.6
Umbria	509	453	-11.0
Marche	189	168	-11.1
Lazio	8,770	8,117	-7.4
Center	***19,294***	***18,011***	**-6.6**
Abruzzo	1,050	648	-38.3
Molise	79	73	-7.6
Campania	7,150	6,573	-8.1
Puglia	3,155	2,734	-13.3
Basilicata	444	254	-42.8
Calabria	924	1,192	+29.0
Sicilia	4,397	3,963	-9.9
Sardegna	995	562	-43.5
South and islands	***18,194***	***15,999***	**-12.1**
Italy	***82,476***	**67,928**	**-17.6**

1. ACCESS AND UTILIZATION OF ART SERVICES IN ITALY, 2020

1.1. Access to ART service

Figure 1 shows the regional distribution of the 197 ART authorized centres in 2020, but only 185 performed at least one ART cycle.

The largest number of ART centres is concentrated in Northern Italy (80 centres the 40.6% of the total) and in the Southern area (70 centres the 35.5% of the total), irrespective of the amount of their activity.

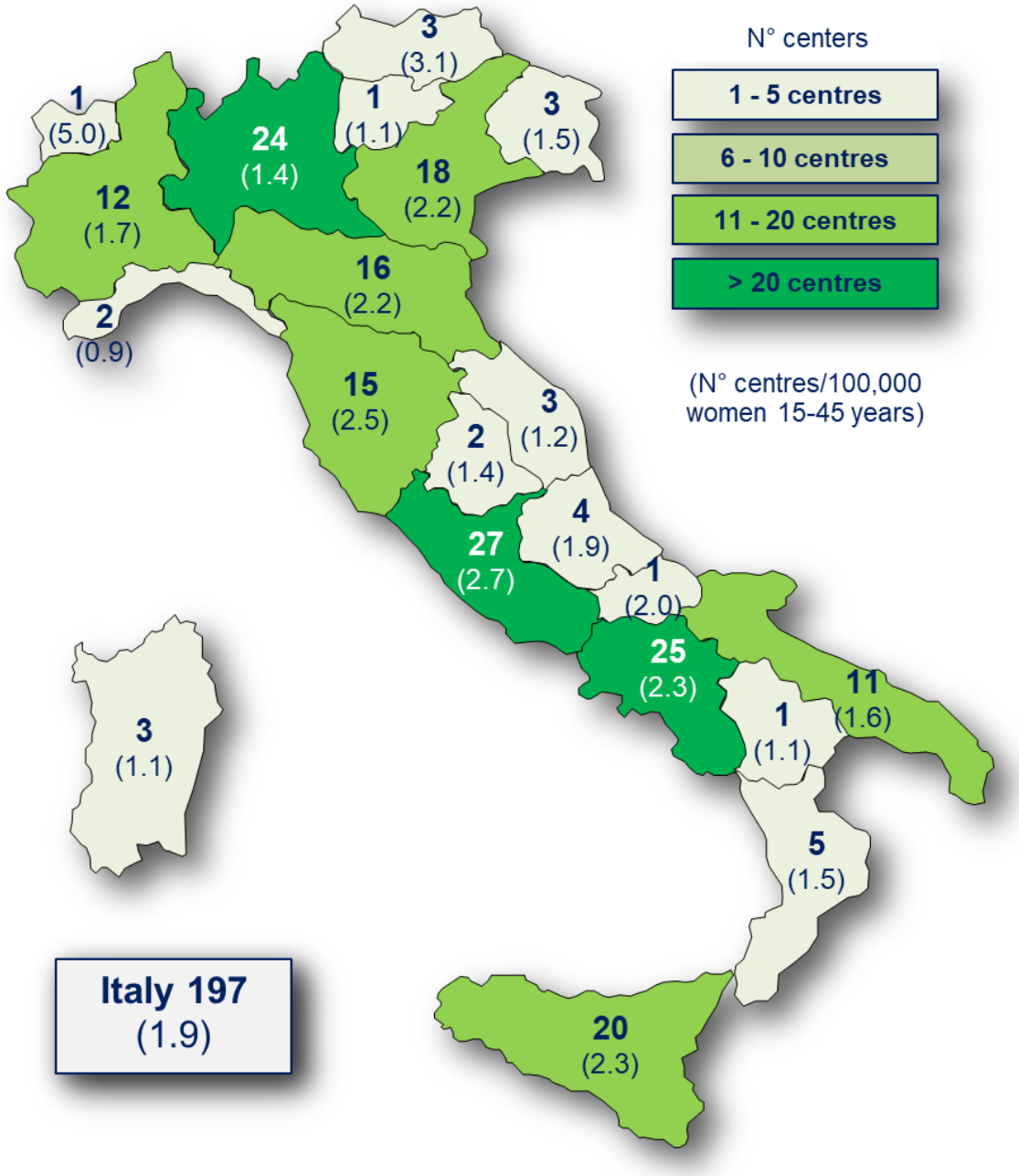


Figure 1. Regional distribution of the ART authorized centres and in brackets the number of centres per 100,000 women of reproductive age (15-45 years)*, 2020
*Average resident population in Italy in 2020: source ISTAT.

Table 1 shows the geographical distribution of ART centres according to the type of services offered. Overall, the number of active centres was 197 in 2020: 90 (45.7%) operating within the National Health Service (public and private) and 107 (54.3%) 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 79.5%, while in the Central and in the South of Italy, there were mainly private facilities (59.6% and 71.4%, respectively).

Table 1. ART authorized centres distribution by region and type of service, 2020

Region and geographical area	ART centres	Art centres 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	24	12	50.0	10	41.7	2	8.3
Liguria	2	2	100	0	0	0	0.0
North-West	***39***	***20***	***51.3***	***11***	***28.2***	***8***	***20.5***
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	27	5	18.5	1	3.7	21	77.8
Central	***47***	***13***	***27.7***	***6***	***12.8***	***28***	***59.6***
Abruzzo	4	2	50.0	0	0	2	50.0
Molise	1	0	0	0	0	1	100
Campania	25	6	24.0	0	0	19	76.0
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	20	5	25.0	0	0	15	75.0
Sardegna	3	3	100	0	0	0	0
South and islands	***70***	***20***	***28.6***	***0***	***0.0***	***50***	***71.4***
Italy	**197**	**72**	**36.5**	**18**	**9.1**	**107**	**54.3**

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 481 cycles (+75.5%) and of 3,842 cycles (+143.2%), respectively. The latest European data available refers to the activity of year 2018[1].

The number of started cycles per million inhabitants (calculated only for the 21 countries that have reported data of 100% of the centres) was 1,402 cycles in Europe versus 1,297 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 (2005-2020) and in Europe (2005-2018)

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	1,402	7,341	7,581
2019	1,341	-	7,697	-
2020	1,117	-	6,525	-

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 3,702 cycles offered in Puglia region to 14,904 cycles provided in Toscana region. More in general, only seven regions in Northern and central area have numbers above the national average (6,525 cycles), while all the Southern regions have numbers below the average.

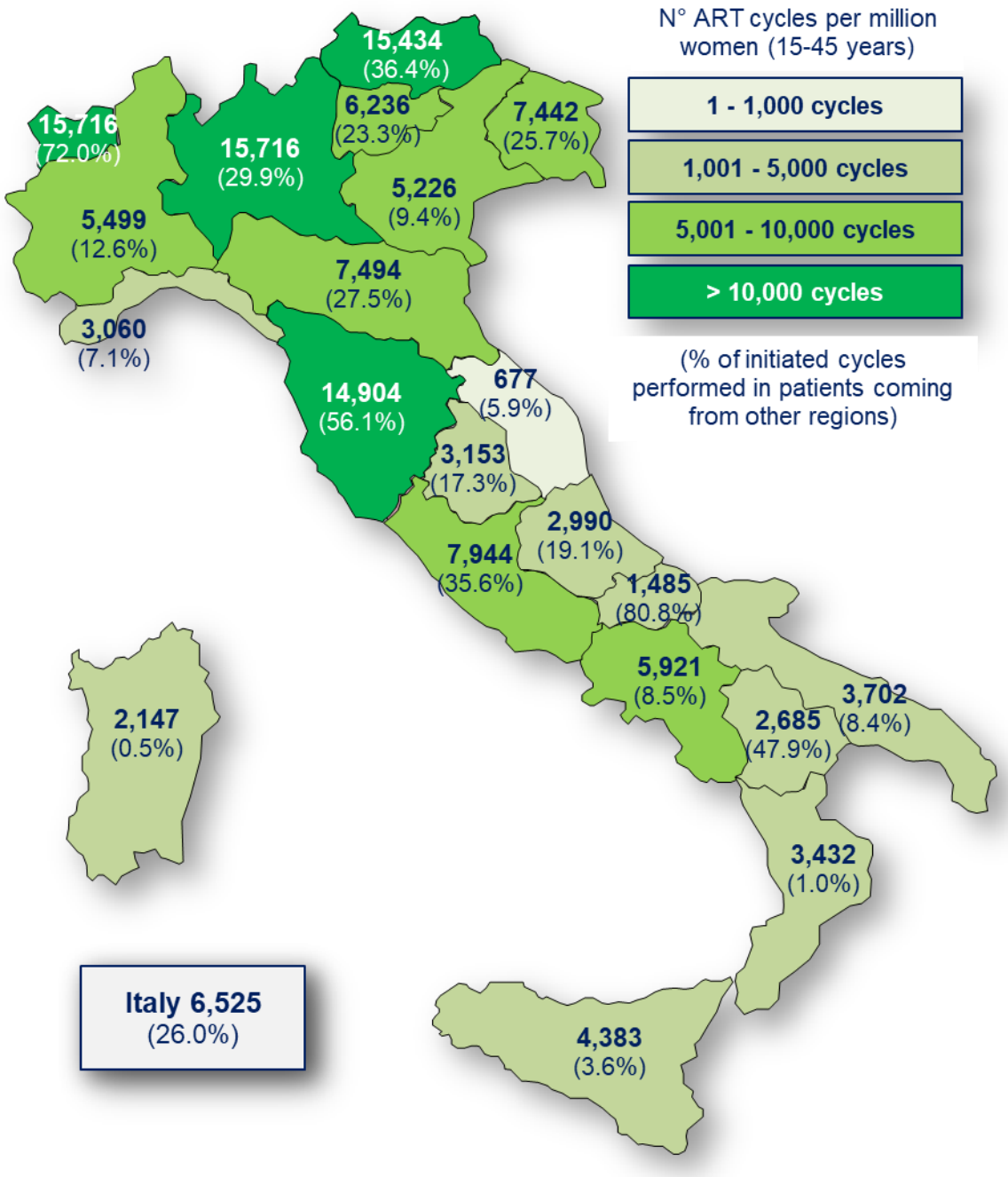


Figure 2. Regional distribution of the number of initiated ART cycles per million women of reproductive age (15-45 years)* and in brackets the percentage of initiated cycles performed in patients coming from other regions, 2020.

*Average resident population in Italy in 2020: source ISTAT.

Since its establishment, IARTR collected data on 183,932 infants, of which 154,016 born from ART and 29,916 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 2020 10,258 babies are born alive from ART procedures in Italy that represent the 2.5% of the national babies born in the country in the same year. These values are an expression of the application of the ART in the different regions, but they do not faithfully reflect the number of births because the cycles carried out also include the treatments performed on patients coming from outside the region (for example in Toscana region, 56.1% of cycles are performed on patients coming from other regions).

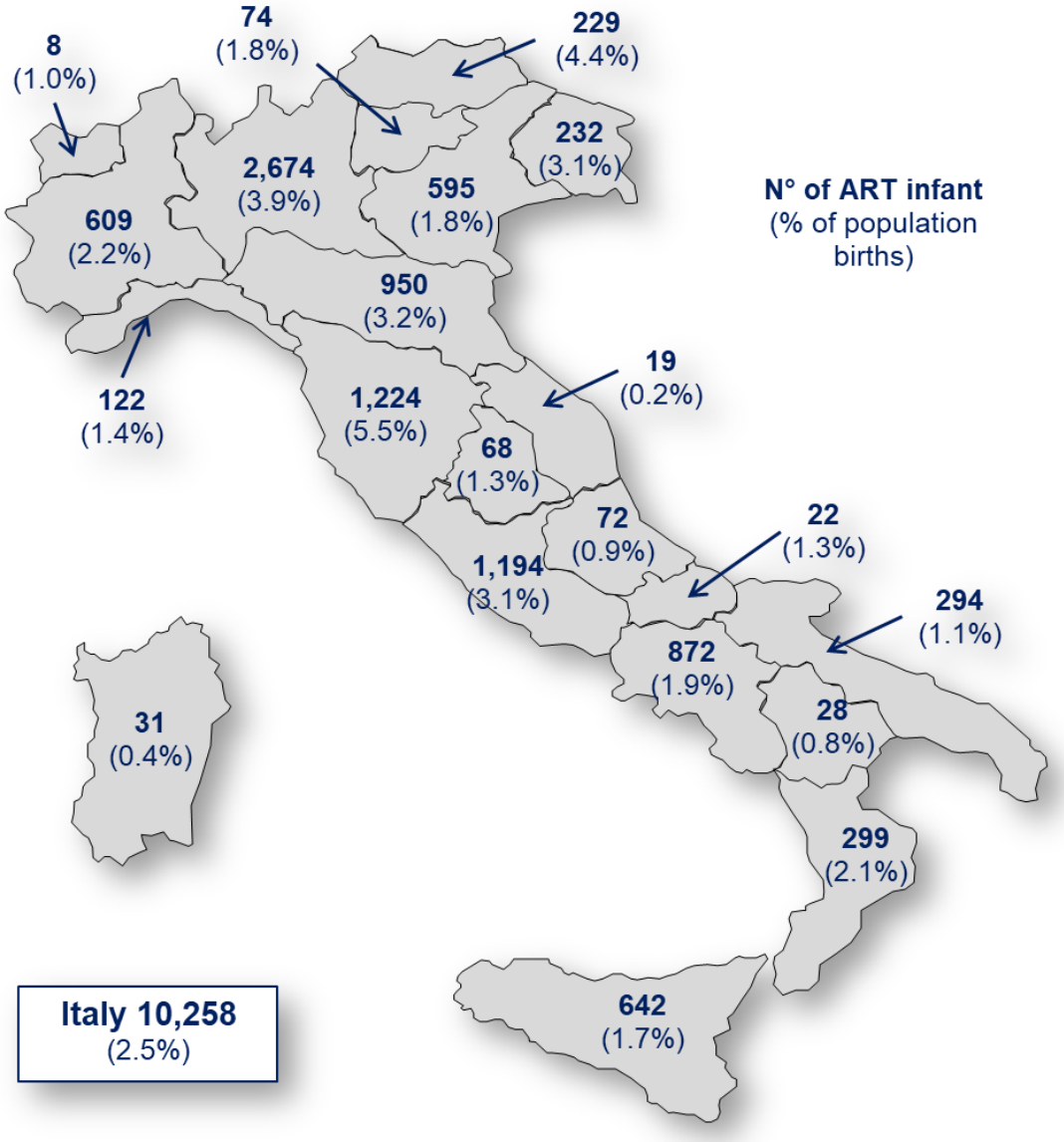


Figure 3. Regional distribution of the babies born in 2020 from ART cycles, also with donation, and the percentages in relation to the annual number of children born*.
*Number of live babies born in Italy in 2020: source ISTAT.

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, with a slight decline in 2020 due to the impact of the CoVID-19 pandemic on ART activity

The value of 2.5% for ART treatments in 2020 is lower to that of the European average in 2018 (3.0%) and in other similar country such as the United Kingdom (2.9%). However, it should be considered that part of this increase is due to a strong contraction in births in Italy.

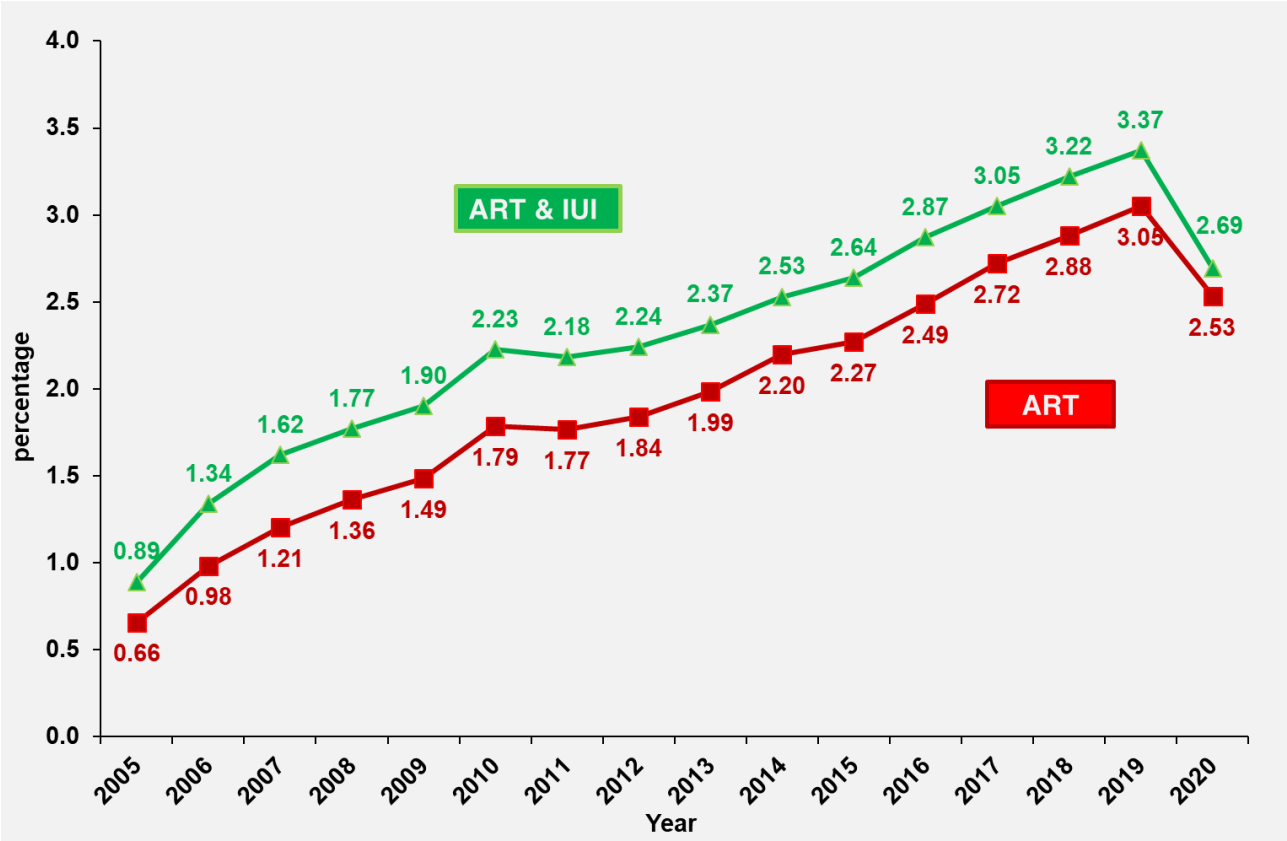


Figure 4. Time-trends of the percentage of live babies born after ART also with donation cycles and after ART & IUI with donation cycles in relation to the annual national number of children born in Italy, 2005-2020.

2. EFFICACY OF ART IN 2020 AND TIME TRENDS FROM 2005 TO 2020

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 67,927 ART cycle performed in Italy in 2020 was made with a fresh procedure with partner gametes (57%). Then 28.4% of the cycles were performed with a FET, 1.6% with a FO and the remaining 12.9% (8,787 cycles) with a gamete donation (see **Figure 5**).

