

Trends over 15 years in ART in Europe: an analysis of 6 million cycles[†]

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STUDY QUESTION: Was the European IVF Monitoring (EIM) Consortium, established in 1999 by ESHRE, able to monitor the trend over time of ART in Europe?

SUMMARY ANSWER: The initial aims of the EIM programme (to collect and publish regional European data on census and trends on ART utilization, effectiveness, safety and quality) have been achieved.

WHAT IS ALREADY KNOWN: ART data in Europe have been collected and reported annually in *Human Reproduction*.

STUDY DESIGN, SIZE, DURATION: A retrospective data analysis and summary of the first 15 years of ART activity in Europe (1997–2011) was carried out, using the key figures from the annual ESHRE reports and focusing on how the practice of ART has evolved over the years.

PARTICIPANTS/MATERIALS, SETTING, METHOD: A total of 5 919 320 ART cycles are reported, including IVF, ICSI, frozen embryo relacment and egg donation, resulting in the birth of more than 1 million infants. A total of 1 548 967 IUIs are also reported, including husband/partner's semen and donor semen cycles. The most relevant and complete data are analysed and discussed.

MAIN RESULTS AND THE ROLE OF CHANCE: With some fluctuations, the number of countries and clinics reporting to EIM increases significantly from 1997 to 2011. A constant increase was also registered in the number of annual cycles reported. Since 2005, the estimation of the EIM coverage on the total European activity was >80%. In countries with 100% of coverage, the mean availability of ART increased from 765 cycles per million inhabitants in 1997 to 1269 cycles per million inhabitants in 2011, and the proportion of ART infants of the total number of infants born in the country increased from 1.3% to 2.4%. The proportion of women aged > 39 years undergoing IVF and ICSI cycles gradually increased. For 12 consecutive years, the proportion of ICSI versus IVF cycles showed a marked increase before reaching a plateau from 2008. The proportion of transfers with three or more embryos decreased constantly and the proportion of SETs increased over the time period. The triplets deliveries were reduced from 3.7% in 1997 to less than 1% since 2005 (0.6% in 2011). The effectiveness (evaluated as clinical pregnancy rate per aspiration and per embryo transfer) increased until 2007, then the figure remained stable. The cumulative percentage of documented pregnancy losses was 17%. No differences have been noted in terms of outcomes in the IUI cycles.

LIMITATIONS, REASONS FOR CAUTION: The data presented are accumulated from countries with different collection systems, regulations, insurance coverage and different practices. Each year a number of countries have been unable to provide some of the data.

WIDER IMPLICATIONS OF THE FINDING(S): The first summary of 15 years of the EIM reports offers interesting data on census and trends on ART utilization, safety and quality in Europe. The primary aim of the ESHRE effort in supporting European data collection has been reached. Owing to its importance inside and outside the professional community, European data collection and publication on ART have to be supported and implemented.

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WHAT DOES THIS MEAN FOR PATIENTS?

This report looks at trends in fertility treatment in Europe over a period of 15 years and includes information about 6 million assisted conception cycles and more than a million births.

In 1999, the European Society of Human Reproduction and Embryology (ESHRE) set up a group to monitor IVF and produce an annual report. It has been a challenge to get information from across Europe reported in exactly the same way, but this has been gradually improving. The information takes time to collect and verify, so this report covers treatment up until 2011.

This latest report shows that live birth rates from assisted conception had been rising until 2007 but have remained stable since then. Around 2.4% of all births in Europe in 2011 were from assisted conception. The number of cycles where three or more embryos were transferred has gone down steadily. The multiple birth rate has also gone down from nearly 30% to 19%, and the number of triplet births after IVF across Europe is now below 1%. The researchers note that despite an overall downward trend, different countries have very different multiple birth rates. There is a growing percentage of women aged 40 and over having IVF treatment. The number of cycles where ICSI (a treatment for male fertility problems where a sperm is injected directly into the egg) rather than standard IVF was used had been rising but is now stable. Around three-quarters of all cycles use ICSI.

The researchers say that not all cycles in all countries are yet reported, so the true number of cycles of treatment in this period over Europe could be more than 7 million cycles, but the information collected helps to highlight trends in treatment.

Introduction

Results from IVF treatments have been published in several reports since the early application of the technique from national registers in Germany (1982), France (1986) and UK (1990). Later on, regional data were collected and summarized from USA and Canada since 1996 (SART, 1999), Australia and New Zealand since 1997 (Hurts et al., 1997) and Latin America since 1997 (Zegers-Hochschild and Galdames, 1997). In 1999, ESHRE organized an IVF data collection programme for Europe. A consortium was established, named EIM (European IVF Monitoring) that included representatives from the European countries participating in data collection.

