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Assisted reproductive technology: Impact on society and need for surveillance

Christian De Geyter, Division Chief and Research Group Leader

Reproductive Medicine and Gynecological Endocrinology (RME), University Hospital, University of Basel, Vogesenstrasse 134, CH-4031, Basel, Switzerland

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Since the first successful treatment with conventional in vitro fertilization (IVF) in 1978 assisted reproductive technology (ART) has become an integral part of modern medicine and now plays a key role in the fulfillment of family planning. At least five million of infants have been born as a result of ART and in some countries the proportion of infants born after ART now exceeds 5%. Such an impact of ART on society and demography call for adequate surveillance including vigilance of occurring adverse events, especially when novel technology is introduced. In many countries the activities in ART are being recorded and analyzed by national registries, either on a voluntary or on a compulsory basis. Despite all endeavour, the data sets are still incomplete and complications are underreported. In addition, the published reports usually contain cross-sectional data only, collected and analyzed on an annual basis. However, current ART is now developing towards a segmented longitudinal approach, in which single therapeutic steps may be spread over prolonged time intervals. In the near future, ART-data should be handled and reported in a cumulative fashion. The final outcome of ART, defined by the birth of a healthy baby or by the final consumption or destruction of cells and tissues, must be made traceable to one single initiating event, such as the first day of ovarian stimulation or the collection of oocytes, even if that event took place several years earlier. In failed cases or when frozen material was lost or destroyed or transported, negative outcome events should be recorded in order to avoid overestimation of treatment efficacy. To all stakeholders, both surveillance and vigilance in ART are crucial steps towards better quality control and full transparency.

E-mail address: christian.degeyter@usb.ch.

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Why assisted reproductive technology (ART)?

The term ART denominates all interventions including the in vitro handling of human oocytes, spermatozoa and embryos for the purpose of reproduction. Among those interventions are in vitro fertilization (IVF), embryo transfer (ET), intracytoplasmic sperm injection (ICSI), embryo biopsy, pre-implantation genetic testing, assisted hatching and cryopreservation of either gametes or embryos [1]. The broader term "medically assisted reproduction" (MAR) also includes insemination, either with partner sperm or donor sperm [1]. More recent developments consist of the surgical removal, the processing and the cryopreservation of gonadal tissues of both men and women, both before and after puberty, offered to individuals diagnosed with cancer and scheduled for potentially gonadotoxic chemotherapy.

All these technologies originated after early scientific work carried out in the sixties and seventies of the previous century. Appriopriate laboratory conditions for human oocyte maturation and embryo culture in vitro were elaborated [2,3] in parallel to laparoscopic recovery of preovulatory oocytes [4]. The first successful IVF leading to the birth of Louise Brown in 1978 [5] became the ignition event for a revolution-like global spread of ART. Reproductive medicine, including ART being its most effective treatment modality, has become an integral part of modern patient care.

ART may also be seen as the logical result of present-day family planning, which started with the introduction of the first oral contraceptives in the early sixties. Since then, birth control pills and other forms of contraception have profoundly changed society. The possibility of family planning not only allowed women to pursue a professional career, but also helped to postpone reproduction. This trend is still ongoing today (as exemplified by Swiss data [6]: Fig. 1). In a substantial number of couples delayed family planning inevitably contributes to infertility [7].

In addition to delayed conception, modern family planning impacts the number of children born per family. The focus of more mature parents on fewer children has stimulated the need for high quality fetomaternal medicine aiming at identifying and avoiding all potential fetal health threads, which are more prevalent at the advanced age of the parents-to-be, and for optimal obstetrical and neonatal care,