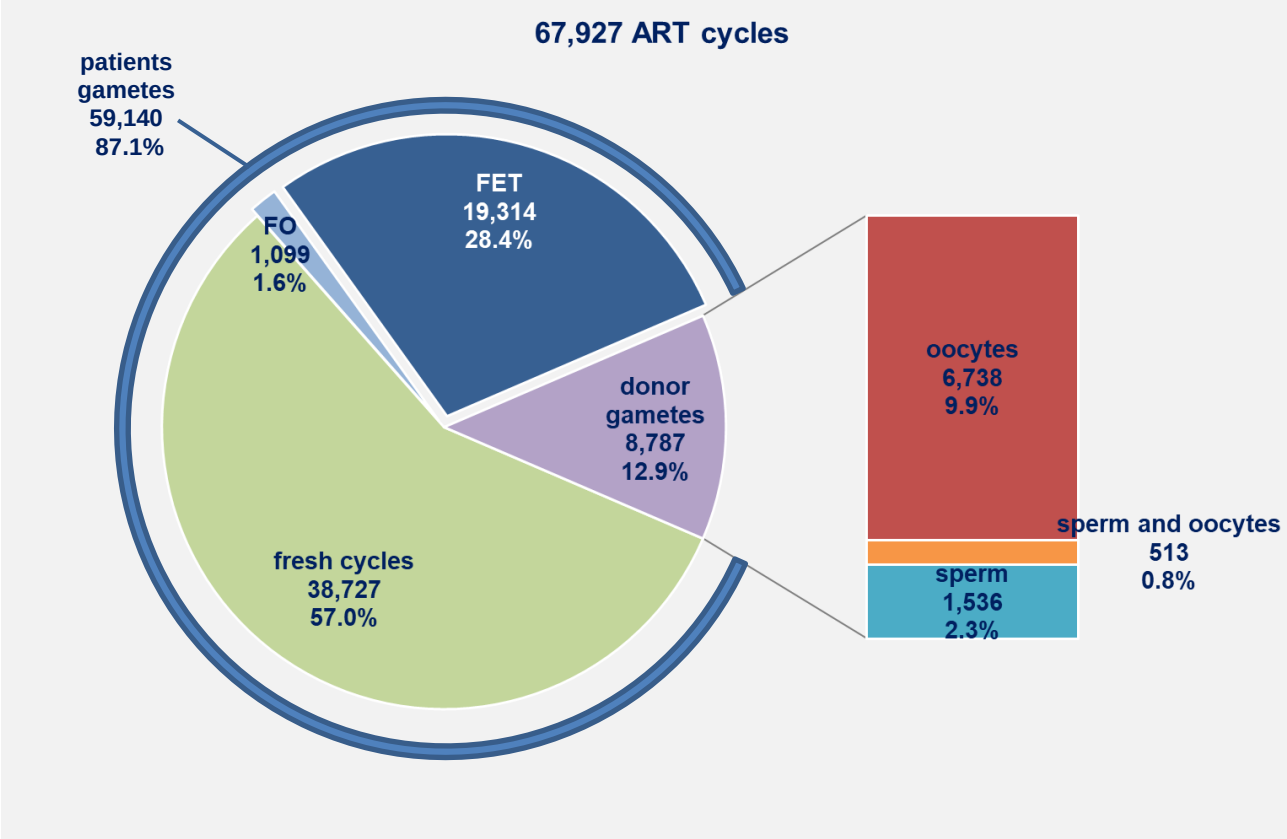


Figure 5. ART cycles performed in 2020.

2.1.2. How did the types of ART treatments 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 technologies, and therefore the probability of obtaining a pregnancy. **Figure 6** shows the percentage of ART transfers performed in 2020 according to women's age. As expected, ART treatment with their own oocytes are the most applied treatment in women from ≤34 years till 42 years of age, while after 42 years of age the cycles performed with donor gametes reach 57.6% of application. In younger patients, FET was the most commonly used ART procedure.

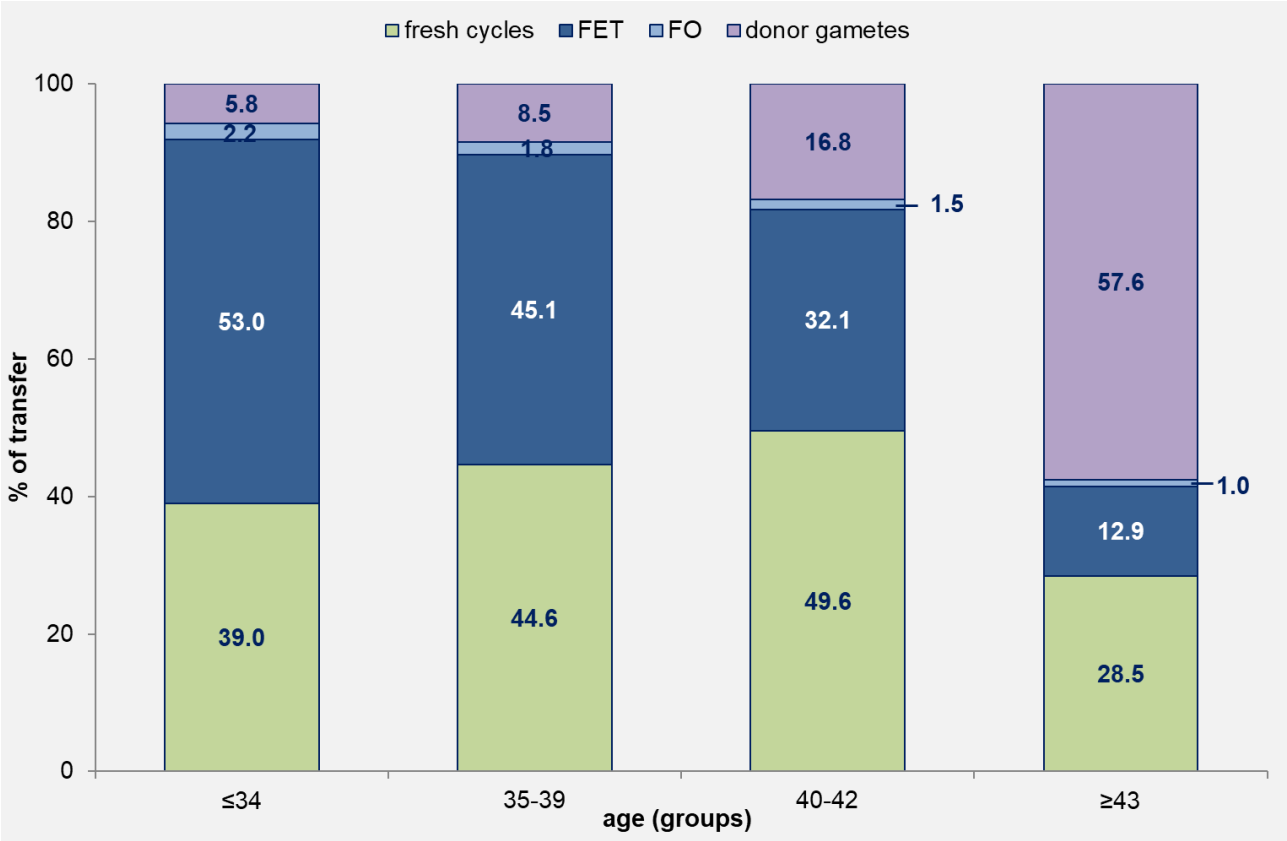


Figure 6. Types of ART procedure performed by female patients' age groups, 2020.

2.2. ART non-donor cycles

2.2.1. What are the causes of infertility of couples in ART treatment using fresh cycles in 2020?

- ***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].

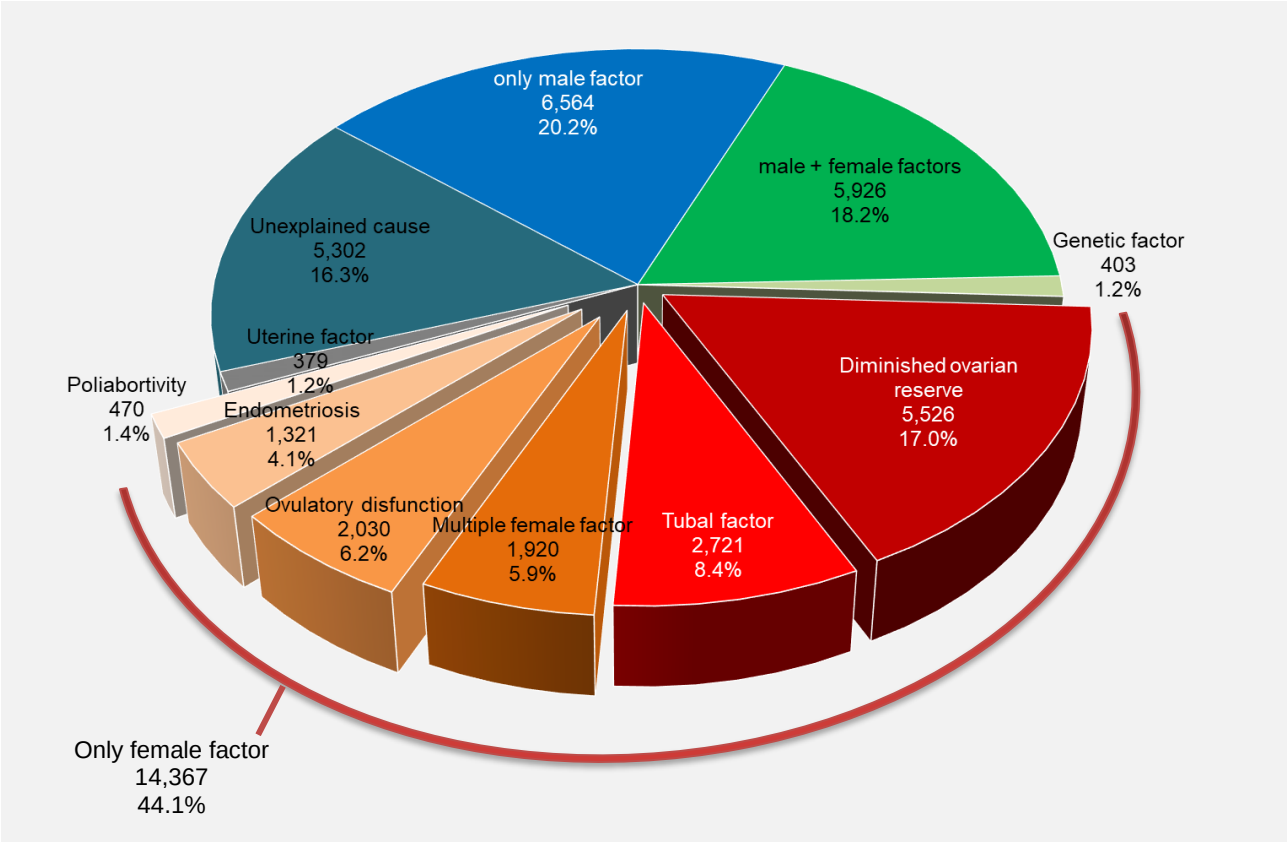


Figure 7. Causes of infertility of couples in ART treatment using fresh cycle, 2020

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 2020. Of the 38,782 cycles, 89.8% resulted in an egg retrieval, 50.2% in an embryo transfer, and 21.1% were estimated 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 19). Among the outcomes, we must also consider the 12.8% of pregnancies lost to follow-up and the 26.6% of monitored pregnancies that do not reach the delivery due to miscarriages or ectopic pregnancies (see **Figure 12**).

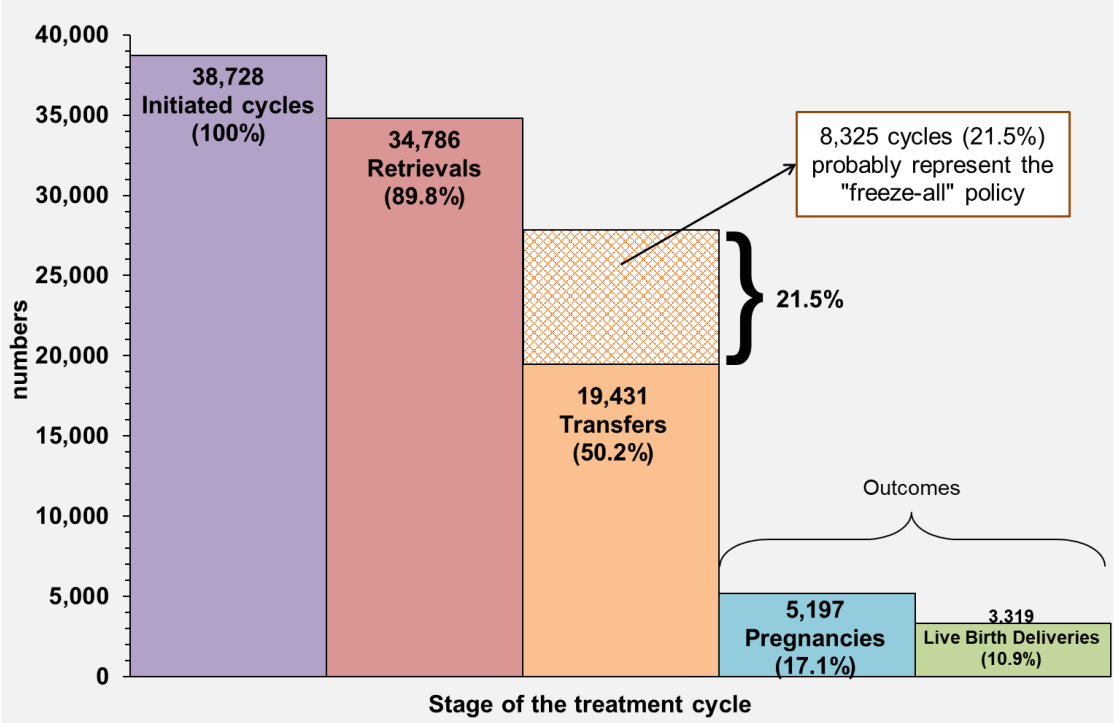


Figure 8. Outcomes of ART using fresh cycles by stage of the treatment cycle, 2020.

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 treatments). 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 62.3% in 2019 to 67.5% in 2020 in younger patients and from 50.7% to 53.7% in older ones.

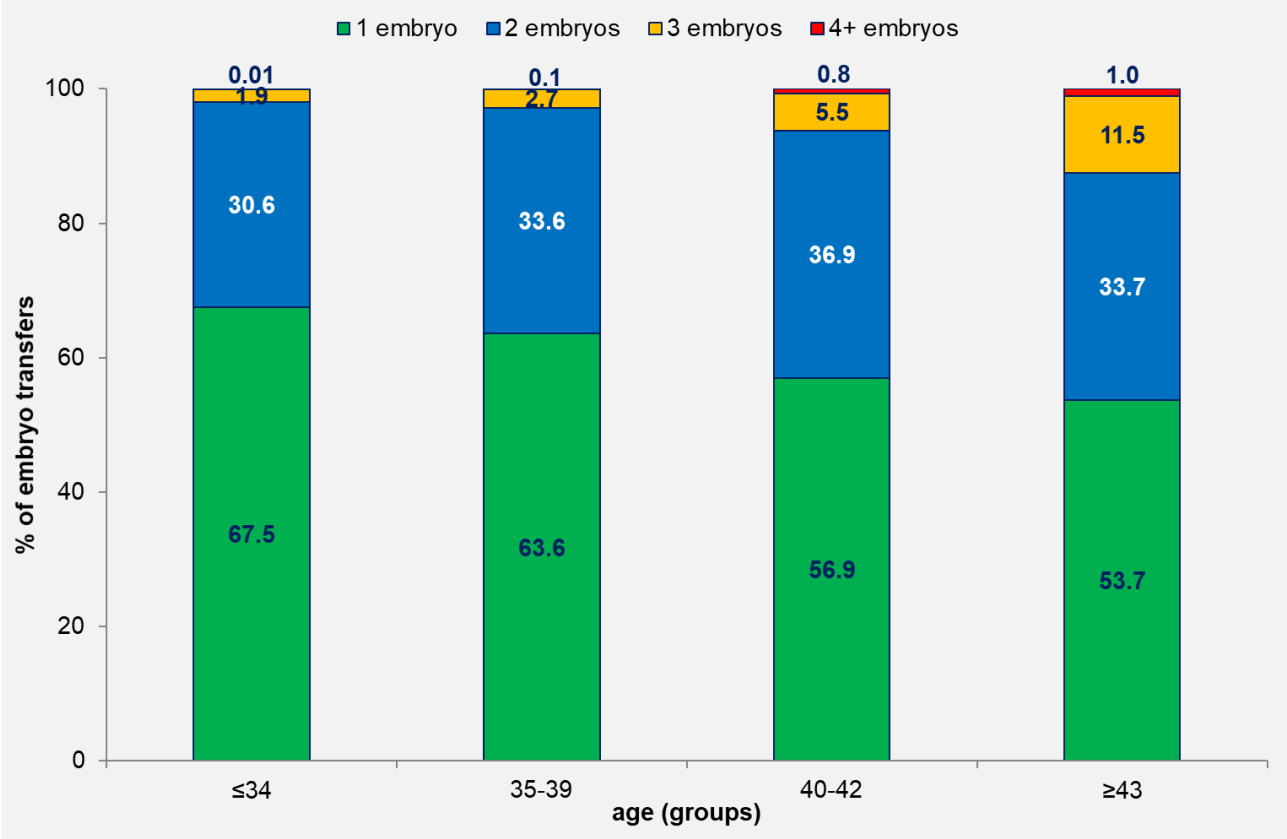


Figure 9. Distribution of embryo transfers according to the number of embryos transferred (ART total) by female patients' age groups, 2020.

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 treatments. Overall, the rates after FET (Frozen Embryo Transfer) were higher than others treatments, 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].

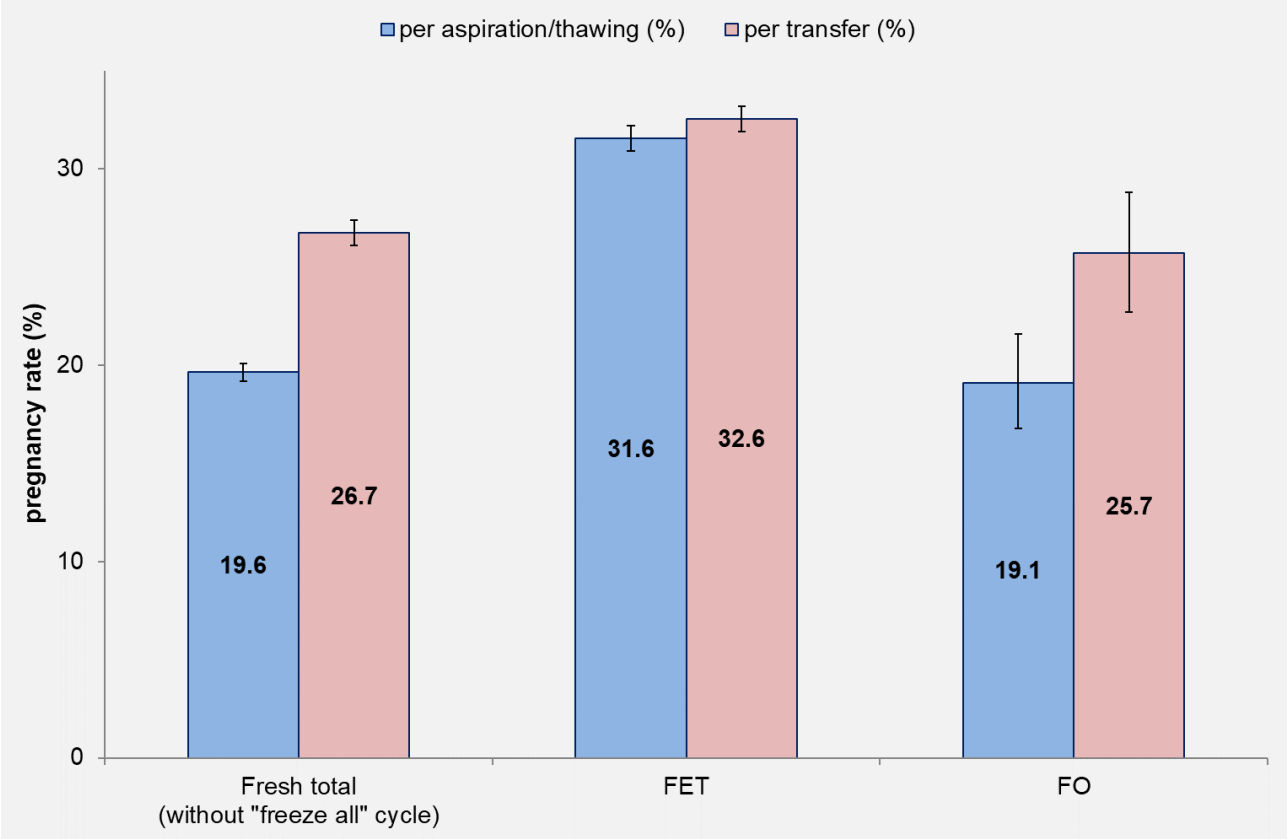


Figure 10. Pregnancy rates per aspiration/thawing and per transfer according to different ART procedures, 2020.

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 doubles 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.

