Journal Pre-proof

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PII: S1472-6483(23)00154-2
DOI: https://doi.org/10.1016/j.rbmo.2023.02.015
Reference: RBMO 3189

To appear in: *Reproductive BioMedicine Online*

Received date: 20 December 2022
Revised date: 28 February 2023
Accepted date: 28 February 2023

Please cite this article as: Anja Pinborg , Christophe Blockeel , Alison Campbell , Giovanni Coticchio , Juan A Garcia-Velasco , Pietro Santulli , Christian De Geyter , Christine Wyns , The time has come for harmonized international ART registration, *Reproductive BioMedicine Online* (2023), doi: https://doi.org/10.1016/j.rbmo.2023.02.015

The time has come for harmonized international ART registration

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Abstract

For more than two decades, the European IVF Monitoring (EIM) Consortium has collected data on IVF in Europe with the aim of surveilling quality and safety of ART treatments, to ensure the highest performance with the lowest risk for patients and their offspring. Likewise, the Society for Assisted Reproductive Technology (SART) in the United States and the Australia/New Zealand Assisted Reproduction Database (ANZARD) collect, process and publish data in their regions. The better the legal framework for ART surveillance, the more complete and reliable are the datasets. Worldwide, the landscape of ART regulation is fragmented, and until there is a legal obligation to report ART data in all countries, with appropriate quality control of data collected, the reported outcomes should be interpreted with caution. Once uniform and harmonized data are achieved, consensus reports based on collective findings can begin to address key topics such as cycle segmentation and complications. Improved registration systems and datasets allowing optimized surveillance should be developed in collaboration with patient representatives to consider patients' needs, especially aiming to provide higher transparency about ART services. Support from national and international reproductive medicine societies will also be essential to the future evolution of ART registries.

Keywords: ART registration; Europe; IVF data monitoring; Registries; Reproductive outcomes; Surveillance

Start of ART registration and its value in Europe and beyond

Since 1997, the European IVF Monitoring (EIM) Consortium, comprising representatives of national registries on assisted reproductive technology (ART) and other ART experts throughout Europe, has collected, audited and published regional data on IVF practices and outcomes. The aim of the EIM programme is to monitor the quality and safety of IVF interventions and report on clinical results and ART practices to learn how to deliver the best outcomes with the lowest risk for patients and their offspring (De Geyter et al., 2020). Year by year, more countries have been included. The latest reported data were from 39 countries, incorporating 1422 clinics offering ART services and a total of 1 007 598 ART treatment cycles; 23 countries had compulsory ART registration requirements and provided comprehensive national level data to the EIM from all centres performing ART (Wyns et al., 2022). In many countries, collection of ART data has been driven by the reproductive medicine societies and the healthcare professionals rather than government or health authorities. Furthermore, in 16 of 39 national health authorities in Europe the

registration of ART cycles is voluntary; hence, data from only a proportion of clinics are available for reporting to the EIM consortium. This incomplete reporting exists even in some of the largest countries in Europe having extensive ART activity (Wyns et al., 2022). Such a wide variation in reporting is a significant barrier to comprehensive EIM data collection and compromises the quality of the reported data, thus requiring cautious interpretation and comparison of resulting datasets. Initiatives and investment are needed to tackle these fragmented policies and improve the consistency and completeness of ART data reporting across Europe in order to obtain data of sufficient quality to allow robust surveillance and meaningful reporting that can inform best practices in ART clinics.