In countries with already-existing national registers, data were obtained from their annual reports; in countries without national IVF registers, key persons were identified by the Society to co-ordinate data collection from their respective countries. The aim of the EIM programme was to publish annual data on the quantity, availability, effectiveness and safety of IVF in Europe, and to follow trends over time (ESHRE, 2001a).

From the very beginning it was clear that compiling European data would face several problems. First of all, existing national registers were generated through different methods of collection and different validation systems, often without uniformity in definitions. Some countries would be unable to provide some data or to contribute to the collection in a stable manner. Additionally, Europe was (and remains) a mosaic of countries with different social-cultural approaches to ART, clearly expressed by different regulations, guidelines and practices, including different reimbursement policies (Global Reproductive Health- IFFS Surveillance, 2016). Such factors contribute to the heterogeneity of data obtained from different countries. Recognizing and understanding these shortcomings, ESHRE decided to launch the collections but at the same time recommended that results should be interpreted with caution (ESHRE 2001a).

The European data collection was started for treatments initiated during 1997 and the first report was published in 2001 (ESHRE 2001). The 15th annual report (covering the activity in 2011) was published in 2016 (Kupka et al., 2016).

The present paper provides a picture of these 15 years of ART activity in Europe (1997–2011), using the key figures from the annual ESHRE reports and focusing on how the practice of ART has evolved over the years. The results are primarily presented in tables and figures, with only short comments in the text.

Materials and Methods

Data are collected from the 15 annual reports published in *Human Reproduction* (ESHRE 2001a,b, 2002; Nyboe Andersen et al., 2004, 2005, 2006, 2007, 2008, 2009; de Mouzon et al., 2010, 2012; Ferraretti et al., 2012, 2013; Kupka et al., 2014, 2016).

The annual reports include data on IVF, ICSI, frozen embryo replacement (FER) and egg donation (ED) cycles. During later years, pooled data on PGD/PGS, IVF and frozen oocyte replacements have been added. The total number of cycles reported each year is the sum of all these cycles. Data on IUI using husband/partner (IUI-H) and donor (IUI-D) semen were collected for 2001 and onwards.

The EIM programme also collected information on reporting methods and size of the clinics, number of treatment cycles per technique, availability, age distribution, number of embryos transferred, pregnancies and deliveries, multiple pregnancies and deliveries, complications and weeks of gestation according to the number of newborn. During the years, the collection system was modified to harmonize the data forms of The International Committee Monitoring Assisted Reproductive Technologies (ICMART) and to implement the use of the international ICMART/World Health Organization glossary (Zegers-Hochschild et al., 2009).

The individual annual reports include several tables presenting the data from each single contributing country. As expected, each year a number of countries

were unable to provide some data. In the present paper, only the most relevant and complete data are analysed and discussed. The numbers reported (in terms of totals, percentages and ranges) are the overall data from each year.

Results

Participation and reporting methods

Data on participation are presented in Table I. The number of countries and the number of clinics providing data to the EIM increased consistently during the years, as 482 clinics reported in 1997 and 1064 in 2011. Among countries, the participation rate ranged from <25% to 100%. The number of countries reporting data from all the clinics did not increase, but some of the most populous countries (France, Germany and UK) have had a coverage >95% since the beginning, and Italy from 2005. The overall coverage (estimated as all participating clinics over the total number of clinics) was less than 70% in 1997 and over 80% after 2005. Over the years, the proportion of countries with compulsory data collection increased from 33% in 1997 to 51% in 2011. The proportion of registers based on individual forms (i.e. cycle-by-cycle data) remained the same: 33% in 1997 and 30% in 2011.

Quantity

The total number of cycles reported increased steadily from 203 225 in 1997 to 609 973 in 2011 (Table I). This marked increase was partly related to a better coverage but also to a true expansion of ART utilization across Europe.

Table I Number of countries and clinics participating to the European IVF Monitoring (EIM) collection each year, number of countries reporting data from all the clinics (100% coverage) and estimation of the EIM coverage on the overall European activity in ART.