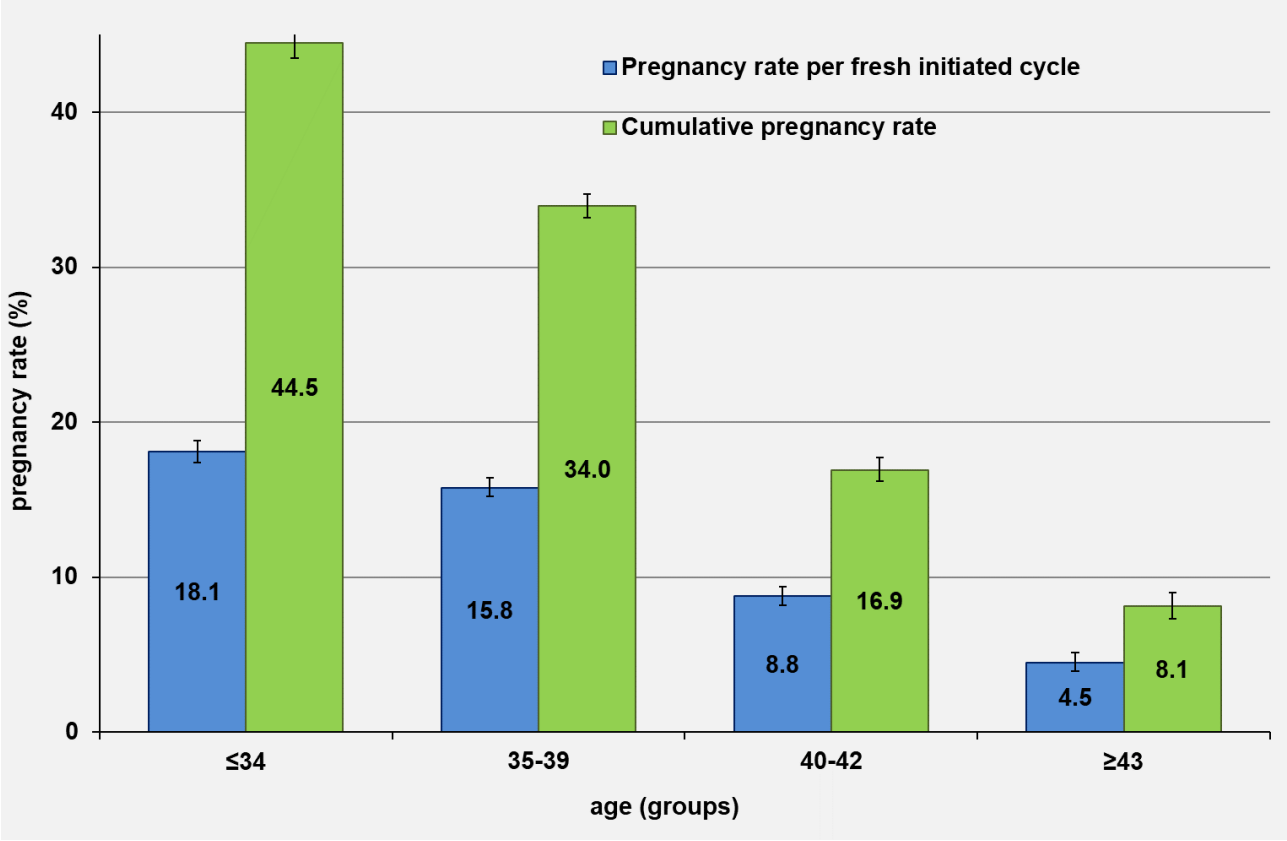


Figure 11. Pregnancy rates per aspiration and cumulative pregnancy rates per aspiration, by female patients’ age groups, 2020.

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 2020. Of the 4,534 monitored pregnancies issued from fresh cycles 73.4% resulted in a delivery, of which 7.6% were multiple, and the 24.8% in a miscarriage. In FET and FO procedures the 74.1 % and 75.7%, respectively, resulted in a delivery. The percentages of multiple deliveries in FET (3.3%) are significantly lower then in fresh cycles, while the percentage of miscarriages shows no significantly difference both in FET (25.2%) and FOR (22.7%) when compared with fresh one.

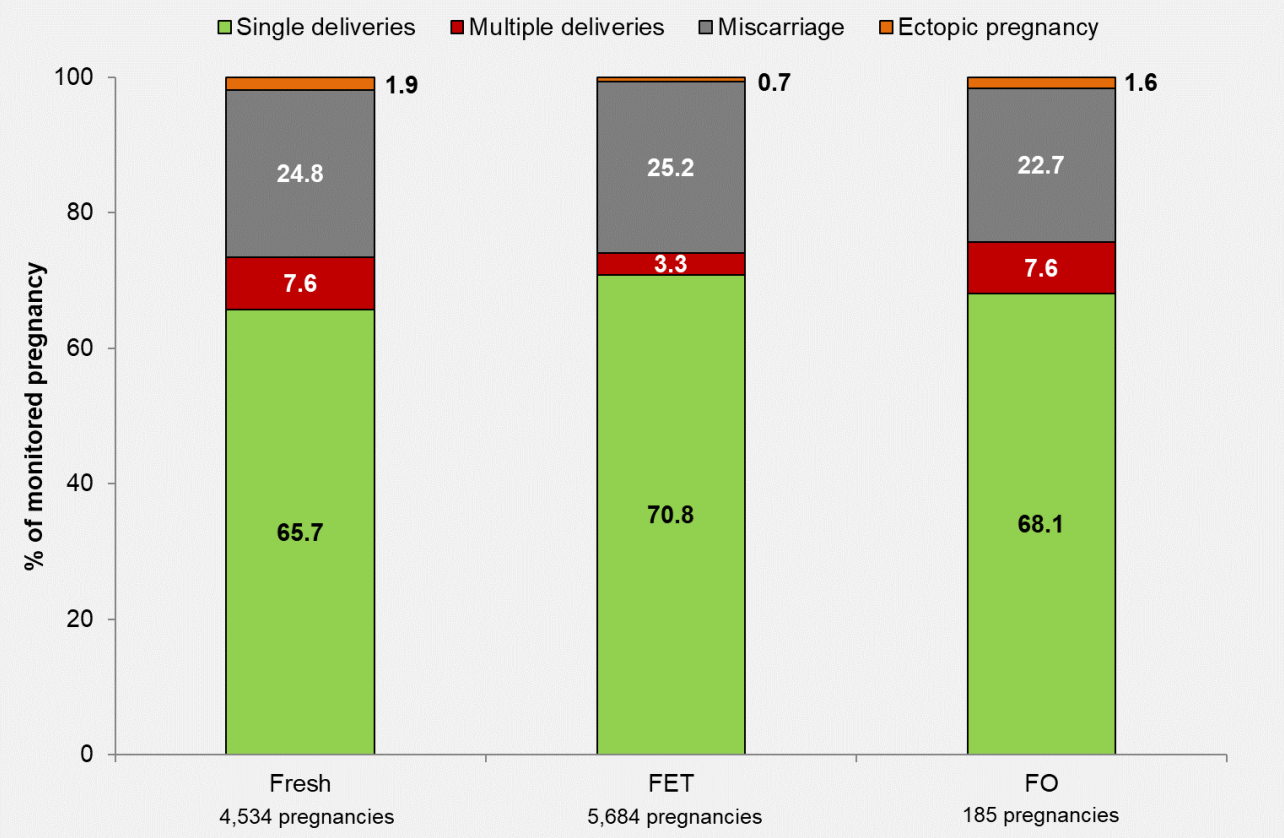
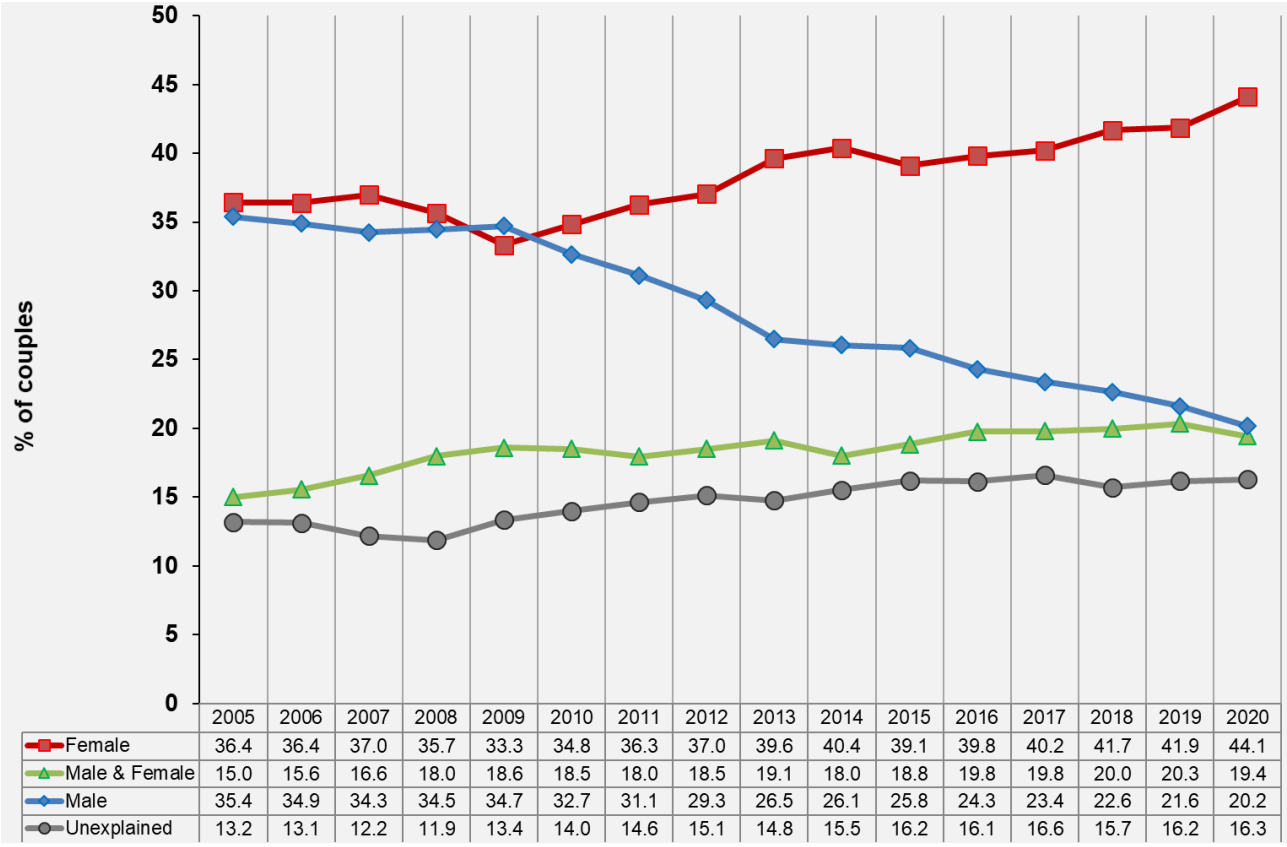


Figure 12. Comparison of the outcomes of monitored clinical pregnancies that resulted from ART non-donor procedures, 2020.

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 2020. 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 63.6% in 2020.



	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
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	44.1
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	19.4
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	20.2
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	16.3

Figure 13. Time-trends of gender distributions of infertility causes among patients who had ART using fresh cycle, 2005-2020.

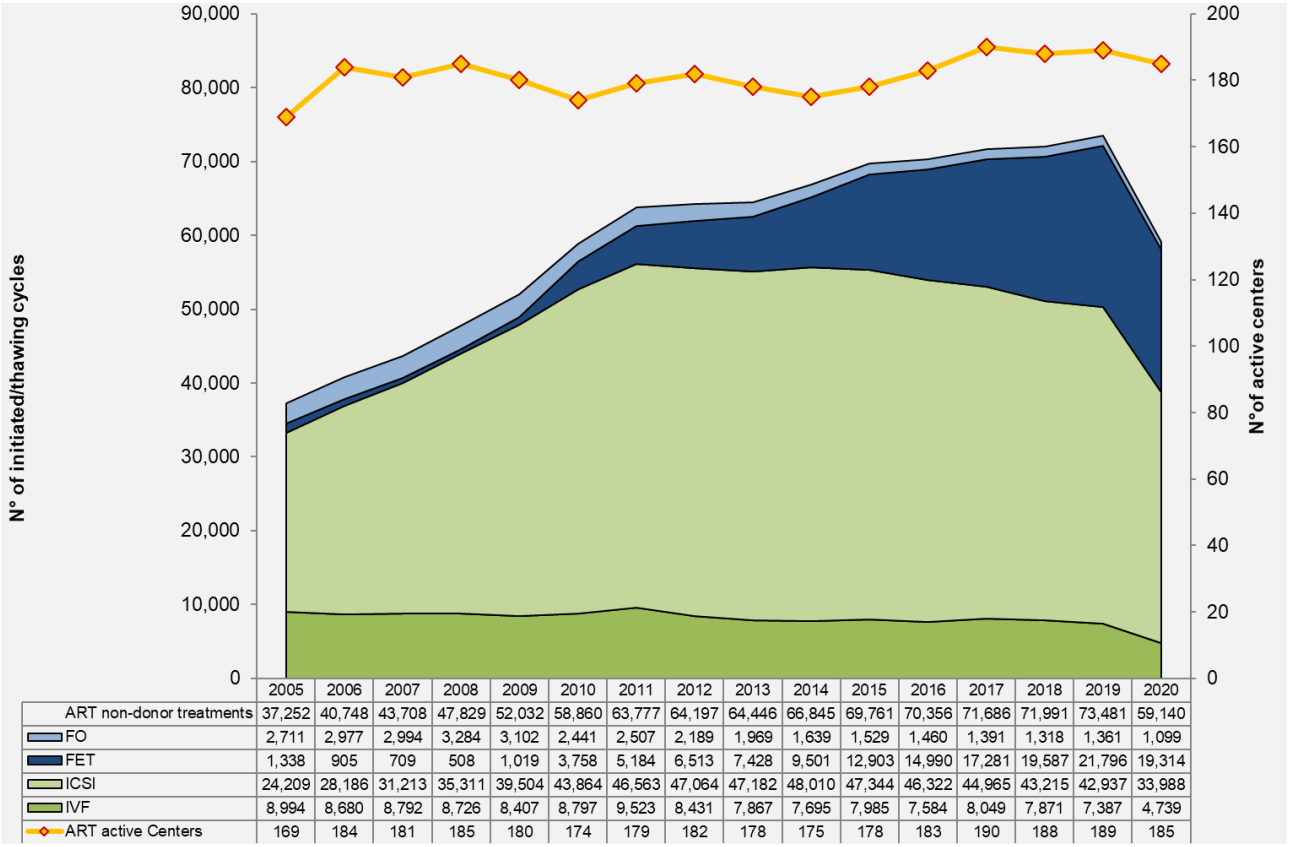
2.2.8. Is the use of ART-non donor procedures change over time?

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 2020.

Despite the decrease in activity due to the covid-19 pandemic, the numbers of initiated cycles in 2020 were higher than the level of 2010, and the average increase of 4% for each year 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 and 33,988 in 2020, while IVF cycles decreased from 8,994 to 7,387 and 4,739 respectively. In addition, FET thawing increased from 1,338 to 21,796 and 19,314, while FO procedures decreased from 2,711 to 1,361 and 1,099.

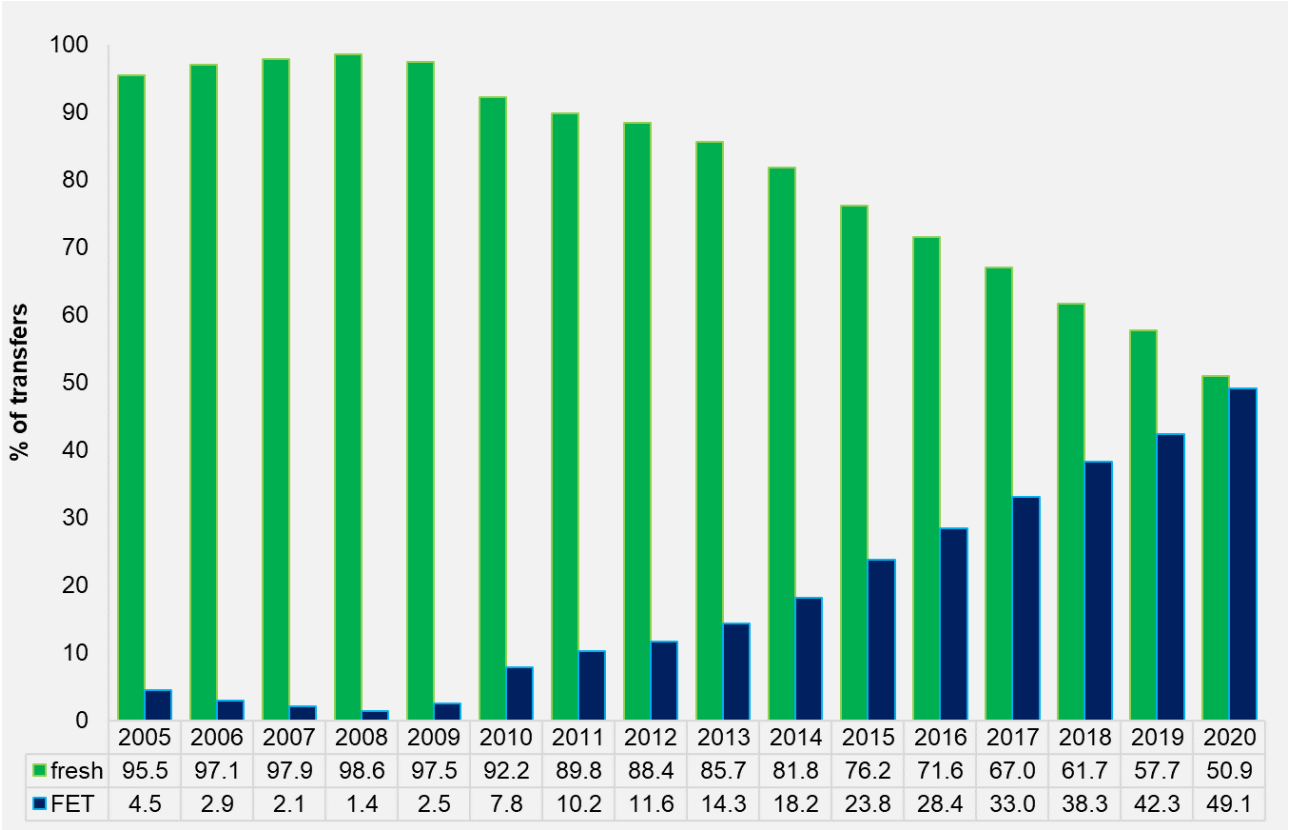


	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
ART non-donor treatments	37,252	40,748	43,708	47,829	52,032	58,860	63,777	64,197	64,446	66,845	69,761	70,356	71,686	71,991	73,481	59,140
FO	2,711	2,977	2,994	3,284	3,102	2,441	2,507	2,189	1,969	1,639	1,529	1,460	1,391	1,318	1,361	1,099
FET	1,338	905	709	508	1,019	3,758	5,184	6,513	7,428	9,501	12,903	14,990	17,281	19,587	21,796	19,314
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	44,965	43,215	42,937	33,988
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	8,049	7,871	7,387	4,739
ART active Centers	169	184	181	185	180	174	179	182	178	175	178	183	190	188	189	185

Figure 14. Time-trends of ART non-donor initiated cycles/thawings and number of active ART centres, 2005–2020.

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 transfer performed highly increased from 2.5% in 2009 to 49.1% in 2020. In comparison with some European countries[1], such as France, Spain and Sweden, for 2018 last European data available, Italy still shows the lowest number of FET cycles performed, but they are steadily increasing.