A recent retrospective analysis comparing ART data from the EIM register with data reported to the United States (USA) Centers for Disease Control and Prevention (CDC) and Australia/New Zealand Assisted Reproduction Database (ANZARD) showed that in all three regions, the number of ART cycles increased substantially over the last 20 years (5.3-fold in Europe, 4.6-fold in the USA, 3.0-fold in Australia and New Zealand) (De Geyter et al., 2020). This report identified a large variation across regions in practices such as use of 'freeze-all' cycles, numbers of replaced embryos and resulting multiple pregnancy rates, with a trend to fewer multiple deliveries with the increasing adoption of freeze-all in the USA and Australia/New Zealand, and later in Europe. Since 2012, there has been a striking similarity across all three continents in the most documented adverse event of ART, premature birth (<37 gestational weeks), which appears to be associated with the degree of multigestation. This clearly points towards a need for improved surveillance and continuous efforts on promoting single embryo transfer strategies worldwide. Recent publications from the Nordic countries have reported that preterm birth and cerebral palsy in ART children have declined after the introduction of a single embryo transfer policy (Opdahl et al., 2020, Spangmose et al., 2021). Thus, it is possible to improve outcomes and lower risk by introducing new strategies based on the knowledge from national ART data. For couples undergoing ART, the emotional and financial burden of treatment may be high and it is important that they choose ART clinics, treatments and procedures based on up-to-date knowledge of their performance and safety. Poorly informed choices, due to lack of accurate information, could result in futile ART attempts, for example in clinics with suboptimal cryopreservation practices. These could both diminish the likelihood of successful ART treatment, resulting in delayed childbirth or permanent childlessness, and lead to the decision of the patients to discontinue their treatments.

Evolution of ART strategies and the role of surveillance towards improvement of ART performance

In the beginning of the ART era, the efficacy of ovarian stimulation treatments was poor and high-dose gonadotrophin stimulation was used without escape strategies, resulting in a high risk of severe ovarian hyperstimulation syndrome (OHSS). Fresh transfer of multiple embryos was commonly performed resulting in multiple-birth rates of 30–40%, bringing high risk of preterm births and high rates of cerebral palsy in the offspring. Thus, ART was a high-risk treatment for women who, apart from the couple's reproductive disorder, were otherwise healthy. Today, ART treatments are safer as better understanding has led to the implementation of improved treatment strategies to minimize the risk of OHSS. Gonadotrophin-releasing hormone (GnRH) antagonist protocols with GnRH agonist trigger and cycle segmentation with freeze-all in case of high risk of OHSS have reduced the risk for women significantly. Further, blastocyst culture and vitrification with better embryo selection have facilitated the implementation of single embryo transfer to reduce multiple pregnancies.

Optimized embryo cryopreservation techniques, GnRH antagonist protocols, GnRH agonist triggers and demands of higher efficacy have led back towards the use of more aggressive gonadotrophin stimulation regimens and greater use of freeze-all rather than fresh embryo transfer strategies. This has also been driven by other treatment needs such as oocyte or embryo vitrification for fertility preservation for benign or malignant indications, oocyte donation and preimplantation genetic testing. Further, new stimulation approaches that do not compromise the oocyte quality such as duo-stimulation (Vaiarelli et al., 2018, Vaiarelli et al., 2020) and progestin-primed ovarian stimulation (Ata et al., 2021) also promote cycle segmentation and postponement of embryo transfer. Hence, with a 'freeze-all for all' strategy, the endometrium condition and implantation window become of less or no importance in the ovarian stimulation cycles.

Is this development beneficial to patients, considering the longer waiting time to pregnancy when embryo transfer is postponed, and the potential financial burden to the couple of expensive freezing procedures, which could limit or postpone access to ART treatments? Will this extended time to pregnancy lead to higher patient drop-out rates? Cumulative outcome data have shown that the number of withdrawals or dropouts after one completed treatment cycle can exceed 40%, even in a country with full reimbursement of all treatment costs (McLernon et al., 2016). Harmonized and uniform registration of freeze-all cycles and cycle-by-cycle registration allowing calculation of cumulative pregnancy and live birth rates can help to find answers to these important questions. Cumulative outcome rates can only be calculated if individualized data and generally accepted coding systems are introduced; this would allow tracking of cases over time, from one institution to another and even across countries (De Geyter et al., 2016).