Year	Countries reporting to EIM	Clinics reporting to EIM	Countries with 100% coverage	Estimation of the EIM coverage	Cycles ^a
1997	18	482	10 (55%)	70%	203 225
1998	18	521	9 (50%)	73%	232 225
1999	22	538	8 (36%)	72%	258 460
2000	22	569	9 (41%)	70%	279 267
2001	23	579	12 (52%)	78%	289 690
2002	25	631	13 (52%)	72%	324 238
2003	28	725	15 (54%)	72%	365 103
2004	29	785	14 (48%)	70%	367 066
2005	30	923	16 (53%)	81%	418 111
2006	32	998	20 (62%)	86%	458 759
2007	33	1029	18 (54%)	85%	493 184
2008	36	1051	19 (53%)	84%	532 260
2009	34	1005	21 (62%)	85%	537 463
2010	31	991	16 (52%)	82%	550 296
2011	33	1064	17 (51%)	81%	609 973

^aThe total number of cycles (IUI excluded).

Table II reports the total number of cycles, aspirations, fresh and FERs, ED cycles, deliveries and infants born after ART during the first 15 years of EIM activity. Altogether, almost 6 millions ART cycles (5 919 320) have been reported, giving rise to the birth of more than 1 million infants.

Importantly, the number of cycles, deliveries and infants is not complete. Each year, some countries were unable to report the number of initiated cycles (reporting only the aspirations) and many countries had no complete follow-up of pregnancies to delivery. The proportion of pregnancies lost for follow-up ranged from 10% to 18%.

Availability

Availability, estimated as number of cycles per million inhabitants, was analysed for each year in those countries where the national data coverage was 100%. As shown in Fig. 1, the mean availability increased from 765 cycles per million in 1997 to 1269 cycles per million in 2011. Wide differences existed among countries and during the 15 years, the number ranged from 110 to 2893 cycles per million inhabitants.

Fig. 2 shows the proportion of infants born after ART as a percentage of the total number of infants born in the country. The mean percentage increased from 1.3% in 1997 to 2.4% in 2011, with differences among countries, ranging from 0.2% to 5.9%.

Age distribution

Fig. 3 presents the proportion of women aged 35–39 years and >40 years undergoing IVF/ICSI treatment. As seen, the proportion of women being 40 years or more gradually increased over the time period. The cycle outcome (pregnancies and deliveries) in relation to age has been reported by EIM only from 2006. As recorded in all the EIM reports, the pregnancy and delivery rates in IVF and ICSI cycles decrease with advancing age (data not reported—see the individual annual reports).

Treatment cycles per technique and the number of embryos transferred

The number of cycles for each ART technique and the number of embryos transferred were almost complete sets of data in all the 15

Table II From cycles to infants: total number of aspirations, embryo transfers, deliveries and infants born after ART during the 15 years analysed.

Total number cycles	5 919 320
Aspirations (IVF + ICSI)	4 227 027
Fresh embryo replacements (IVF + ICSI)	3 774 533
Frozen embryos replacements (FER)	1 079 054
Egg donation cycles (ED)	178 027
Total deliveries	931 722
IVF deliveries	302 492
ICSI deliveries	455 787
FER deliveries	129 629
ED deliveries	43 814
Total number of infants born after ART	1 154 386

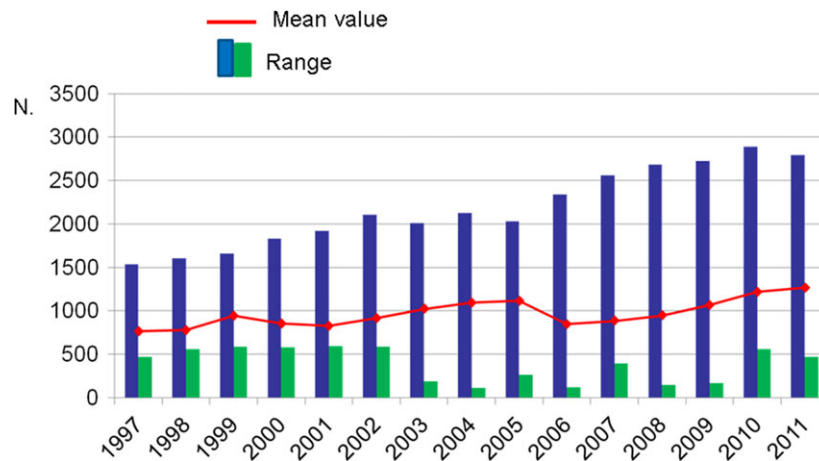


Figure 1 Availability: number of cycles / million inhabitants in countries where all clinics reported to the national register (100% coverage). The red line represents the mean annual value from all countries; the columns, the maximum value (blue column) and the minimum value (green column) registered each year among the countries.