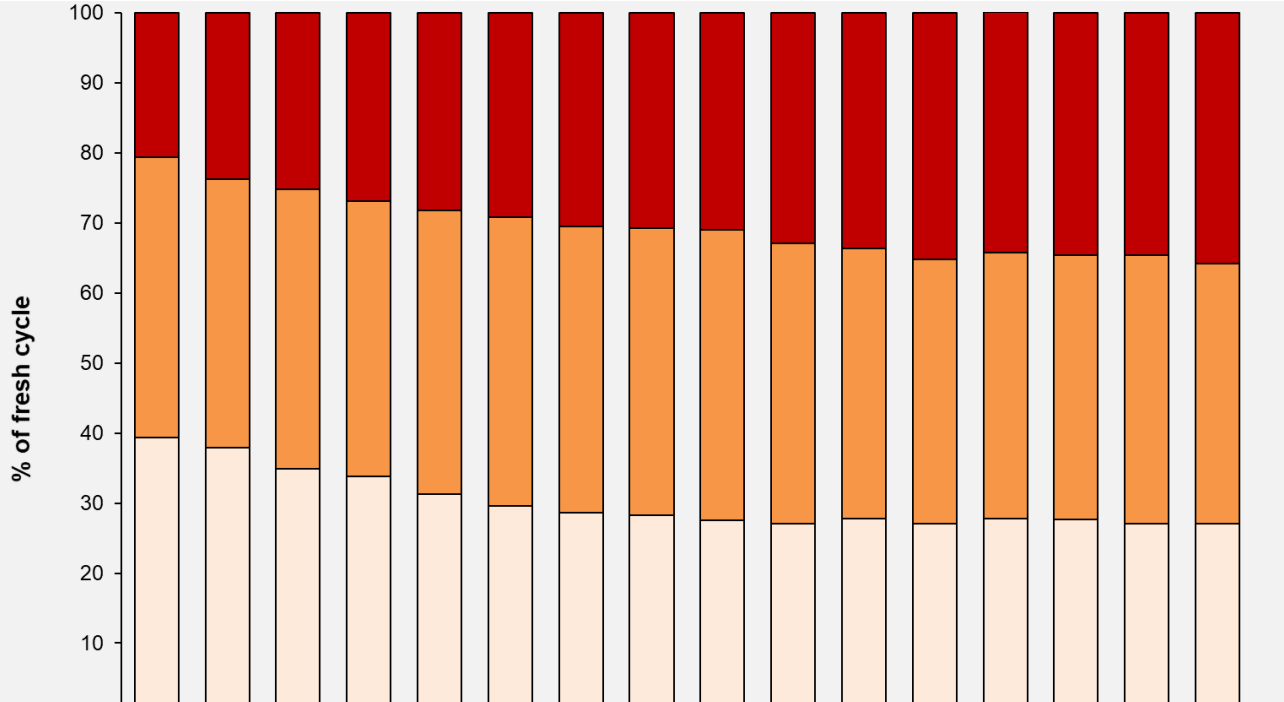
	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
fresh	95.5	97.1	97.9	98.6	97.5	92.2	89.8	88.4	85.7	81.8	76.2	71.6	67.0	61.7	57.7	50.9
FET	4.5	2.9	2.1	1.4	2.5	7.8	10.2	11.6	14.3	18.2	23.8	28.4	33.0	38.3	42.3	49.1

Figure 15. Time-trends of proportion of fresh versus frozen transfer (2005-2020).

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 2020.

For women older than 40 the percentage of fresh cycles performed increased from 20.7% in 2005 to 35.8% in 2020, while the percentage of fresh cycles performed in women ≤34 years old decreased from 39.3% in 2005 to 27.1% in 2020. Overall, the mean age of women who had fresh cycles increase over time from 35.3 to 36.9 years.

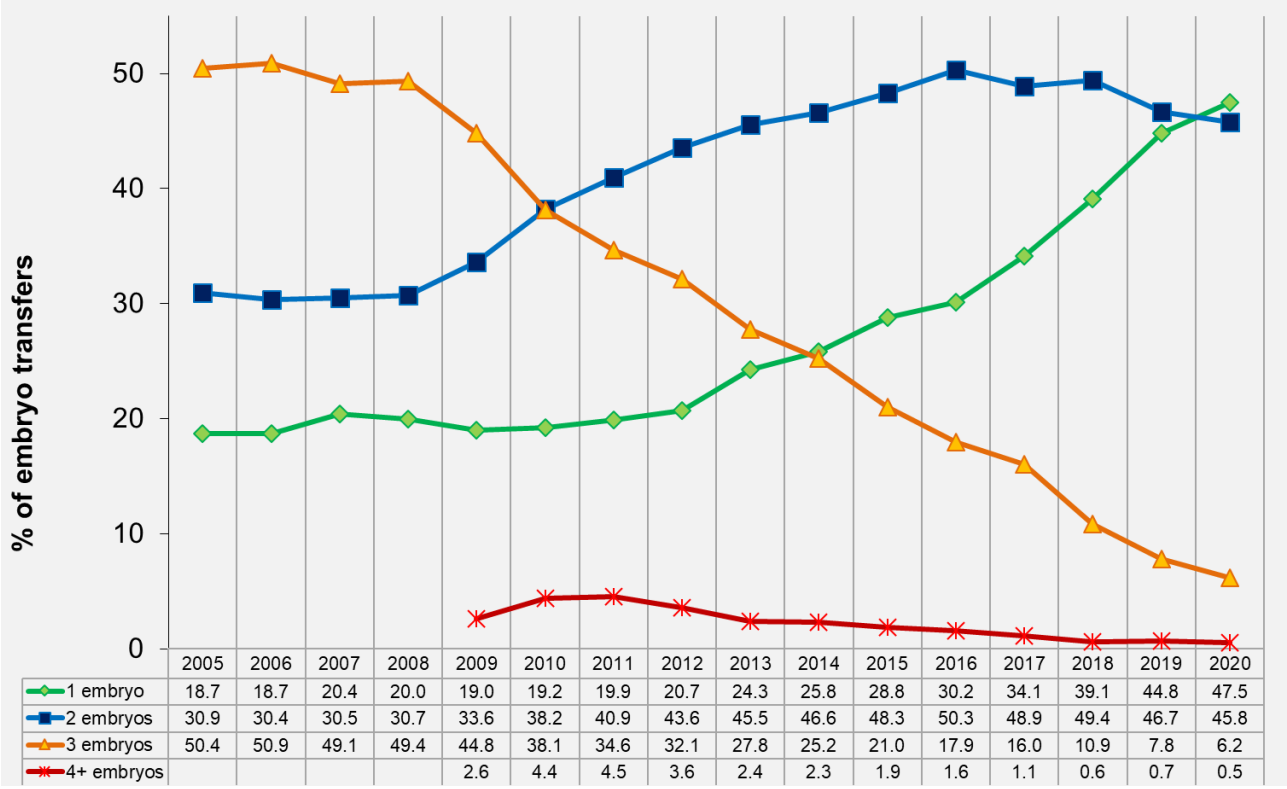


	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
mean age	35.3	35.5	35.8	35.9	36.2	36.3	36.5	36.5	36.6	36.7	36.7	36.8	36.7	36.7	36.8	36.9
≥40	20.7	23.8	25.2	26.8	28.2	29.2	30.5	30.7	31.0	32.9	33.7	35.2	34.3	34.6	34.6	35.8
35-39	40.0	38.3	39.8	39.4	40.5	41.2	40.9	41.0	41.5	40.0	38.5	37.8	38.0	37.8	38.3	37.1
≤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	27.1

Figure 16. Time-trends of fresh initiated cycle's distributions by age classes of female patients, 2005-2020.

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 2020, the single embryo transfers increased from 18.7% to 47.5% 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 6.2% in 2020. 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 0.5% in 2020, after having been quite stable during time. The average number of embryos transferred decreased from 2.3 embryos per transfer in 2005 to 1.6 in 2020. This trend is similar in most European countries[1].



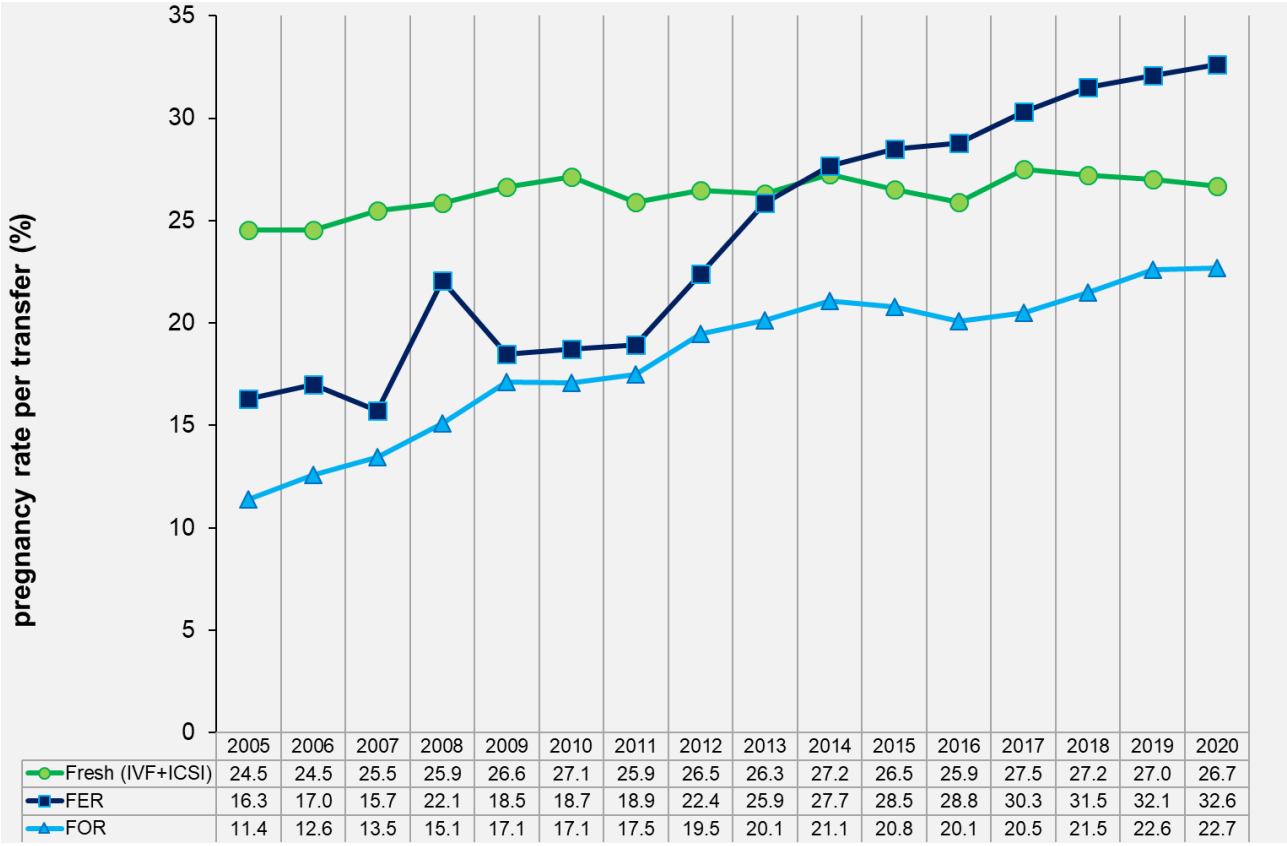
	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
1 embryo	18.7	18.7	20.4	20.0	19.0	19.2	19.9	20.7	24.3	25.8	28.8	30.2	34.1	39.1	44.8	47.5
2 embryos	30.9	30.4	30.5	30.7	33.6	38.2	40.9	43.6	45.5	46.6	48.3	50.3	48.9	49.4	46.7	45.8
3 embryos	50.4	50.9	49.1	49.4	44.8	38.1	34.6	32.1	27.8	25.2	21.0	17.9	16.0	10.9	7.8	6.2
4+ embryos					2.6	4.4	4.5	3.6	2.4	2.3	1.9	1.6	1.1	0.6	0.7	0.5

Figure 17. Time-trends of transfer by number of embryos transferred, 2005-2020.

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 32.6% in 2020, those with fresh oocytes slightly increased from 24.5% to 26.7%, and those with frozen oocytes doubled from 11.4% to 22.7%. 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.

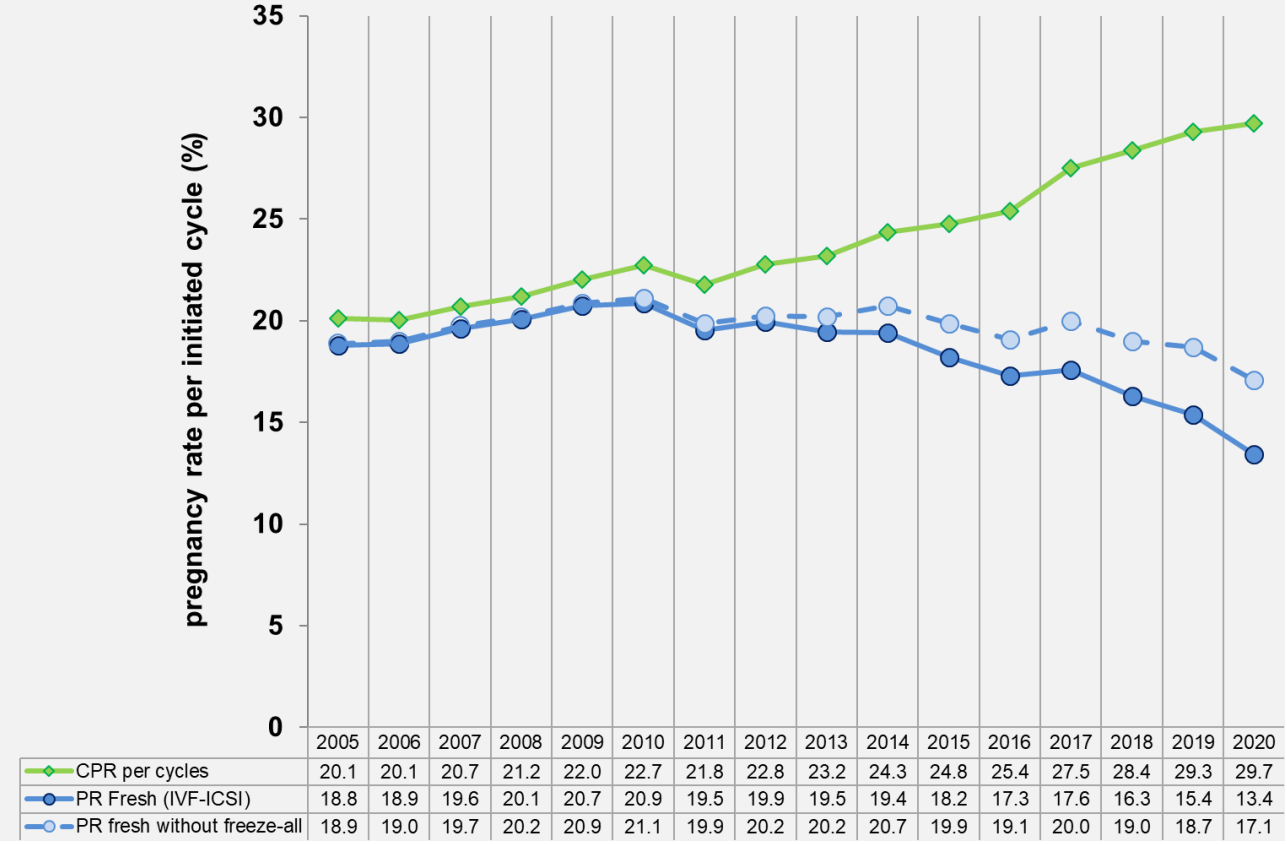


	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Fresh (IVF+ICSI)	24.5	24.5	25.5	25.9	26.6	27.1	25.9	26.5	26.3	27.2	26.5	25.9	27.5	27.2	27.0	26.7
FER	16.3	17.0	15.7	22.1	18.5	18.7	18.9	22.4	25.9	27.7	28.5	28.8	30.3	31.5	32.1	32.6
FOR	11.4	12.6	13.5	15.1	17.1	17.1	17.5	19.5	20.1	21.1	20.8	20.1	20.5	21.5	22.6	22.7

Figure 18. Time-trends of pregnancy rate per transfer for fresh, thawed embryos (FET) and thawed/warmed oocytes cycles (FO), 2005-2020.

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 +73.7% in 2020. 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. The declining trend of the pregnancy rate in fresh cycle is similar to that shown by the European data[1].

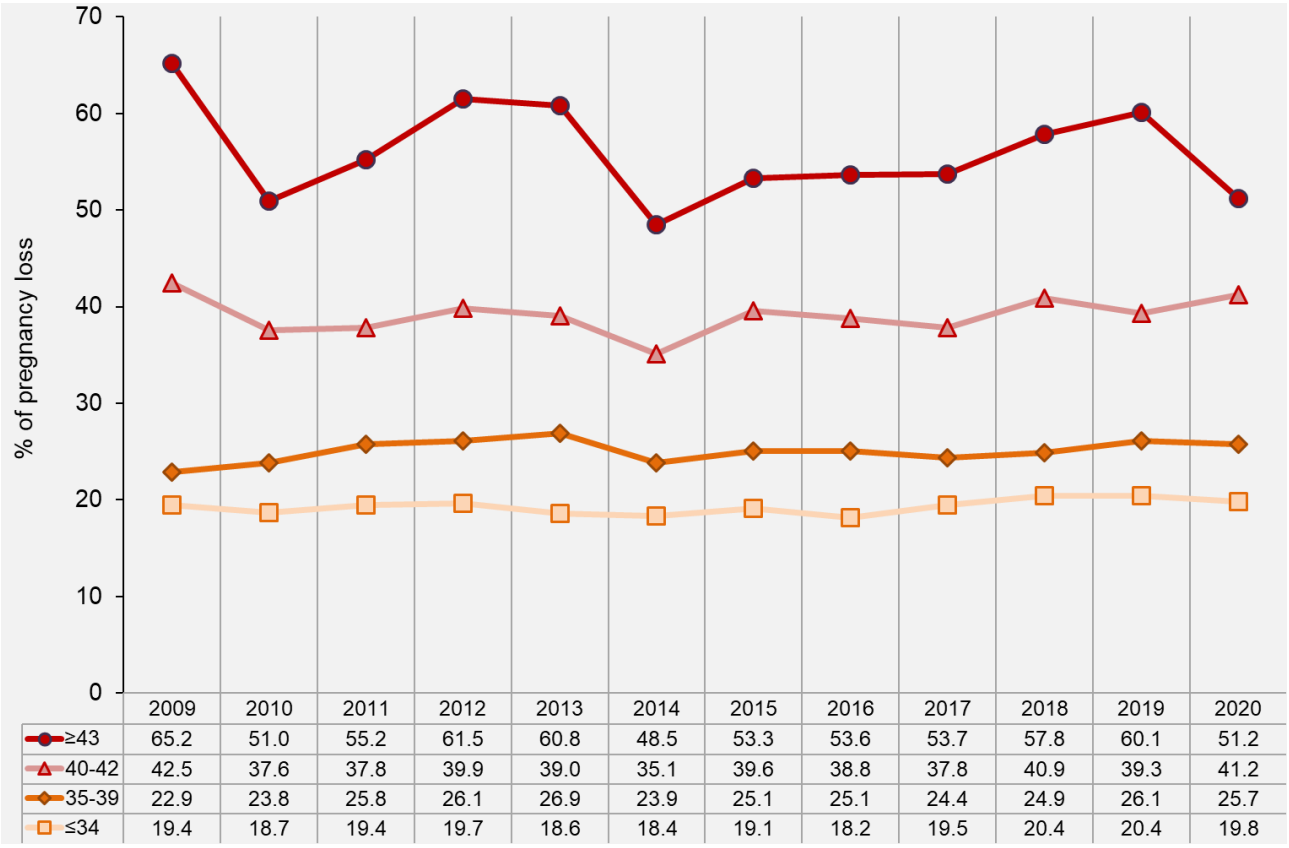


	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
CPR per cycles	20.1	20.1	20.7	21.2	22.0	22.7	21.8	22.8	23.2	24.3	24.8	25.4	27.5	28.4	29.3	29.7
PR Fresh (IVF-ICSI)	18.8	18.9	19.6	20.1	20.7	20.9	19.5	19.9	19.5	19.4	18.2	17.3	17.6	16.3	15.4	13.4
PR fresh without freeze-all	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	17.1

Figure 19. Time-trends of pregnancy rate per initiated cycle for fresh and cumulative pregnancy rate per initiated cycle, 2005-2020.

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 of missed pregnancies have an unstable trend for patients over 42 years due to small numbers, while they are quite stable in the remaining age groups.



	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
≥43	65.2	51.0	55.2	61.5	60.8	48.5	53.3	53.6	53.7	57.8	60.1	51.2
40-42	42.5	37.6	37.8	39.9	39.0	35.1	39.6	38.8	37.8	40.9	39.3	41.2
35-39	22.9	23.8	25.8	26.1	26.9	23.9	25.1	25.1	24.4	24.9	26.1	25.7
≤34	19.4	18.7	19.4	19.7	18.6	18.4	19.1	18.2	19.5	20.4	20.4	19.8

Figure 20. Time-trends of percentages of total pregnancy loss using ART non-donor cycles by female age groups, 2009-2020.

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 61) for more detailed data on activity and outcomes regarding ART donor cycles in 2020.

2.3.1. Which gametes were used in ART donor cycles in 2020?

Figure 21 shows the distribution of the types of the 8,787 ART cycles using donor gametes applied in Italy in 2020 and the origin of the donated frozen oocytes. In about 82.5% of ART donor cycles, fresh or frozen donated eggs were used, in 17.5% of cycles there is a donation of male gametes only. In the oocyte donation cycles, almost all cycles (98.1%) were performed with oocytes obtained from a foreign bank.