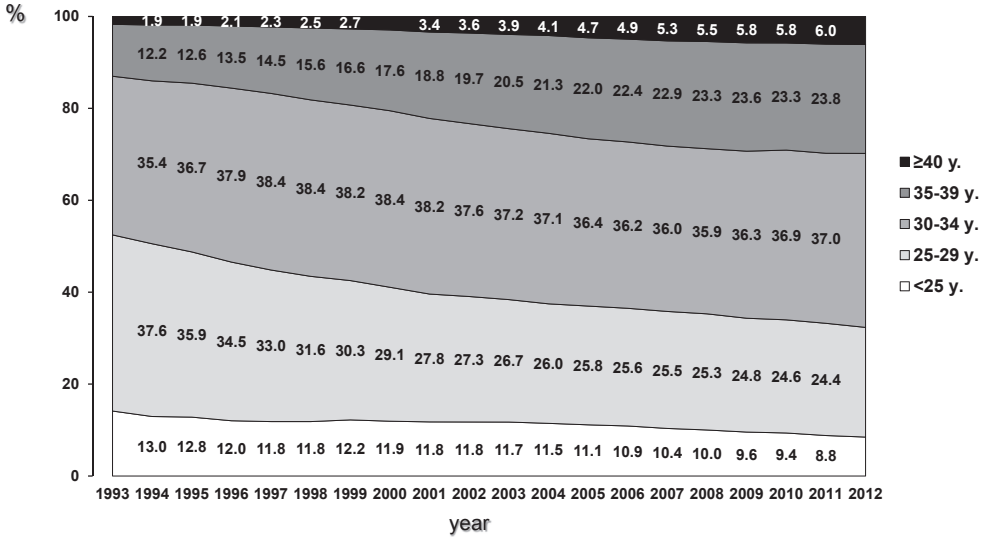

Fig. 1. The age of women giving birth in Switzerland between 1993 and 2012 was extracted from the data base constructed and published by the Swiss Federal Office of Statistics (BfS). During this observation period the proportion of women giving birth at the age of 35–39 years or older has nearly doubled, whereas the age of women giving birth at the age of 40 years or older has risen more than threefold [6]. Published with permission of Swiss Medical Weekly.

eliminating all risks to the mother and to the baby. This „precious baby syndrome“ attitude is also closely linked to the genetic testing of preimplantation embryos and even whole genome screening of the parents-to-be.

Current impact of ART on demographics

These societal attitudes but also new medical and laboratory opportunities have a created a thriving industry specifically dealing with family planning, reproduction, pregnancy and birth. Pharmaceutical industry is involved in producing the sophisticated medications needed to control ovarian and uterine functions during all ART procedures. Other industries have taken over the production of the culture media (including quality control), the increasingly sophisticated equipment of the embryology lab and the production of the surgical devices needed for oocyte collection, embryo transfer and many other interventions. Professional teams offering ART services are typically multidisciplinary and consist of highly specialized physicians, clinical embryologists, nurses, psychologists and administrative personnel. The increasing complexity of treatment options demand frequent networking with other medical disciplines, such as medical geneticists (as in preimplantation genetic testing), oncologists (as in fertility preservation), urologistis (for testicular sperm extraction), obstetricians, and others.

Whereas during the early days of ART oocytes were retrieved surgically, transvaginal ultrasound-guided oocyte collection has transformed ART to an outpatient treatment, that can be performed outside of any hospital environment. Easy access private institutions offering low threshold ART-services have become a common picture in cities throughout the world.

As a result of all these activities more than five million infants have meanwhile been born from ART [8], Europe being the most active continent [9]. In countries with virtually full data coverage, the data demonstrate that the relative proportion of children born after ART with respect to all newborn children continues to rise (Fig. 2). However, the use of ART may be highly variable in different countries and depends on many factors, such as access to reimbursement of treatment costs [10,11] and cultural openness to this technology [12]. In the most active country worldwide, Denmark, as many as 6.3% of all newborn children are born after ART [9]. In parallel to the rising ART treatment numbers more multiple births (the most frequent complication in ART) are being observed as well. More multiple pregnancies invariably cause an unprise in the number of premature children, born potentially with compromised future health.

For many reasons the ever rising impact of ART on reproductive choice has provoked and is still provoking intensive political debate. As a result, most countries have imposed legal frameworks, which may vary considerably from one country to another. However, the continuously expanding therapeutic opportunities in ART will continue to ferment the political debate. Objective, accurate and, if possible, controlled data are needed to rationalize this debate.

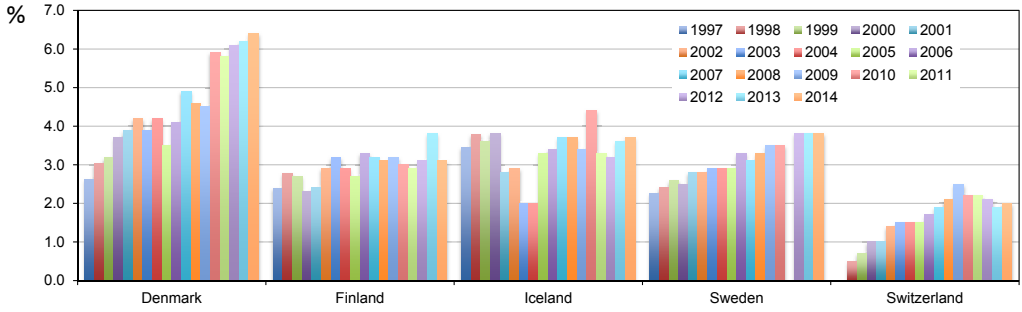

Fig. 2. The relative proportion of children born after ART is compared with that of all children born in a number of European countries with virtually full coverage of ART data. The data are taken from the respective EIM-reports, all published in Human Reproduction, and available online (www.eshre.com).