Most frozen embryo transfer (FET) cycles are performed in hormone-replacement transfer (programmed) cycles without development of a corpus luteum, with significantly increased risks of preeclampsia and macrosomia. Recent research has indeed shown the crucial importance of the corpus luteum, and the detrimental effects a lack of corpus luteum has on maternal cardiovascular modifications during pregnancy and risk of preeclampsia (Busnelli et al., 2022). Such knowledge about FET cycles is a good example of the importance of surveillance through global high-quality ART registration. Besides easily pinpointing associations between specific ART treatment types and adverse outcomes, this example of the association between FET and preeclampsia and macrosomia will help to define research questions to study mechanisms behind these associations and eventually contribute to new and safer strategies.

Challenges in ART registration

Over the last 20 years, the impact of ART has been steadily increasing due to the growing number of ART cycles performed and its increasing contribution to birth rates; there is broad variability in treatment modalities offered across the nations, driven by factors including national regulation, clinical preference/priorities and knowledge. Although data reporting has reached high levels of completeness, inaccuracies and inconsistencies remain and need to be identified and quantified. The new diversity in ART treatment modalities and the increasing use of cryo-storage require organizational changes in the registration of ART, and there is a need for stakeholders to optimize surveillance and data quality assurance (Rimmer et al., 2022). Initiatives that already exist include the Core Outcome Measure for Infertility Trials (COMMIT), an international consortium of researchers, healthcare professionals and people with fertility problems, which has developed a core outcome dataset for general infertility research (Duffy et al., 2021). A core outcome set for male infertility is also being established to address the unique challenges pertinent to male infertility research (Rimmer et al., 2022). However, while these efforts focus on achieving harmonized parameters and definitions, such datasets are intended for use in clinical trials and are not designed for long-term longitudinal assessment with the ultimate goal of both surveillance and vigilance. To this end, a number of requirements should be fulfilled; these include the need for a consensus on tools to handle the long-term evaluation of outcomes at a patient level of new treatment modalities such as cycle segmentation in duo-stimulation and freeze-all cycles. In this context, cumulative outcomes are preferable although challenging. This is exemplified in the current EIM registry, which is based on retrospective aggregated data where the only possibility to have a cumulative approach (based on all transfers resulting from one aspiration) is to use a proxy for the *true* cumulative delivery rate; this is calculated as the ratio between the total number of deliveries from fresh embryo transfers and FET performed during a same calendar year (numerator) and the number of aspirations during the same year (denominator) (Wyns et al.,

2022). Timely uptake of novel technologies is another common shortcoming of national and regional registries, which are all slow to introduce new data parameters to record. For instance, while freeze-all cycles entered practice in 1999, they were only registered from 2008 in CDC, 2011 in ANZARD and 2017 in EIM (De Geyter et al., 2020).

Strategies to improve ART registration

The better the legal framework for ART surveillance, the more complete and reliable are the datasets. Europe faces a highly fragmented landscape of ART regulation, and until uniform national reporting is established in all European countries, together with appropriate quality control of the submitted data, the reported numbers and calculated incidence rates should be interpreted with caution. National reporting can be obtained by establishing a well-functioning electronic system based on harmonized parameters and definitions collected by the EIM consortium under the umbrella of the European Society of Human Reproduction and Embryology (ESHRE). Once uniform and harmonized data are achieved, developing consensus on how to act on the cumulative outcomes and complications will be the next step. Increasing the awareness of all stakeholders about the importance of surveillance is key and legal pressure should aim to prioritize vigilance and surveillance of ART at a national level. Surveillance and vigilance are well accepted and inherent parts of patient care in several medical disciplines, such as blood transfusion, organ transplantation and drug treatment. It is now time that surveillance and vigilance become incorporated into patient care in reproductive medicine as well. There is a need to develop a GDPR-compliant information technology solution that can be adapted to the many different ART registration systems used by European countries. In fact, one such initiative, the European monitoring of Medically Assisted Reproduction (EuMAR) data registry, supported by European Union funding granted recently to ESHRE, is being developed to provide a standardized, web-based platform to collect cycle-by-cycle data entries from professional groups across Europe. The aim is for EuMAR to be integrated into the proposed European Health Data Space initiative of the European Commission, which aims to enhance digital health data management within the European Union to support increased surveillance and vigilance, which in turn will allow improved safety and efficacy monitoring.