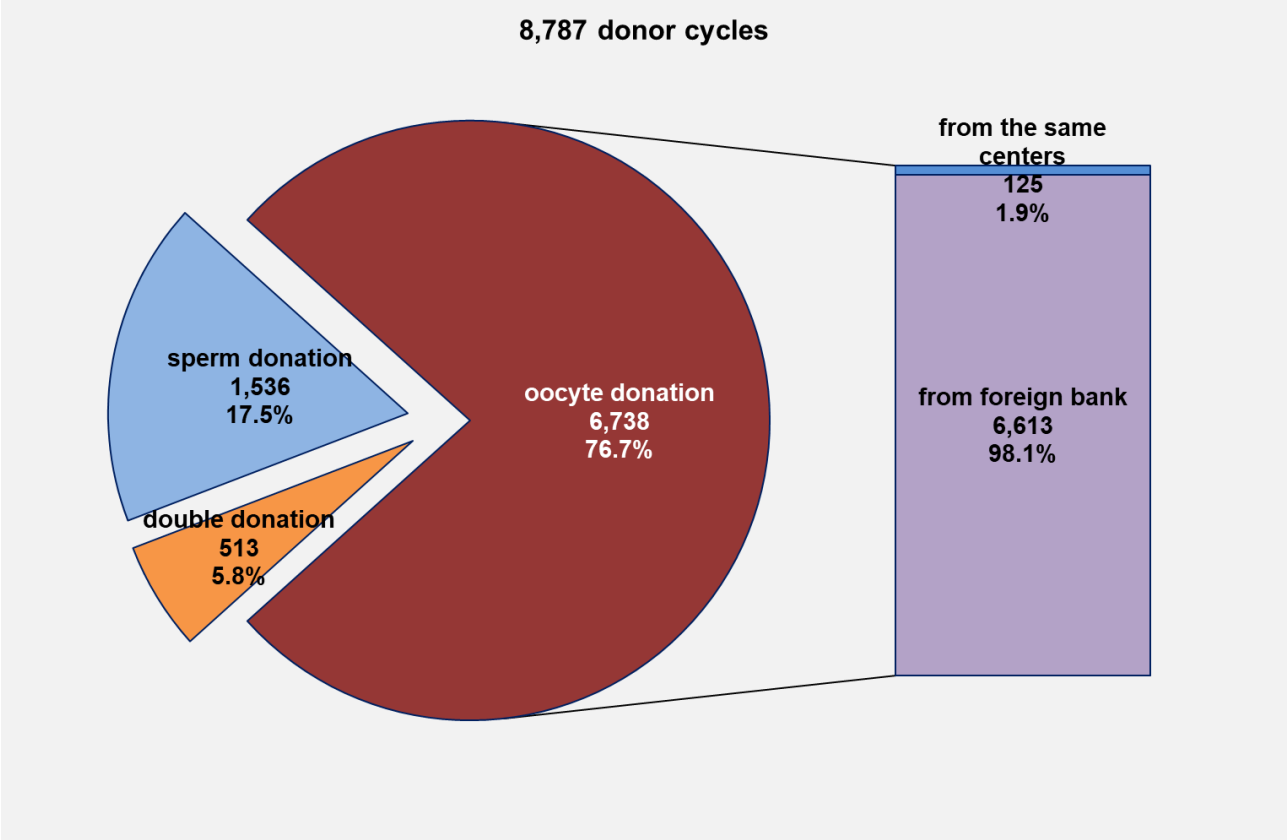


Figure 21. Distribution of all ART cycles using donor gametes and origin of the oocytes for the donor oocyte cycles, 2020. Total cycles = 8,787.

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 (63.6%): the using of donated oocyte growing considerably with the age of the recipient women.

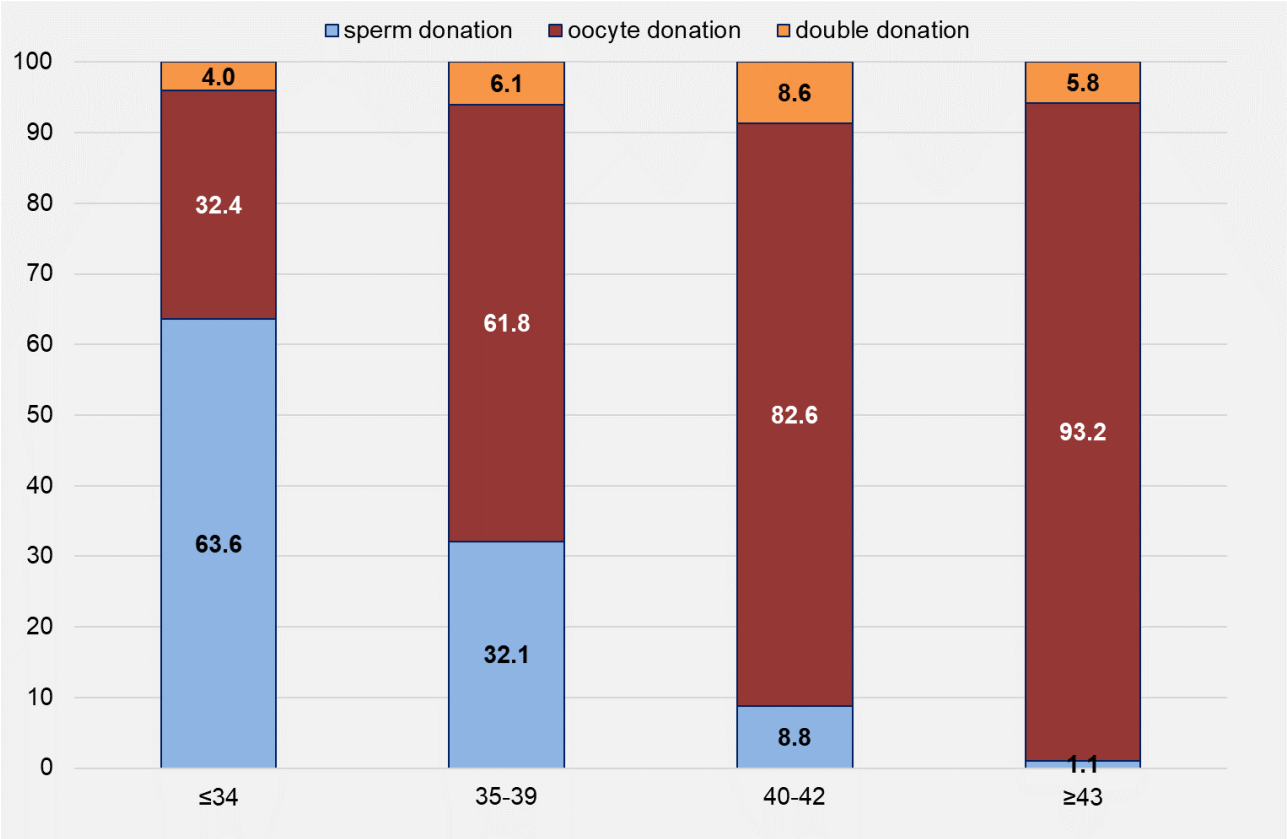


Figure 22. Distribution of donated gametes by recipient female age groups, 2020.

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.

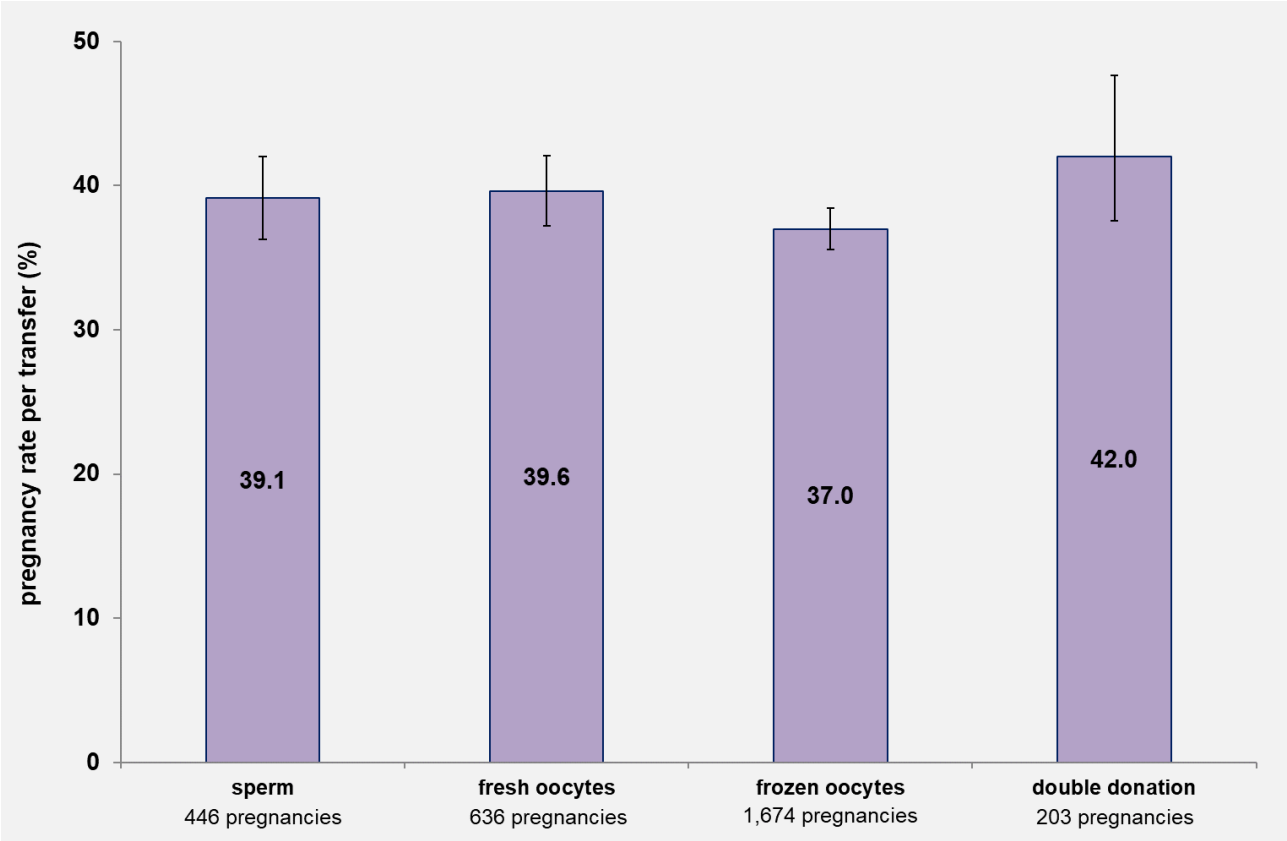


Figure 23. Distribution of pregnancy rate per transfer using donor gametes, 2020.

2.3.3. What were the outcomes of pregnancies obtained in ART donor cycles in 2020?

Figure 24 shows the outcomes of the 2,581 monitored clinical pregnancies obtained from the application of ART donor procedures in Italy in 2020. Of the 368 monitored pregnancies obtained from sperm donation 6.5% resulted in multiple deliveries and 23.1% in an abortion. In frozen donor oocyte cycles the multiple deliveries rate (4.9%) and percentage of abortion (24.7%) were significantly higher than in fresh donor oocyte ones (2.5% and 20.0% repectively). 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.

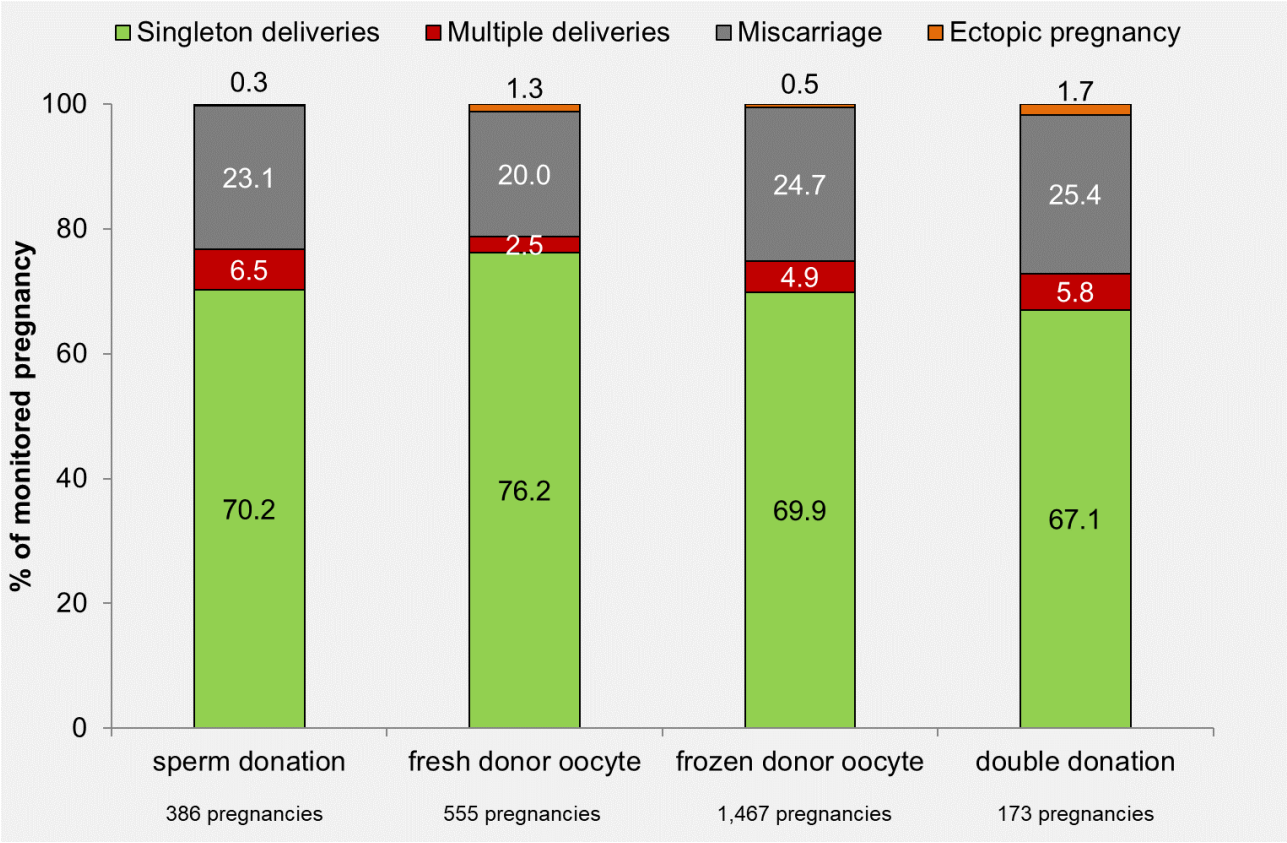


Figure 24. Comparison of the outcomes of monitored clinical pregnancies that resulted from ART donor cycles, 2020.

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 2020?

PGT activity, recorded from 55 centres, involved 3,598 tests (3,155 in fresh cycles and 443 in thawing ones). **Figure 25** shows the distribution of the application of PGT (Preimplantation Genetic Testing) cycles in Italy. A total of 873 pregnancies (44.2% per transfer) and 693 deliveries (35.2% per transfer) resulted from fresh cycles, while 160 pregnancies (46% per transfer) and 124 deliveries (35.6% per transfer) resulted from frozen embryo cycles. Please check on summary table (see page 60) for more detailed data on activity and outcomes regarding PGT cycles in 2020.

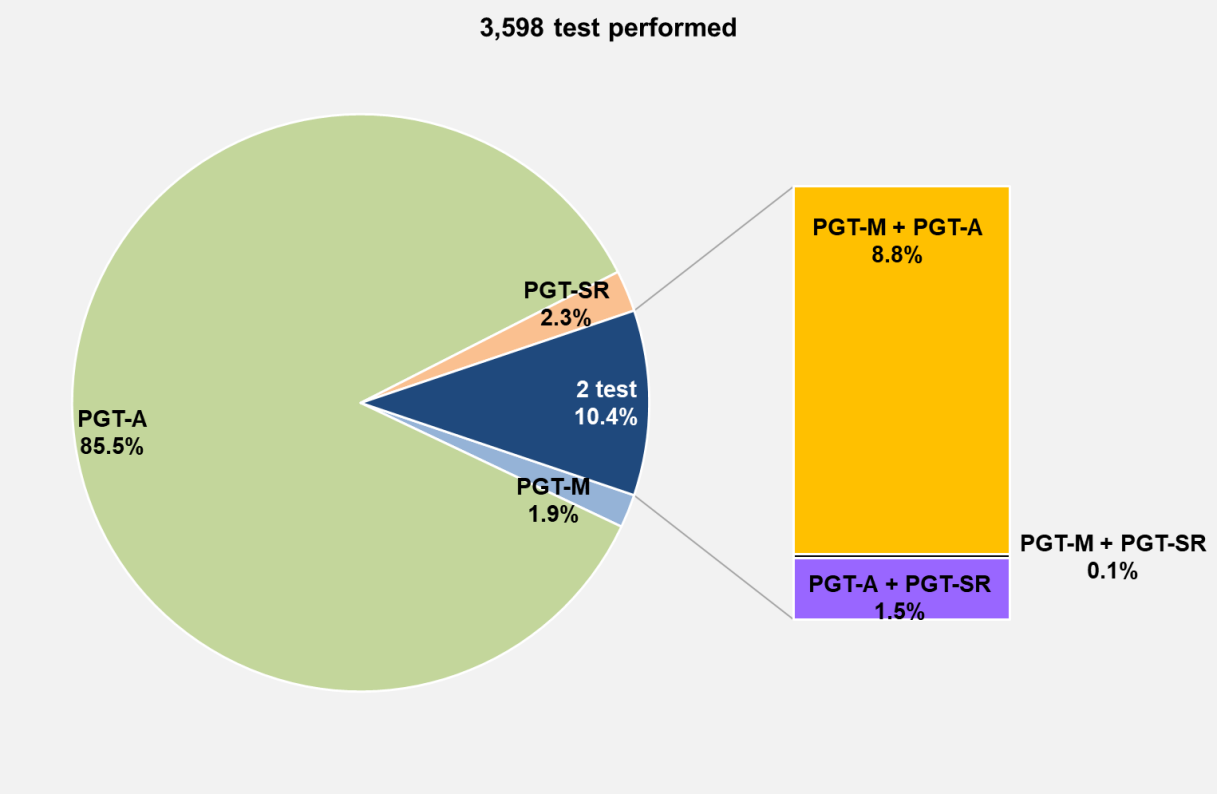
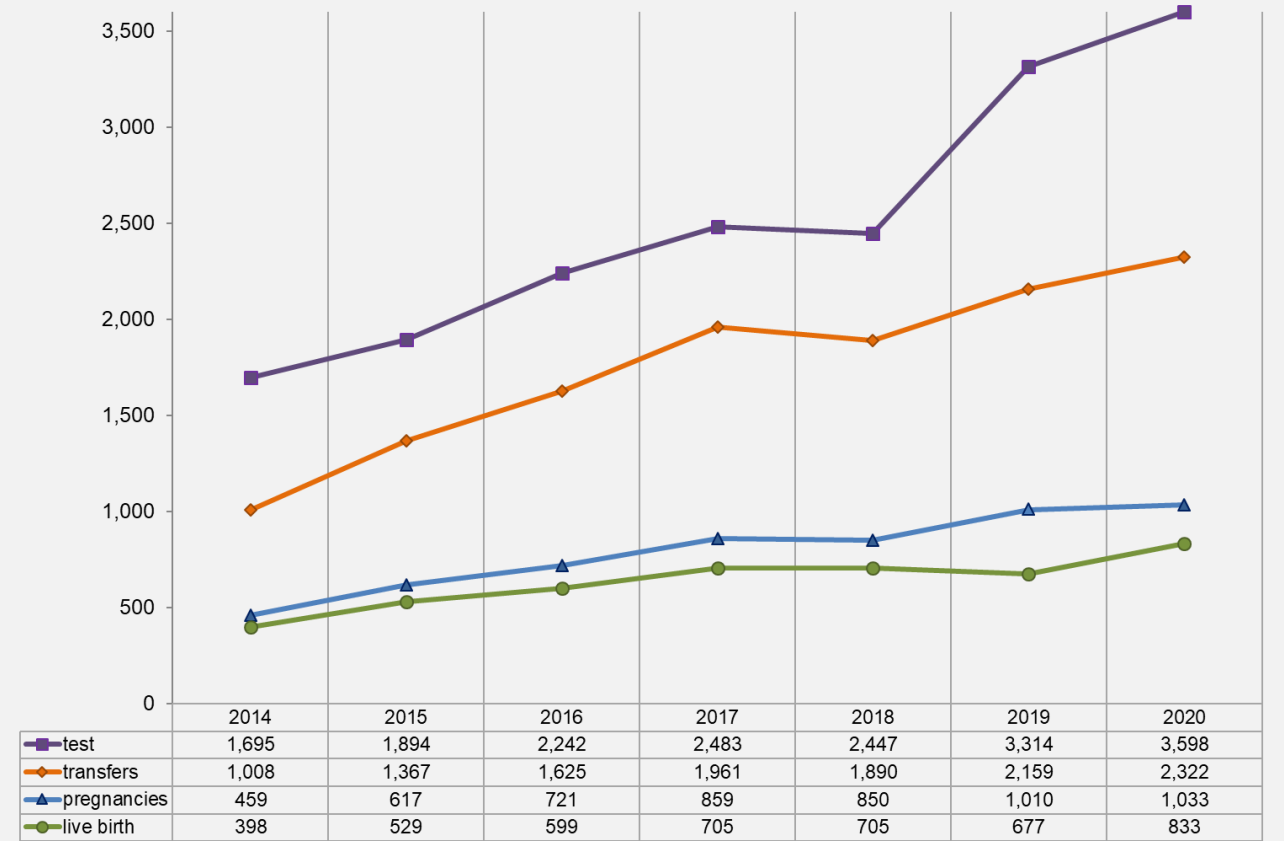


Figure 25. Distribution of PGD/PGS tests, 2020.