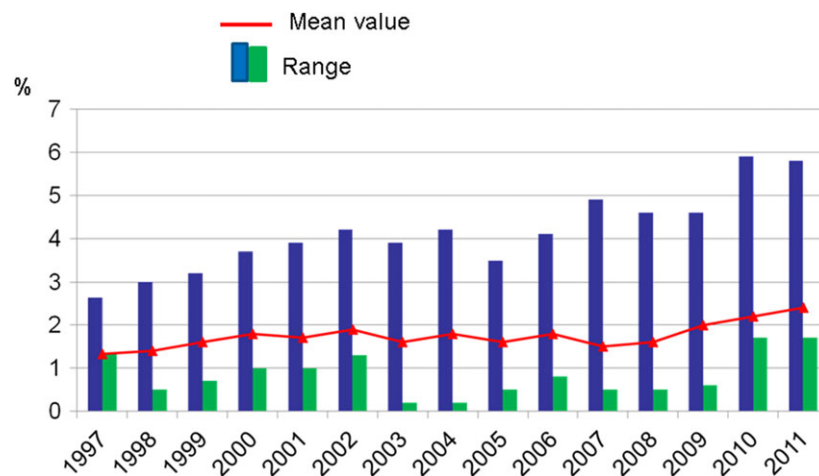


Figure 2 ART infants: percentage of ART infants of the total infants born in the countries where all clinics reported to the national register (100% coverage). The red line represents the mean annual value from all countries; the columns, the maximum value (blue column) and the minimum value (green column) registered each year among the countries.

reports. The proportion of IVF versus ICSI cycles is presented in Fig. 4. For 12 consecutive years, an increase in the proportion of ICSI was seen and it exceeded the use of IVF from 2002 onwards. Since 2008, a plateau seems to have been reached, where ICSI represents around two-thirds and IVF one-third of fresh cycles. A marked variation in the relative proportion of IVF and ICSI exists within Europe (see the annual reports).

Fig. 5 presents the proportion of transfers performed with one embryo, two embryos, three embryos and more than three embryos in each year. When the EIM programme was started in 1997, three

embryo transfers represented the majority and transfers with more than three embryos reached almost 15%. A clear trend in transferring fewer embryos has been continuously recorded over the years, despite some differences among countries. Already in 2000, dual embryo transfers became the most frequently used in Europe and the proportion of transfers with more than three embryos decreased from 15% in 1997 to less than 2% since 2006. At the same time, the percentage of single embryo transfers (SETs) started to increase, exceeding the number of three embryo transfers in 2005. The EIM reports are unable to discriminate between elective SET (eSET) and compulsory SET.

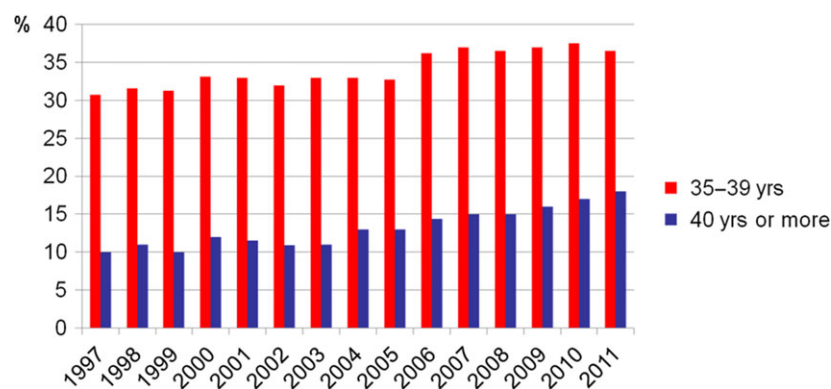


Figure 3 Female age: proportion of advanced aged patients of the total number of women undergoing IVF and ICSI cycles each year. Red column: 35–39 years; blue column: 40 years or more year