Proper registration can set pivotal standards, as evidenced with the adoption of the single-embryo transfer strategy: the Nordic countries and Belgium were pioneers in this approach, not least due to their registration of multiple birth after ART, and many other countries followed. As an example, the Swedish Quality Registry on IVF (Q-IVF 2023) is a very effective system that provides clinicians with annual reports including cumulative outcome figures. In the Swedish system both the “cumulative live birth rate per

oocyte retrieval and year of treatment, including all embryo transfers within one year after oocyte retrieval" and the "proportion of live births per oocyte retrieval and the first embryo transfer (fresh or frozen) within 6 months after oocyte retrieval" are reported on a national basis. The first increased from 28.8% in 2007 to 43.2% in 2019 and the latter from 23.6% in 2007 to 32.9% in 2019, showing that with a strict single-embryo transfer policy cumulative live birth rates per oocyte pick-up has increased (Q-IVF 2022).

Eventually, besides cycle-by-cycle registration of uniform datasets including a patient identifier (De Geyter et al., 2016), variables monitored should be expanded to include intention-to-treat data, with recording of all initiated cycles, to enable evaluation of drop-out rates and cycle cancellations. The involvement of stakeholders may be improved through the introduction of continuous benchmarking as an indication to ART centres of their performance, and uniform reporting of medical and laboratory data, which will benefit the follow-up of participating individuals.

Another limitation to be addressed in the existing ART registries is the low reporting of outcomes in the offspring. In Europe, data collection for children born from ART cycles is only possible in a few countries where data from ART cycles, mothers and children can be cross-linked with a unique maternal ID number (Opdahl et al., 2015). Linkage between registries is indeed the way forward to address this shortcoming. In this regard, the Nordic experience from the Committee of Nordic ART and Safety (CoNARTaS) has already shown that it is possible to link ART data from more countries with both short- and long-term follow-up of the children. Such developments will help to define ART programs of excellence, particularly those applying high quality cryopreservation facilitating single embryo transfer strategies, that can reduce the high preterm birth rates that have been reported with ART.

Improved registration and datasets allowing optimized surveillance should be developed in collaboration with patient representatives to incorporate patient's needs and requirements, especially aiming to provide higher transparency about ART services. Furthermore, support from national and international reproductive medicine societies will be essential for future evolution of ART registries.

Authors' roles

All authors contributed to the concept and drafting of the manuscript.

Acknowledgements

This opinion paper is a joint effort of the members of the International Consortium on Fertility Opportunities (ICFO). Editorial assistance was provided by Joanne Fitz-Gerald, BPharm, at FourWave™ Medical Communications.

Funding statement

ICFO is an industry-funded initiative supported by Gedeon Richter. Editorial assistance was funded by Gedeon Richter. The sponsor had no role in the preparation or review of the manuscript.

Disclosures

AP has received personal fees and research support from Gedeon Richter, MSD, Ferring, Merck, Organon, IBSA and Cryos.

CB has received personal fees and non-financial support from Abbott, Besins, Ferring, Gedeon Richter, Merck, MSD and Organon.

AC has received speaker and advisory board fees and expenses payments from Gedeon Richter, Cooper, Theramex, Merck and Ferring.

GC has received personal fees from Gedeon Richter and non-financial support from Gedeon Richter and in previous years from IBSA and Excemed.

JAGV has received grants and speaker fees from Gedeon Richter, MSD, Merck Serono, Ferring and Theramex. At the time of submission, JAGV was Joint Chief Editor of *Reprod Biomed Online*; journal policy recused the author from having any role in the peer review of this manuscript.

PS has received grants and speaker fees from Gedeon Richter, Merck Serono, Ferring, Ipsen and Besins Healthcare.

CDG has received grants from Ferring, MSD and IBSA and participated in the global advisory board of Ferring and the Swiss national advisory board of MSD.

CW has received speaker and advisory board fees from Gedeon Richter, Merck and Ferring and research grants from Ferring.

Data availability statement

No new data were generated or analysed in support of this research.

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