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 2020. At the same time, the number of analysis performed increased from 1,695 cycles in 2014 to 3,598 cycles in 2020. Since 2014, the Registry has been collected information on a total of 17,673 cycles in which genetic tests were performed, 12,332 transfers, 5,549 pregnancies obtained and 4,446 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 833 in 2020.



	2014	2015	2016	2017	2018	2019	2020
test	1,695	1,894	2,242	2,483	2,447	3,314	3,598
transfers	1,008	1,367	1,625	1,961	1,890	2,159	2,322
pregnancies	459	617	721	859	850	1,010	1,033
live birth	398	529	599	705	705	677	833

Figure 26. Time-trend of number of test, transfer pregnancies and live birth after a PGT test, 2014-2020.

3. ART SAFETY INDICATORS

3.1. Safety in ART procedures

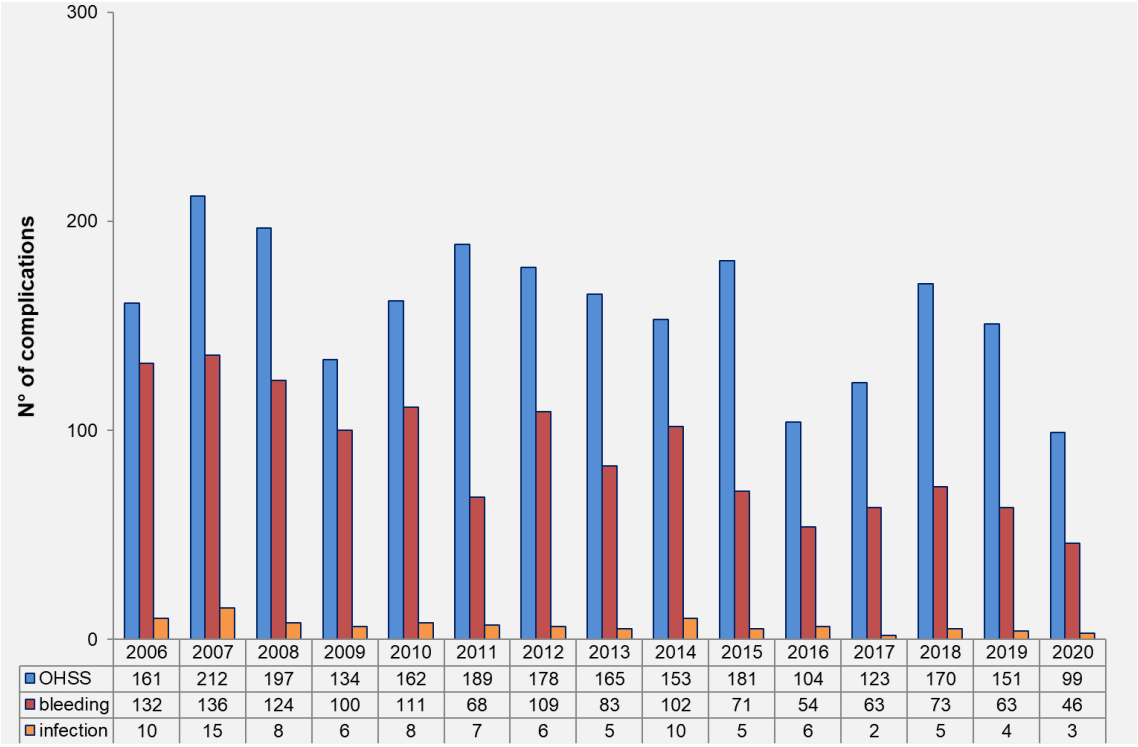
Although ART treatments are considered a safe medical procedure, in few cases some complications could arise during the treatment. These complications could arise at the moment of the ovarian stimulation or during pick-up procedure. Both could affect women's health. Another kind of complication for mother 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.

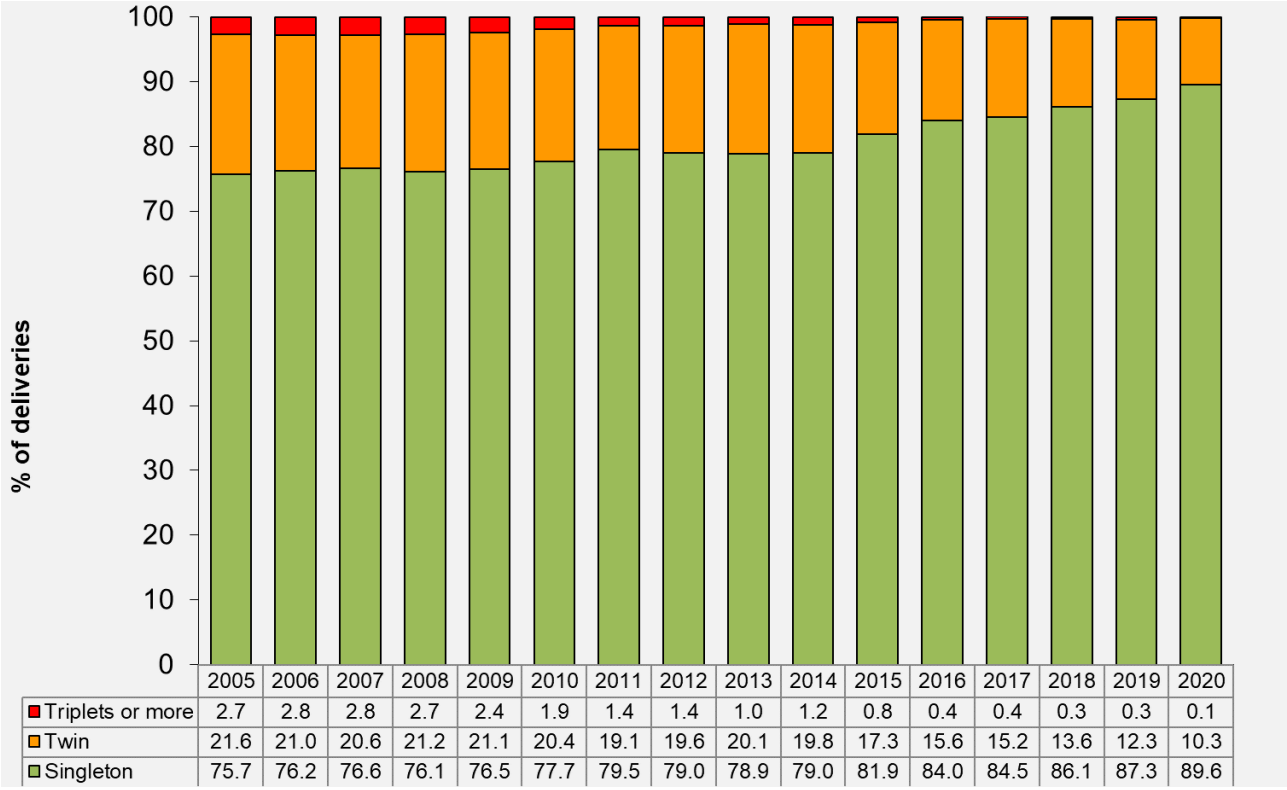


	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
OHSS	161	212	197	134	162	189	178	165	153	181	104	123	170	151	99
bleeding	132	136	124	100	111	68	109	83	102	71	54	63	73	63	46
infection	10	15	8	6	8	7	6	5	10	5	6	2	5	4	3

Figure 27. Time-trends of complications in fresh non-donor ART treatments, 2006-2020.

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

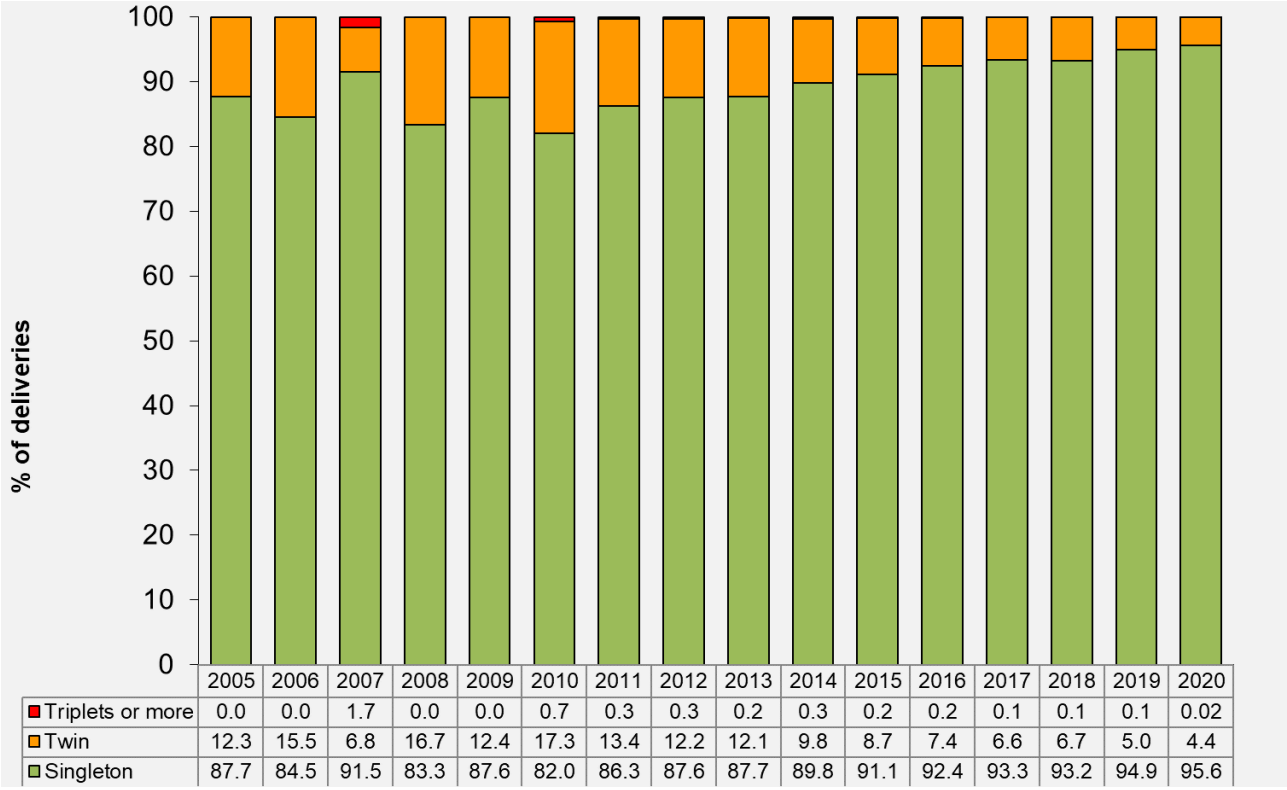
Figure 28 shows trends for multiple deliveries in fresh cycles. From 2005 to 2020, twin delivery percentage decreased from 21.6% to 10.3% while percentages of triplets and more deliveries decreased from 2.7% to 0.1%. These values are similar to the average European values of respectively 12.5% and 0.2% reported in 2018 EIM data[1]. 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	2020
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	0.1
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	10.3
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	89.6

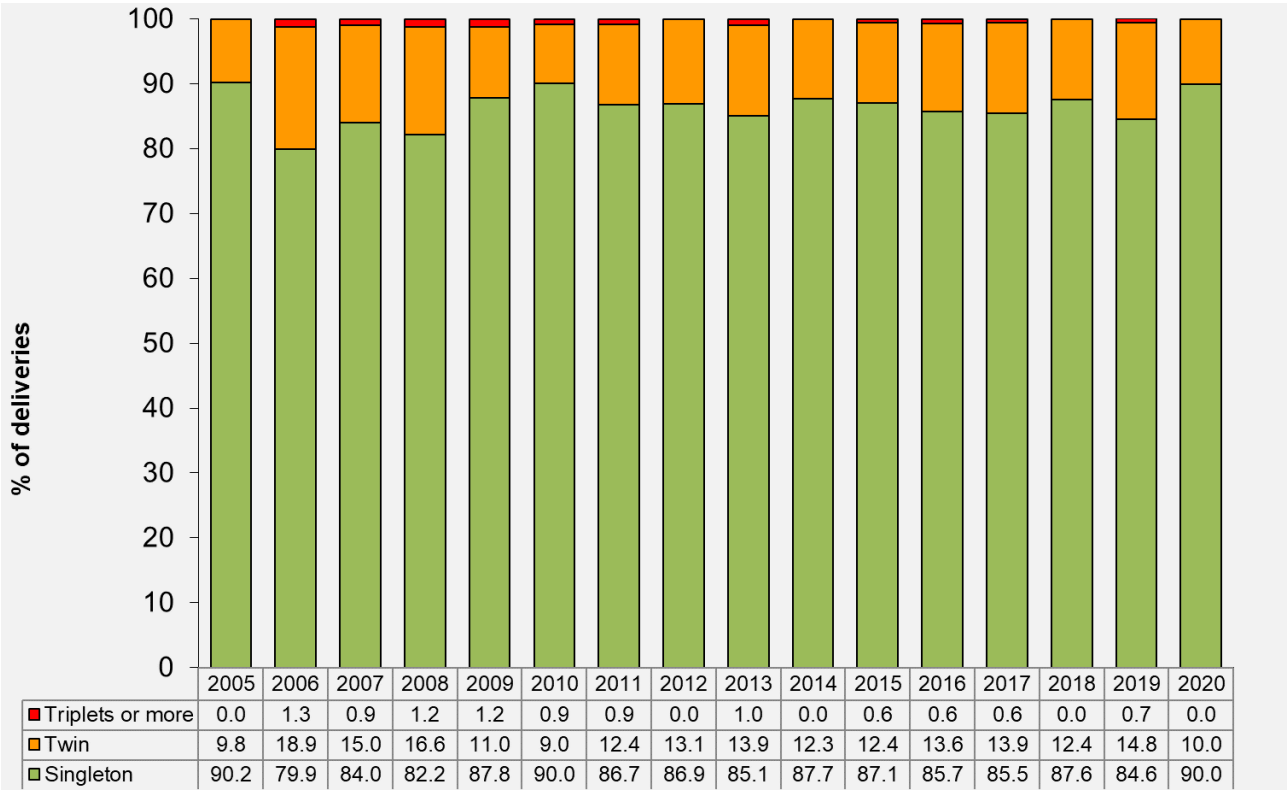
Figure 28. Time-trends of deliveries from fresh cycles according to gestational order, 2005-2020.

The same trends in percentage of the multiple deliveries are founds in FER (**Figure 29**). On the other hand, the FO technique shows an unstable trend in twin deliveries (**Figure 30**).



	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
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	0.02
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	4.4
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	95.6

Figure 29. Time-trends of deliveries from FER thawing according to gestational order, 2005-2020



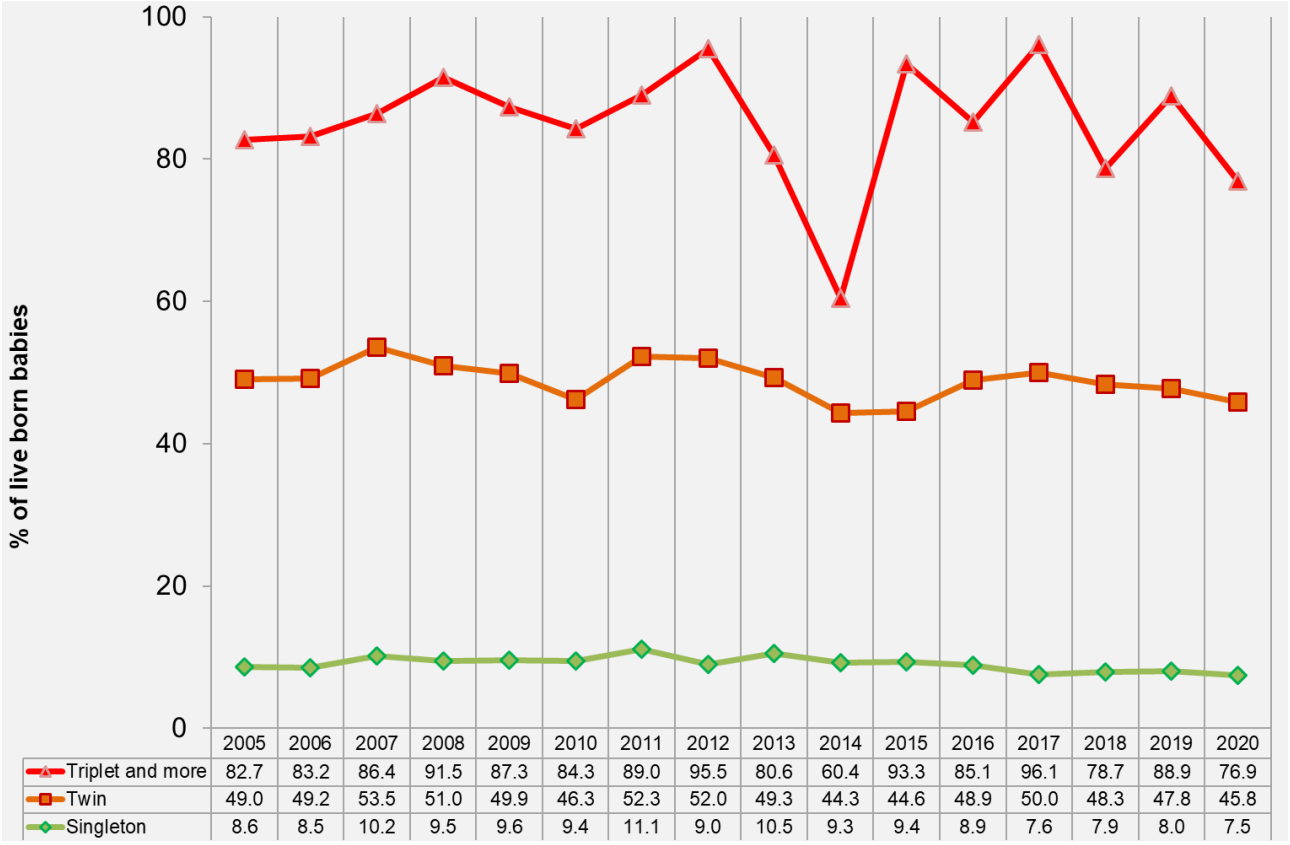
	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Triplets or more	0.0	1.3	0.9	1.2	1.2	0.9	0.9	0.0	1.0	0.0	0.6	0.6	0.6	0.0	0.7	0.0
Twin	9.8	18.9	15.0	16.6	11.0	9.0	12.4	13.1	13.9	12.3	12.4	13.6	13.9	12.4	14.8	10.0
Singleton	90.2	79.9	84.0	82.2	87.8	90.0	86.7	86.9	85.1	87.7	87.1	85.7	85.5	87.6	84.6	90.0

Figure 30. Time-trends of deliveries from FO thawing according to gestational order, 2005-2020

3.1.3. 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 periods. Otherwise, in triplet deliveries, there is a variability from year to year, but overall the trend is downwards from 82.7% in 2005 to 76.9% in 2020 while it is stable or slightly lower in singletons.