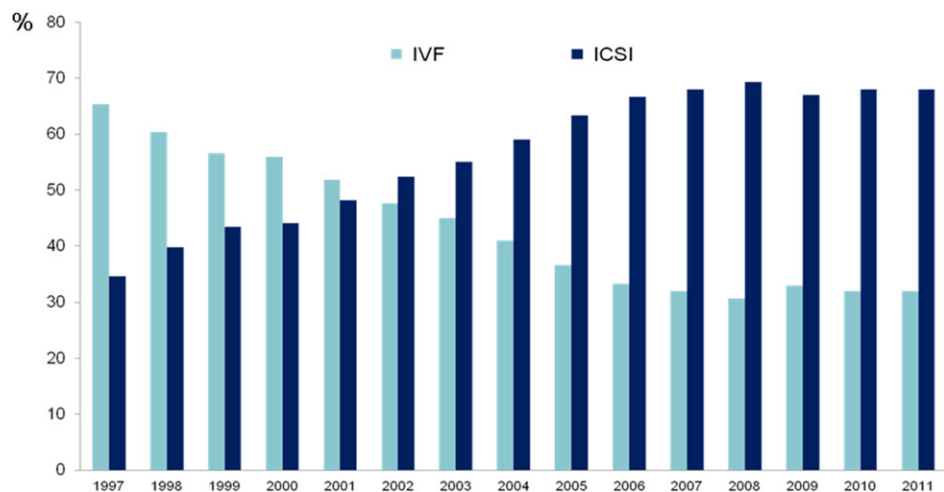


Figure 4 Techniques: proportion of IVF (light blue column) and ICSI (blue column) cycles performed each year. Reprinted with permissions from Kupka et al. (2016).

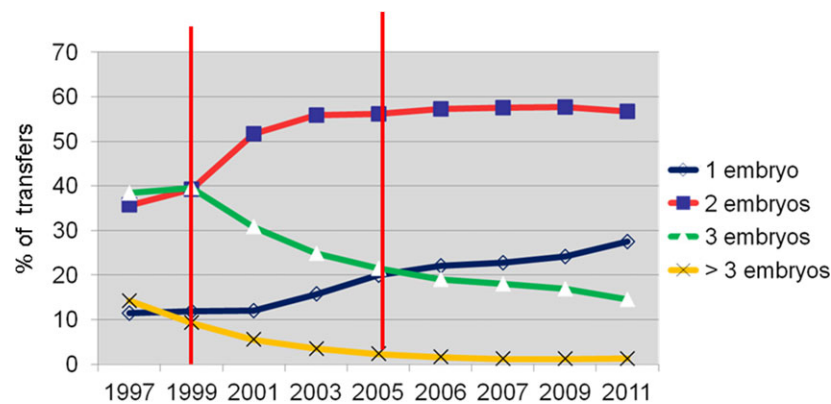


Figure 5 Number of embryos transferred: proportion of transfers performed each year with one (blue line), two (red line), three (green line) and more than three embryos (yellow line).

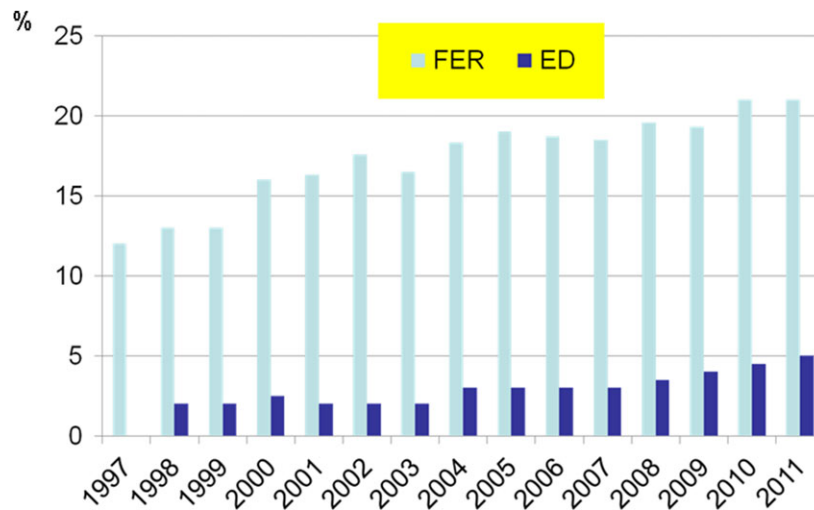


Figure 6 Techniques: the proportion of frozen embryo replacement (FER—light blue column) and egg donation (ED—blue column) of the total cycles.

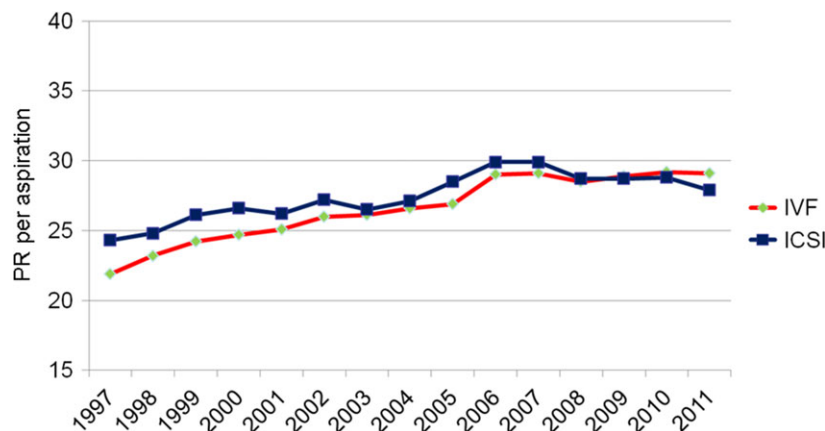


Figure 7 Effectiveness: annual pregnancy rate (PR) per aspiration in IVF (red line) and ICSI (blue line) cycles.