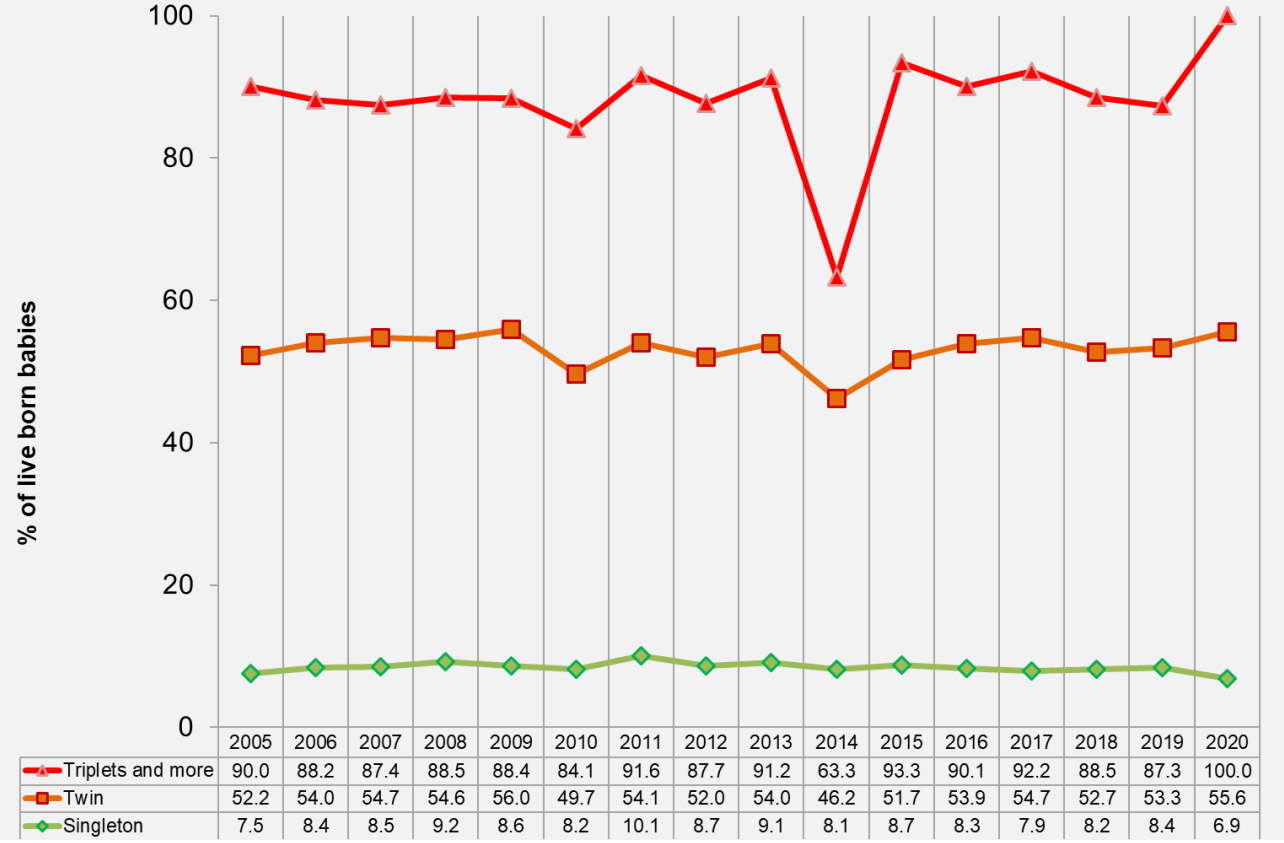
	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Triplet and more	82.7	83.2	86.4	91.5	87.3	84.3	89.0	95.5	80.6	60.4	93.3	85.1	96.1	78.7	88.9	76.9
Twin	49.0	49.2	53.5	51.0	49.9	46.3	52.3	52.0	49.3	44.3	44.6	48.9	50.0	48.3	47.8	45.8
Singleton	8.6	8.5	10.2	9.5	9.6	9.4	11.1	9.0	10.5	9.3	9.4	8.9	7.6	7.9	8.0	7.5

Figure 31. Time-trends of percentage of preterm ART live born babies (<37 week of gestation) by gestational order, 2005-2020.

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 periods. Overall, the trend is also quite stable for triplet and more deliveries from 90% in 2005 to 100% in 2020 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	2020
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	100.0
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	55.6
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	6.9

Figure 32. Time-trends of percentage of ART live born babies underweight (<2,500 gr) by gestational order, 2005-2020.

4. INTRA-UTERINE INSEMINATION PROCEDURES

4.1. Access to Intra-Uterine Insemination service

Figure 33 shows the regional distribution of the 332 Intra-Uterine Insemination (IUI) authorized centres in 2020, but only 274 performed at least one homologous IUI cycle.

The majority of centres is concentrated in northern Italy (150, 45.2% of the total) and then in the south (117 centres, 35.2% of the total), irrespective of the amount of activity they performed . Even with some differences the access is almost good in all the regions.

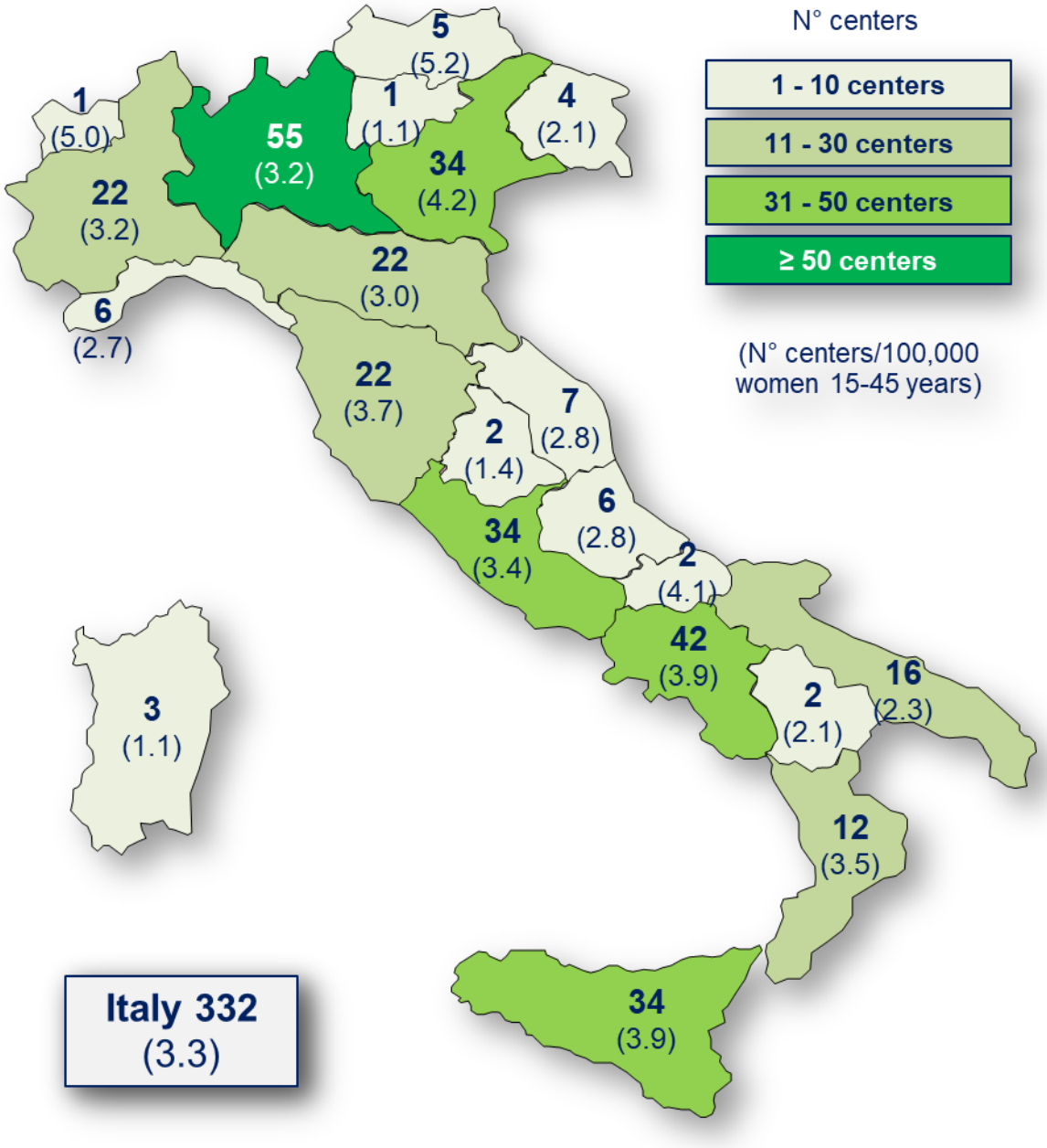


Figure 33. Regional distribution of IUI + ART authorized centres and in brackets the number of centres per 100,000 women of reproductive age (15-45 years)*, 2020.

*Average resident population in Italy in 2020: Source ISTAT.

As shown in **Table 3**, in 2020 there were 332 authorized centres that perform IUI of which only 121 operating within the National Health System (public and private 36.4%) and 211 providing private service (63.6%). Most of public centres that could perform IUI in Italy were in the north: 58 out of 101 centres (57.4%).

Table 3. IUI authorized centres distribution by region and type of service, 2020

Region and geographical area	Total	Type of service					
		public		private covered by NHS		private	
		N	%	N	%	N	%
Piemonte	22	7	31.8	1	4.5	14	63.6
Valle d'Aosta	1	1	100.0	0	0.0	0	0.0
Lombardia	55	17	30.9	10	18.2	28	50.9
Liguria	6	4	66.7	0	0.0	2	33.3
North West	***84***	***29***	***34.5***	***11***	***13.1***	***44***	***52.4***
P.A. Bolzano	5	3	60.0	0	0.0	2	40.0
P.A. Trento	1	1	100.0	0	0.0	0	0.0
Veneto	34	12	35.3	2	5.9	20	58.8
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	***66***	***29***	***43.9***	***3***	***4.5***	***34***	***51.5***
Toscana	22	7	31.8	5	22.7	10	45.5
Umbria	2	1	50.0	0	0.0	1	50.0
Marche	7	2	28.6	0	0.0	5	71.4
Lazio	34	5	14.7	1	2.9	28	82.4
Central	***65***	***15***	***23.1***	***6***	***9.2***	***44***	***67.7***
Abruzzo	6	3	50.0	0	0.0	3	50.0
Molise	2	0	0.0	0	0.0	2	100.0
Campania	42	8	19.0	0	0.0	34	81.0
Puglia	16	4	25.0	0	0.0	12	75.0
Basilicata	2	2	100.0	0	0.0	0	0.0
Calabria	12	3	25.0	0	0.0	9	75.0
Sicilia	34	5	14.7	0	0.0	29	85.3
Sardegna	3	3	100.0	0	0.0	0	0.0
South and islands	***117***	***28***	***23.9***	***0***	***0.0***	***89***	***76.1***
Italy	**332**	**101**	**30.4**	**20**	**6.0**	**211**	**63.6**

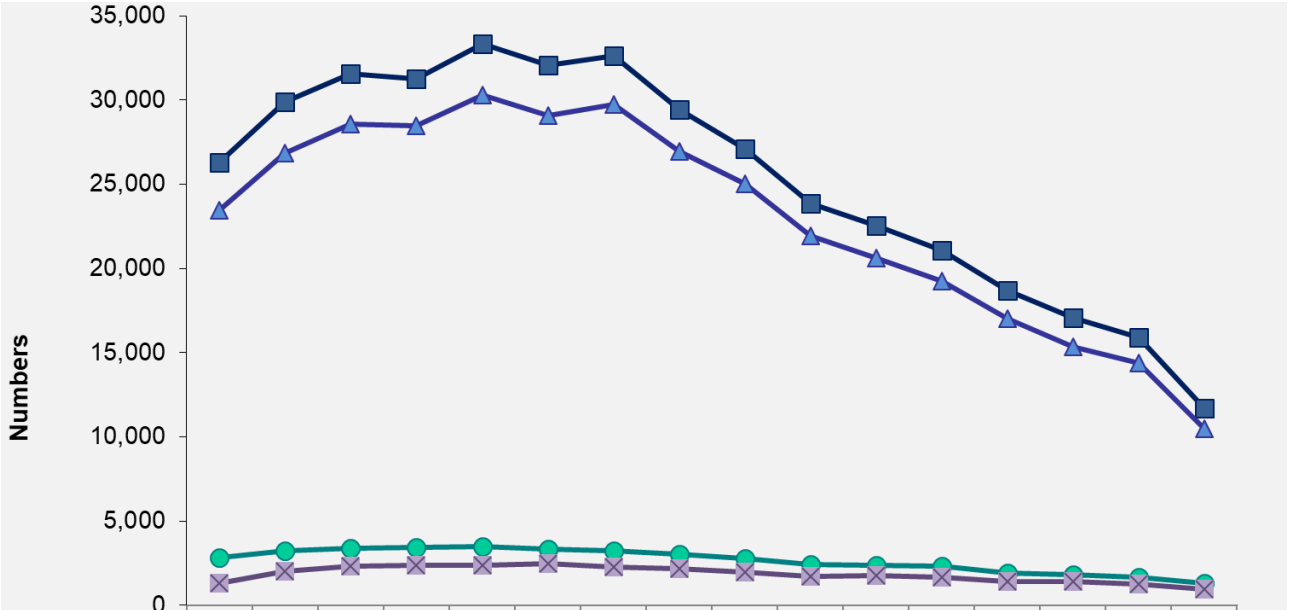
4.2. Efficacy safety and trends of IUI

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 36) the IUI-D procedures have been permitted only after the Italian Constitutional Court sentence in April 2014. For the activity of IUI-D in 2020, please check on Summary table for 2020 (see page 61) for more detailed data.

Figure 34 shows the use of IUI-H from 2005 to 2020. The number of IUI-H cycles decreased from 26,292 to 11,679 after having reached his maximum of 33,335 cycles in 2009. There were no changes in pregnancy rate from 10.7% in 2005 to 11.1% in 2020. The average age of women fluctuates over time around 35 years of age: in 2020 it was 34.9 years.



	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Initiated cycles	26,292	29,901	31,551	31,268	33,335	32,069	32,644	29,427	27,109	23,866	22,549	21,053	18,688	17,083	15,895	11,679
Inseminations	23,463	26,834	28,582	28,497	30,285	29,062	29,749	26,940	25,010	21,942	20,621	19,261	17,004	15,329	14,370	10,496
%	89.2%	89.7%	90.6%	91.1%	90.9%	90.6%	91.1%	91.5%	92.3%	91.9%	91.4%	91.5%	91.0%	89.7%	90.4%	89.9%
Pregnancies	2,805	3,203	3,400	3,414	3,482	3,306	3,246	3,024	2,775	2,392	2,363	2,292	1,924	1,813	1,638	1,291
%	10.7%	10.7%	10.8%	10.9%	10.4%	10.3%	9.9%	10.3%	10.2%	10.0%	10.5%	10.9%	10.3%	10.6%	10.3%	11.1%
Infants	1,291	1,999	2,337	2,357	2,361	2,465	2,275	2,156	1,970	1,682	1,738	1,672	1,392	1,386	1,266	963

Figure 34. Time-trends of outcomes of IUI-H cycles, 2005-2020.

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: 6.5% for pregnancy and 3.3% for delivery in over 43.

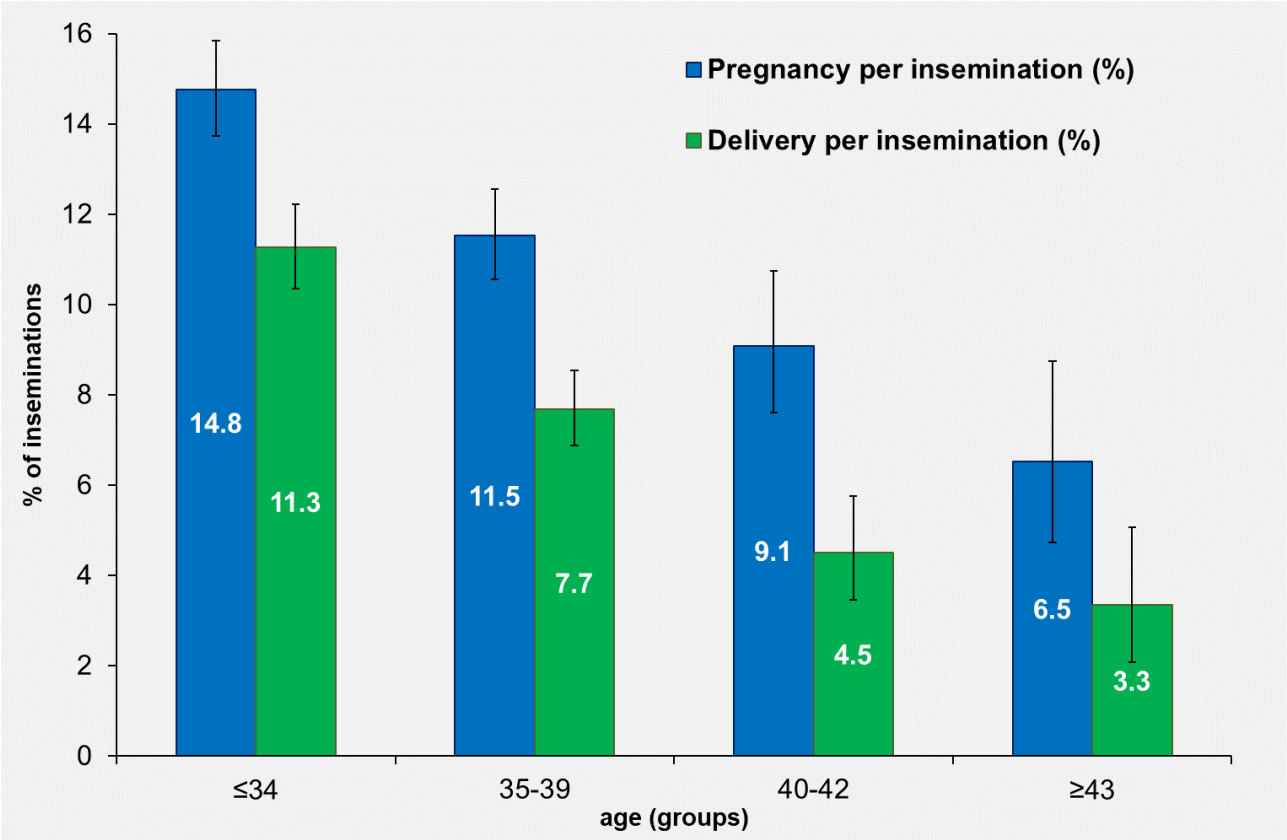


Figure 35. Pregnancy rates and delivery rates per insemination for IUI-H cycles by age groups of female patients, 2020.

4.2.3. What were the outcomes of pregnancies obtained in IUI-H cycles in 2020?

Figure 36 shows the outcomes of the monitored clinical pregnancies obtained from the application of the homologous IUI in Italy in 2020. Of the 1,141 monitored pregnancies in homoulogous IUI cycles 5.8% resulted in multiple deliveries and 20.2% had a miscarriage.

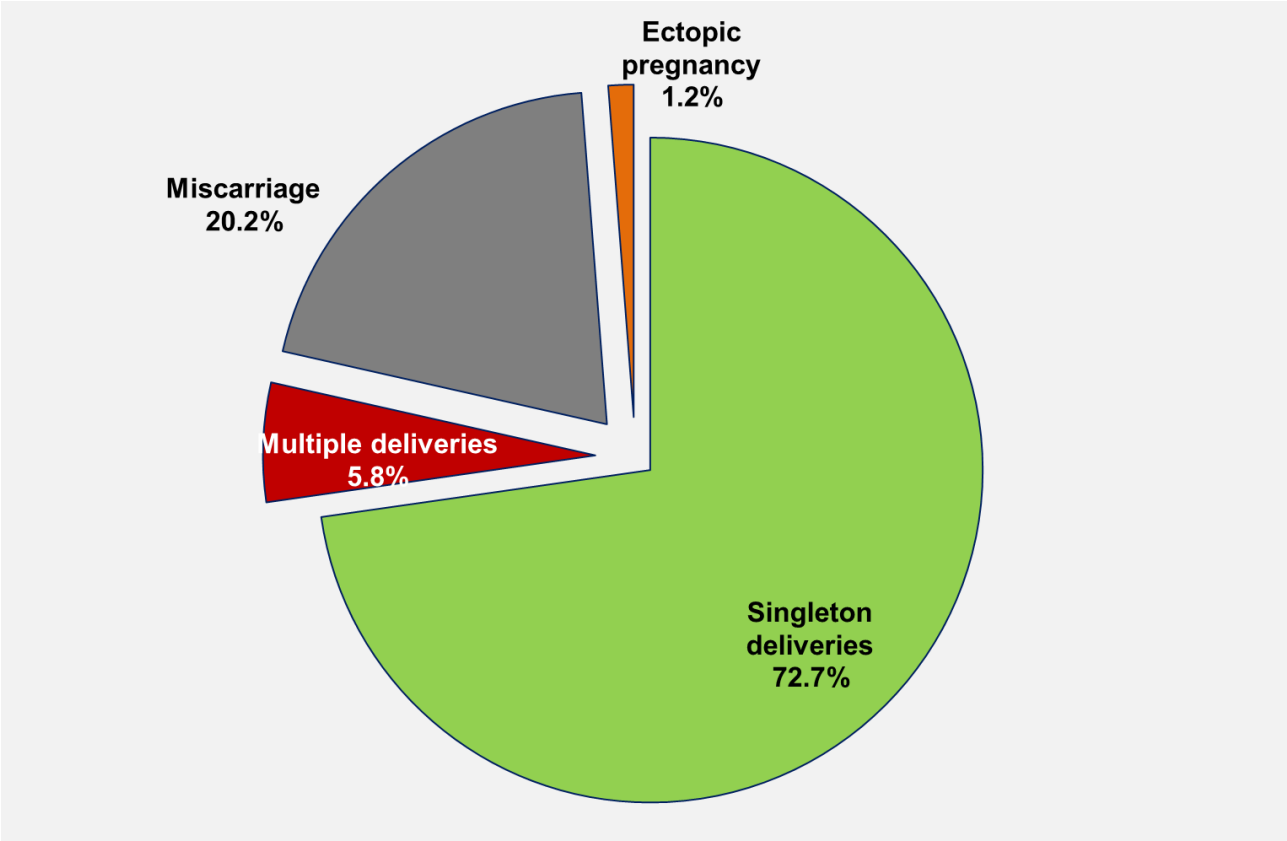
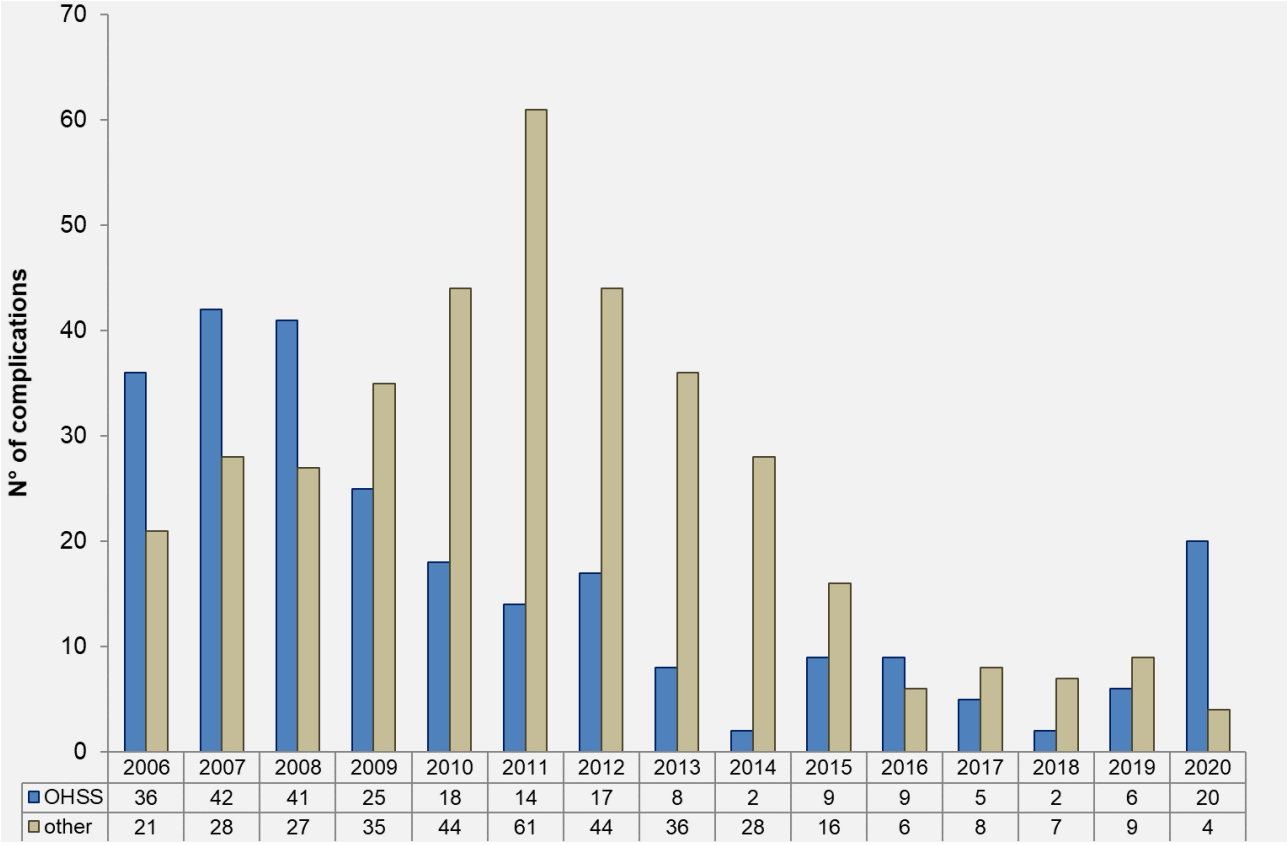


Figure 36. Outcomes of clinical pregnancies that resulted from H-IUI cycles, 2020.

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 2007, going from 42 (0.15% of the inseminations) to 20 (0.19%). Complications for "other causes" also continue to decrease to 4 (0.04%) but only after reaching their maximum value of 61 (0.21%) in 2011.

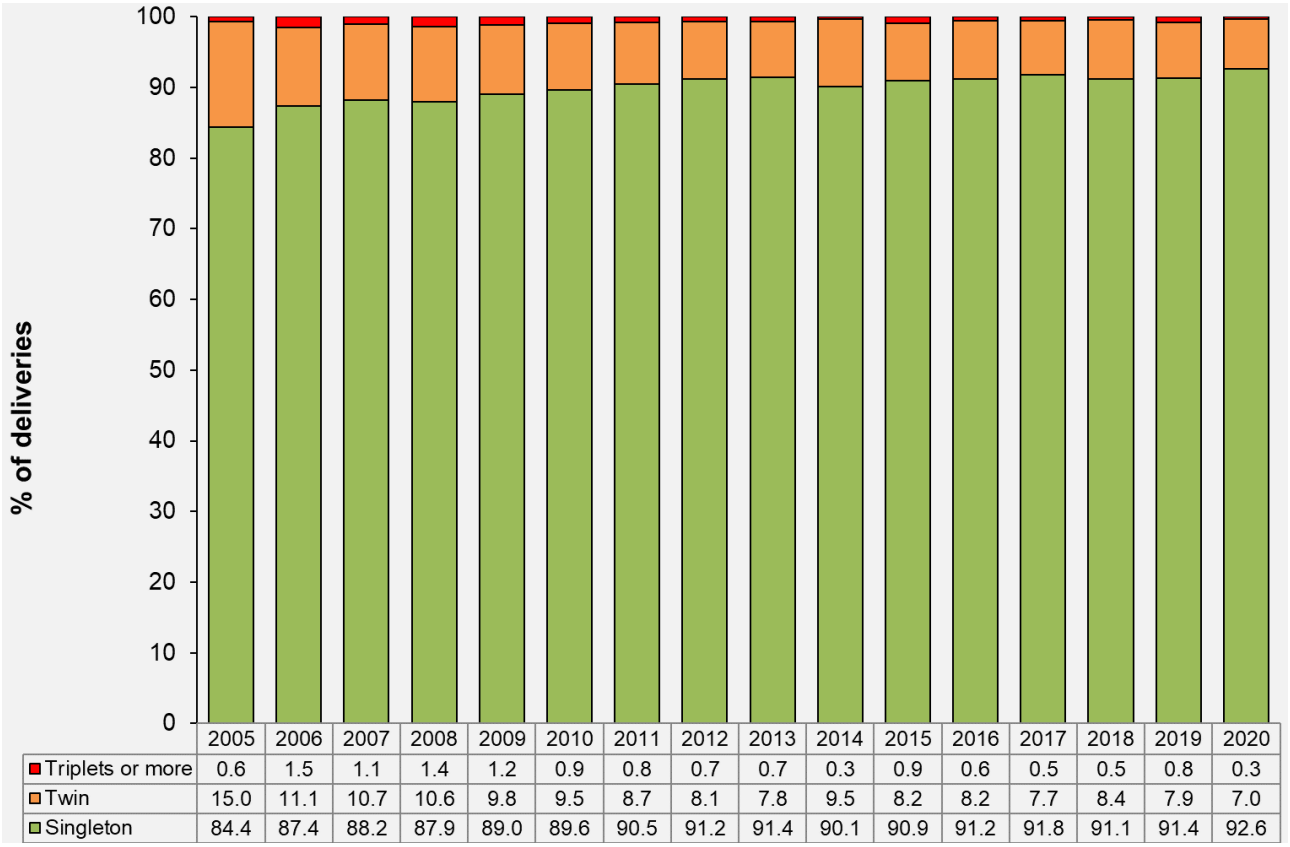


	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
OHSS	36	42	41	25	18	14	17	8	2	9	9	5	2	6	20
other	21	28	27	35	44	61	44	36	28	16	6	8	7	9	4

Figure 37. Time-trends of complications in homologous-IUI treatments, 2006-2020.

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 2020 twin deliveries rates decreased from 15% to 7% 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	2020
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	0.3
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	7.0
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	92.6

Figure 38. Time-trends of deliveries from IUI-H cycles according to gestational order, 2005-2020.

4.3. IUI donor cycles

4.3.1. What was the outcome in IUI donor cycles in 2020?

In total 492 initiated cycles using donor sperm in IUI cycle started in 2020, 22.2% resulted in a clinical pregnancy and 14.6% resulted in a delivery. However, most of these cycles (about 77.8%) did not produce a pregnancy while a small proportion (4.1%) resulted in a pregnancy loss (i.e. ectopic pregnancy or miscarriage).

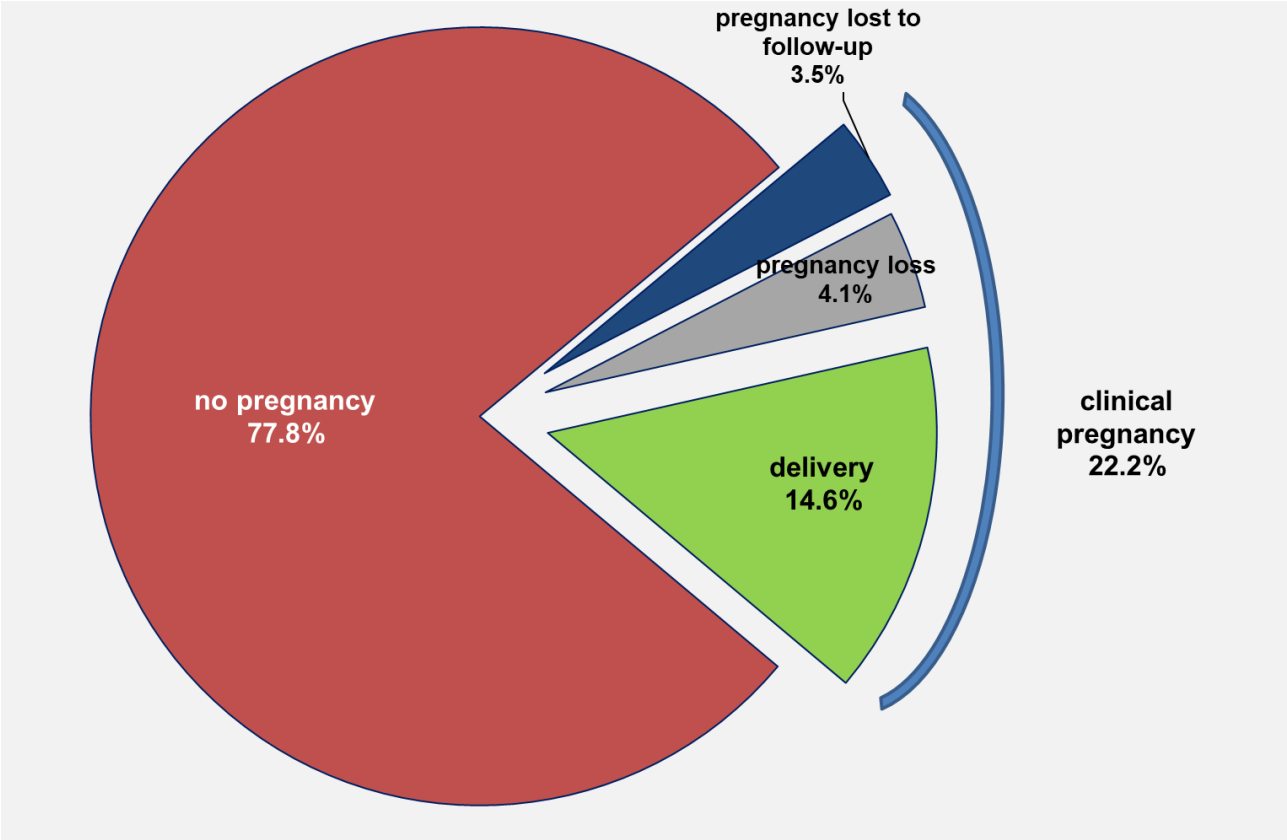


Figure 39. Outcome of IUI-D cycles, 2020 (492 initiated cycles).

APPENDIX

SUMMARY TABLE OF ACTIVITY AND OUTCOME OF ART PROCEDURES YEARS 2014-2020

Summary table of activity and outcome of all ART procedures, 2014-2020

	2014	2015	2016	2017	2018	2019	2020
N° Clinics	362	366	360	366	345	346	332
Clinics reporting data to ISS (%)	100	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	57,243
N° Initiated cycles	90,957	95,110	97,656	97,888	97,509	99,062	76,390
N° Live born	12,720	12,836	13,582	13,973	14,139	14,162	11,226
ART activity (Fresh non donor, Thawing non donor, donor)							
N° Patients	55,859	59,747	63,724	65,943	66,083	67,633	57,243
N° Initiated cycles	67,054	72,048	75,889	78,457	79,735	82,476	67,928
N° Pregnancies	13,642	14,391	15,405	16,793	17,402	17,787	14,462
Cumulative Pregnancy Rate per fresh initiated cycle (%)	24.3	24.8	25.4	27.5	28.4	29.3	29.7
Pregnancies lost to follow-up (%)	10.8	11.3	10.2	11.9	9.7	10.6	10.2
N° Deliveries	9,252	9,512	10,386	11,094	11,428	11,754	9,635
N° Live born	11,037	11,029	11,791	12,454	12,646	12,797	10,258
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	6,525
ART Initiated cycles per 1 million inhabitants	1,103	1,175	1,237	1,275	1,297	1,341	1,117
IUI-H and IUI-D activity							
N° Patients	14,967	14,545	13,798	12,423	11,426	10,985	8,462
N° Initiated cycles	23,903	23,062	21,767	19,431	17,774	16,586	12,171
N° Pregnancies	2,399	2,466	2,429	2,078	1,952	1,767	1,400
Pregnancy Rate per cycle (%)	10.0	10.7	11.2	10.7	11.0	10.7	11.5
Pregnancies lost to follow-up (%)	18.2	16.8	15.0	13.9	11.7	11.2	11.9
N° Deliveries	1,530	1,649	1,629	1,396	1,369	1,249	968
N° Live born	1,683	1,807	1,791	1,519	1,493	1,365	1,047

Summary table of activity and outcome of ART non donor procedures, 2014-2020

	2014	2015	2016	2017	2018	2019	2020
FRESH CYCLES (Non Donor)							
N° Patients	45,985	45,689	44,965	44,279	42,090	41,149	32,562
Average age calculated	36.7	36.7	36.8	36.7	36.7	36.8	36.9
N° Initiated cycles	55,705	55,329	53,906	53,014	51,087	50,324	38,728
N° aspirations	50,794	50,214	48,756	47,911	46,387	46,090	34,785
N° transfers	39,768	37,975	36,038	33,832	30,584	28,731	19,431
N° Pregnancies	10,834	10,081	9,326	9,310	8,307	7,753	5,197
Pregnancies rate per cycles (%)	19.4	18.2	17.3	17.6	16.3	15.4	13.4
Pregnancies rate per cycles without freeze-all strategy (%)	20.7	19.9	19.1	20.0	19.0	18.7	17.1
Pregnancies rate per aspirations (%)	21.3	20.1	19.1	19.4	17.9	16.8	14.9
Pregnancies rate per transfers (%)	27.2	26.5	25.9	27.5	27.2	27.0	26.7
Twin Pregnancies (%)	19.5	17.0	15.6	15.0	13.1	12.3	10.6
Triplet or more Pregnancies (%)	1.4	0.9	0.6	0.5	0.4	0.5	0.2
Pregnancies lost to follow-up (%)	11.9	13.1	11.2	13.4	10.9	10.4	12.8
N° Deliveries	7,277	6,498	6,196	6,029	5,458	5,151	3,327
N° Live born	8,848	7,695	7,172	6,951	6,186	5,797	3,660
FROZEN/THAWED EMBRYOS (FER)							
N° Patients	8,139	10,557	12,485	14,441	16,067	17,562	16,029
Average age calculated	35.4	35.2	35.3	35.3	35.2	35.3	35.3
N° thawing cycles	9,501	12,903	14,990	17,281	19,587	21,796	19,314
N° transfers	8,851	11,849	14,328	16,673	19,016	21,078	18,724
N° Pregnancies	2,448	3,379	4,128	5,059	5,995	6,758	6,096
Pregnancies rate per thawings (%)	25.8	26.2	27.5	29.3	30.6	31.0	31.6
Pregnancies rate per transfers (%)	27.7	28.5	28.8	30.3	31.5	32.1	32.6
Twin Pregnancies (%)	11.2	9.8	9.1	7.7	7.0	5.0	4.8
Triplet or more Pregnancies (%)	0.4	0.4	0.3	0.1	0.1	0.1	0.1
Pregnancies lost to follow-up (%)	5.5	5.6	6.7	7.9	6.6	10.2	6.8
N° Deliveries	1,747	2,403	2,890	3,486	4,127	4,412	4,212
N° Live born	1,929	2,609	3,104	3,703	4,393	4,637	4,382
FROZEN/THAWED OOCYTES (FO)							
N° Patients	1,530	1,418	1,341	1,281	1,201	1,248	977
Average age calculated	35.1	35.2	35.1	35.2	35.4	35.3	35.7
N° thawing cycles	1,639	1,529	1,460	1,391	1,318	1,361	1,099
N° transfers	1,295	1,221	1,187	1,146	1,036	1,071	817
N° Pregnancies	273	254	238	235	223	242	210
Pregnancies rate per thawings (%)	16.7	16.6	16.3	16.9	16.9	17.8	19.1
Pregnancies rate per transfers (%)	21.1	20.8	20.1	20.5	21.5	22.6	25.7
Twin Pregnancies (%)	12.5	10.6	12.2	12.8	9.9	11.2	10.0
Triplet or more Pregnancies (%)	0.8	0.4	1.3	0.4	0.0	0.4	0.0
Pregnancies lost to follow-up (%)	7.0	5.9	4.6	4.7	6.7	7.4	11.9
N° Deliveries	179	170	154	165	153	149	140
N° Live born	199	193	177	190	172	173	153

Summary table of activity and outcome of ART with PGT analysis, 2014-2020

	2014	2015	2016	2017	2018	2019	2020
PGT activity							
N° clinics reporting data (with at least 1 patient treated)	22	33	35	42	46	55	57
N° Patients	1,596	1,799	2,247	2,459	2,653	3,625	4,788
N° Tests performed	1,695	1,894	2,242	2,483	2,447	3,314	3,598
Patient average age	36.1	36.2	36.0	36.0	36.2	36.3	36.5
N° Pregnancies	459	617	721	859	850	1,010	1,033
Pregnancies rate per transfer (%)	45.5	45.1	44.4	43.8	45.0	46.8	47.8
Pregnancies lost to follow-up (%)	1.5	1.5	2.5	3.3	1.9	18.6	5.0
N° Deliveries	383	514	582	693	694	665	817
N° Live born	398	529	599	705	705	677	833

Summary table of activity and outcome of ART procedures with gamete donation, 2014-2020

	2014	2015	2016	2017	2018	2019	2020
ART-Donor activity							
N° clinics reporting data (with at least 1 patient treated)	17	69	83	91	101	96	104
N° Patients	205	2,083	4,933	5,941	6,725	7,674	7,675
N° Initiated cycles	209	2,287	5,533	6,771	7,743	8,995	8,787
N° Pregnancies	87	677	1,713	2,189	2,517	3,034	2,959
Pregnancies lost to follow-up (%)	26.4	15.7	13.9	15.5	13.7	12.1	12.8
N° Deliveries	49	441	1,146	1,414	1,690	2,042	1,956
N° Live born	61	532	1,338	1,610	1,895	2,190	2,063
IUI-D activity (sperm donation)							
N° clinics reporting data (with at least 1 patient treated)	13	52	65	62	73	76	65
N° Patients	32	379	517	487	488	514	374
N° Initiated cycles	37	513	714	743	691	691	492
N° Pregnancies	7	103	137	154	139	129	109
Pregnancies rate per cycles (%)	18.9	20.1	19.2	20.7	20.1	18.7	22.2
Pregnancies lost to follow-up (%)	85.7	30.1	16.8	16.9	16.5	12.4	15.6
N° Deliveries	1	61	98	110	93	90	72
N° Live born	1	69	119	127	107	99	84

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