However, the increase seen in the more recent years is undoubtedly due to an overall increase of the eSET policy. In some European countries, for example Finland, Norway, Sweden, Belgium and Denmark, eSET represents the majority of recent SET.

Fig. 6 presents the proportion of FER and the proportion of ED in relation to the total number of cycles. For FER, the proportion during 1997–2011 increased markedly from 12% to 21%, and for ED, from 2% to 5%.

Effectiveness

As showed in Figs 7 and 8, the overall clinical pregnancy rate per aspiration and per embryo transfer increased for both IVF and ICSI until 2007. In the last four years covered in this publication, the

figures remained relatively stable. A relevant difference was present across countries each year, as expressed by the wide ranging minimum to maximum value (Fig. 9). The clinical pregnancy and the delivery rates per initiated cycle are not reported in the present paper because of the incomplete data. The number of documented pregnancy losses was reported from 2000. The average was 17%, ranging from 21.2% in 2000 to 13% in 2010.

The outcomes registered in FER and ED cycles are reported in Fig. 10.

Multiple births

The multiple delivery rate (twins and triplets or more) is presented in Fig. 11. Overall, triplet deliveries were reduced from 3.7% in 1997 to

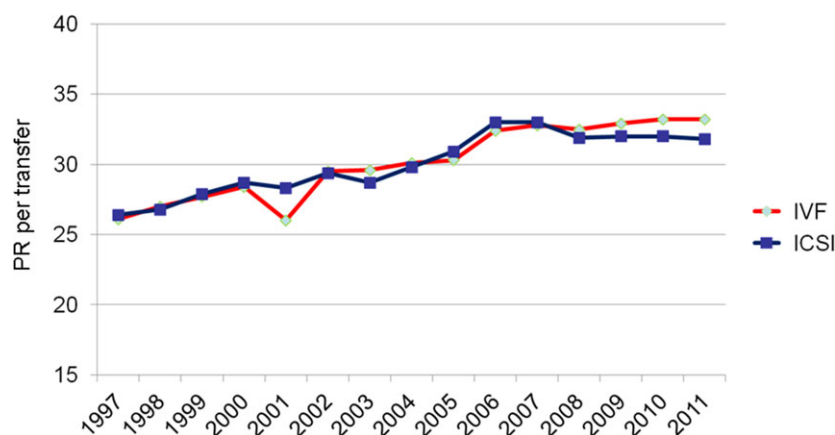


Figure 8 Effectiveness: annual PR per embryo transfer in IVF (red line) and ICSI (blue line) cycles.

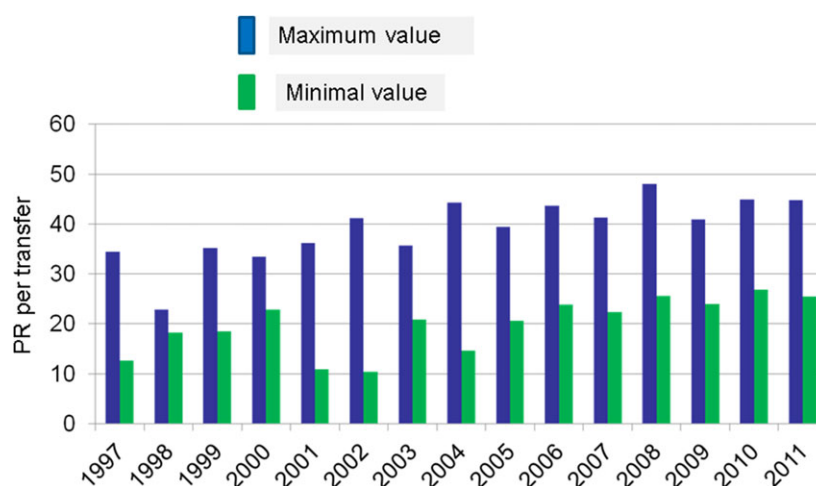


Figure 9 Effectiveness: maximum (blue column) and minimum (green column) PR per embryo transfer registered each year among reporting countries (ICSI plus IVF cycles).

0.6% in 2011. Major differences were present across countries; still in 2011 a few countries reported a triplet delivery rate higher than 4%. The twin delivery rate gradually decreased from 27.8% in 1997 to 18.6% in 2011.

Complications to treatment

Table III shows the complications recorded from 1999. A total of 29 031 ovarian hyperstimulation syndrome (OHSS), 6922 bleedings and 1349 infections have been registered. The highest incidence of OHSS was 1.2% in 2004 and 2005, and the lowest 0.3% in 2010. The total incidence of bleedings plus infections was similar across the years, with a mean value of 0.27%. A total of 20 maternal deaths have been reported.

IUI

Data on use of IUI have been collected since 2001. Data are therefore referring to 11 years. A total of 1 548 967 cycles have been reported during this period: 1 281 203 using husband semen (IUI-H) and 267 764 using donor semen (IUI-D). In the first five years (2001–05), the outcome was reported as clinical pregnancy. A total of 50 736 pregnancies have been recorded out of 429 946 cycles (11.8% per cycle). From 2006, the outcome was reported as delivery and the total reported was 58 154 after 1 119 021 cycles (5.2% per cycle). In IUI-H, the mean pregnancy and delivery rates per cycle were 12.4% and 9.2% in women <40 years and 8.2% and 4.4% in women ≥40 years, respectively. In IUI-D, the mean pregnancy and delivery rates per cycle were 17.6% and 13.7% in women <40 years and 7.7% and 6% in women ≥40 years, respectively. No relevant trends were observed

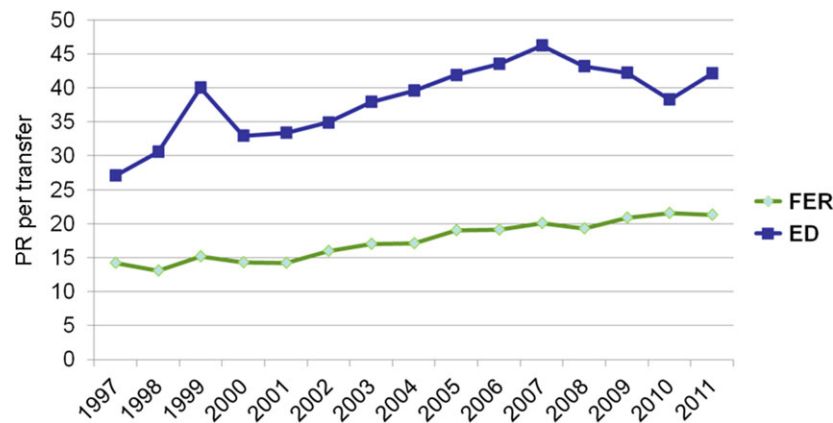


Figure 10 Effectiveness: annual PR per transfer in FER and ED cycles.

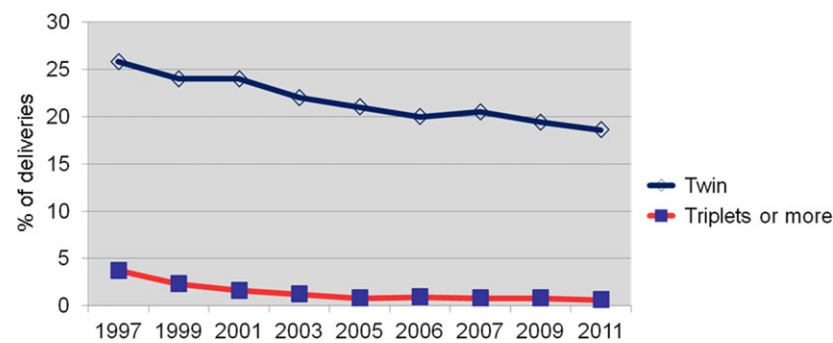


Figure 11 Multiple delivery rate: proportion of twin (blue column) and triplets or more (red column) deliveries of the total deliveries.

over the years. Overall, the incidence of twins and triplets were 10.6% and 1% in patients aged <40 years and 6.5% and 0.2% in women aged ≥40 years, respectively, and these values remained stable during the years.

Discussion

The picture resulting from the analysis of the first 15 years of EIM activity is able to provide data on ART in Europe. Even though, these data should be cautiously interpreted owing to limitations in methodology when accumulating data from countries with different collection systems, regulations, insurance coverage and different practices ([Global Reproductive Health-IFFS Surveillance, 2016](#)).

During the 15 years of activity, ESHRE's EIM programme collected and published data on 5 919 320 ART cycles and recorded a minimum of 931 722 deliveries of 1 154 386 infants. The real numbers are likely to be even higher owing to incomplete coverage of the initiated cycles and to the incomplete data on the pregnancies followed up until delivery. Thus the estimation of the real number of treatment cycles may be 7 200 000 and the true figure in terms of infants born may be 1 400 000.

One of the original main aims of the EIM programme was to monitor the trends over the time. The present publication is the first to summarize these trends. Some main conclusions can be drawn from the data presented.

The proportion of countries with a compulsory register showed a relevant increase, indicating how crucial it is considered by society in general, including the professional societies, to monitor the evolution of ART. However, the majority of registers are still based on cumulative data from each clinic and, although compulsory, collections are often incomplete. It remains a task for national and international organizations to set up high-quality national ART registers.

ART utilization across Europe expanded over the years, and the availability almost doubled from 765 in 1997 to 1269 in 2011. Despite that, the overall availability registered in the last years is still much lower compared to the demand for ART treatment, estimated by ESHRE at 3000 cycles per million inhabitants ([ESHRE Capri Workshop Group, 2001](#)). The data illustrate that availability is a complex product of public and private national health policies, where economic, political and social/cultural factors are the main forces determining the allocation of facilities, personnel and equipment. Only a few countries are able to offer a figure close to the estimated need.

Table III Complications of ART (number and incidence).

Year	Number of severe cases of OHSS	Incidence of OHSS (%)	Number of bleeding	Number of infections	Incidence of bleeding plus infection (%)	Number of maternal deaths
1999	1083	0.9	84	30		1
2000	1586	1.1	388	36	0.4	0
2001	1851	0.9	294	24	0.3	1
2002	2148	1.0	622	227	0.5	2
2003	2646	1.0	799	135	0.2	2
2004	2858	1.2	520	362	0.5	4
2005	3347	1.2	523	207	0.4	0
2006	2753	0.8	544	42	0.2	2
2007	2470	0.8	574	64	0.2	3
2008	2947	1.0	652	49	0.2	1
2009	2137	0.8	570	61	0.1	1
2010	1500	0.3	641	53	0.2	2
2011	1705	0.5	711	59	0.2	1
Total	29 031		6922	1349		20

OHSS, ovarian hyperstimulation syndrome.

Data regarding the age distribution of women undergoing ART showed the same trend reported all over the world (Dyer *et al.*, 2016). Since age is a major factor affecting outcome, aging has to be taken into account when evaluating the overall effectiveness of ART treatments. Despite differences across countries, an overall rising trend of ICSI utilization has been significant for years before reaching a plateau. The reasons for the high proportion of ICSI recorded in Europe and elsewhere are not fully understood, but it is a cause of concern (Evers, 2016).

A clear trend toward transferring fewer embryos was observed in Europe over the 15 years analysed. While reducing the number of embryos transferred, the number of cryopreservation cycles should increase, as also found in this report where cryopreservation cycles almost doubled. Additionally, as expected, the number of multiple deliveries (twins, triplets and more) decreased from 29.5% to 19.2% during the 15 years. This positive trend registered in Europe has been obtained without changing the effectiveness. When the majority of transfers shifted from ≥ 3 to 2 embryos (in 2009), the pregnancy rates per transfer and per aspiration continued to increase; when the proportion of SET started to become relevant (in 2005), the fresh pregnancy rates had a plateau but did not decrease. In addition, with the noticeable decline in the number of embryos transferred, the fresh pregnancy rate is not the best indicator for effectiveness. The best indicator of success may be the cumulative delivery rate (derived from the fresh and frozen cycles), which unfortunately cannot be calculated exactly based on the annual EIM reports.

A positive finding was that the incidence of OHSS declined in the last two years. The cause remains unknown but could be related to better predictors of excessive responses in ART (Broer *et al.*, 2011) and better preventive measures (Devroey *et al.*, 2011).

Since the inception of IUI data collection, no differences have been noted in terms of outcomes.

In conclusion, the present comprehensive analysis of 15 years of activity demonstrates that the initial aims of the EIM programme (to

collect and publish regional European data on census and trends on ART utilization, effectiveness, safety and quality) have been achieved. Data produced by the effort of the EIM Consortium can be utilized as a referent document for several aspects of ART, inside and outside the professional community. ESHRE will continue to support and to implement European data collection and publication by EIM.

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Authors' roles

A.P.F. performed the calculations and wrote the present paper. All the other co-authors reviewed the documents and made appropriate comments for improving the document. The first six authors are the past and present EIM chairman and therefore they have been consecutively responsible of the publication of the first 15 EIM annual Reports summarized in the present paper. L.G. was the member of the ESHRE Executive Committee involved in the EIM Consortium set-up. V.G. from the Central ESHRE Office performed the calculation in each annual EIM report.

Conflict of interest

None declared.

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