Measurement and quantification of ART activities

Considering its impact on society and with view on ongoing controversies all activities in ART should ideally be registered, be analyzed and be made transparent to the public through publications in peer-reviewed, high ranking journals. Surveillance in ART is defined by the continuous and systematic collection of health data needed for the analysis and interpretation of trends in medical care including their safety. Data registration in ART should also include incident complications. Vigilance in ART is defined by the detection, analysis and communication of complications, errors and adverse events occurring during or after ART. Both surveillance and vigilance in ART are not easy tasks. Data on ART are usually collected and scrutinized in regional or national registers. The submission of data to these registers is often made compulsory by law, but in many countries is conducted on a voluntary basis by dedicated professional groups. Data collection in ART is challenging, because it also requires data on the pregnancies, deliveries and the health status of the newborn babies. These data must be requested actively by the institutions involved in ART towards the obstetrical care units. All information linking together the various steps during ART with the final pregnancy outcome and with the health status of their child (ren) can only be collected after having obtained an informed and signed consent of all patients involved.

To the purpose of surveillance in ART the European Society of Human Reproduction and Embryology (ESHRE) has setup the largest data register in ART worldwide in 1999 and the European IVF-monitoring consortium (EIM) published every year its report (for review see: [13]). Other continents and countries have been involved in similar activities. The International Committee for Monitoring Assisted Reproductive Technology (ICMART) is an overarching organization, which is involved in collecting, analyzing and disseminating global data on ART.

Although all these registries have been very influential in the political debates in many countries (such as recently in Switzerland, [14]), most still suffer of incomplete and inaccurate data sets. Most particularly, the European EIM-registry (a consortium of ESHRE) has been confronted with many obstacles while collecting data on ART due to the lack of unifying structures and because of the diversity of countries, each with very different cultural, political and legal systems. This task is further complicated by the high frequency of crossborder reproductive care particularly in Europe and elsewhere, which naturally develops in countries with strict legislation neighboring other countries with a more liberal legislation. Notwithstanding these difficulties most registers in ART, including that of EIM, have succeeded in collecting workable data sets on an annual basis and in disseminating these results in high impact medical journals.

Implementation of new developments in surveillance

Modern ART is increasingly becoming a long term process consisting of sequences of short or intermediate therapeutic steps. The ultimate therapeutic aim (a viable pregnancy) may be delayed deliberately by many months or even years, making conventional cross-sectional analysis per year increasingly obsolete. This is made possible by recent advances in cryopreservation of gametes and embryos. In order to prevent multiple pregnancies fewer embryos are now being replaced per treatment cycle, preferentially one single selected embryo, and the remaining cohort of embryos may be cryopreserved for later thawing often beyond the time limit of the annual data reporting. Increasingly all embryos are stored frozen to prevent complications, such as the ovarian hyperstimulation syndrome (OHSS). Preimplantation genetic testing also involves the cryopreservation of the biopsied embryos until the results of genetic analyses become available.

Other approaches that increasingly impact the therapeutic rationale in ART are the freezing of oocytes for delayed family planning or of gametes and gonadal tissues prior to chemotherapy for fertility preservation of individuals diagnosed with cancer. All these interventions require prolonged storage of reproductive material. Long term storage of biological material inherently carries the risk that it will never be used for procreation, or, alternatively, that it may be transported to another institution, possibly in another country. Currently, data are completely lacking as regards the sourcing, processing, transport and distribution of gametes, embryos or gonadal tissues within individual countries or across borders. These transports inherently carry many risks, such as loss of the gametes

during transport, intermediate disruption of the freezing conditions, mislabeling, contamination of the receiving institution with infectious agents or commercial abuse of the transported gametes or embryos. At present, the outcome of infertility treatments with transported gametes is rarely, if ever, documented in any registry. Recently, a central unifying coding system for Europe was suggested to allow crossborder reproductive care in Europe [15].

Surveillance in ART should become an inherent part of ART and the installment of a compulsory ART data registration through a legal framework has been demonstrated to be highly beneficial [16]. The compliance of the caregivers to any imposed legal obligation needs to be controlled as well. Appropriate legislation is also important for the informed consent to be signed by every single individual undergoing ART.

Analysis of the data sets should be directed from crosssectional (for example over a period of one year) to cumulative data analysis, in which the results of one single intervention such as oocyte pickup or ovarian tissue biopsy is recorded and followed until the delivery of at least one healthy child. If oocytes, embryos or gonadal tissues are destroyed, on purpose or accidentally, this event should also be notified as the end point of the intervention. If a patient decides to change the treating institution, all data on the previous treatments and eventual biological material should be made identifiable such that the previous intervention and the final results can be made traceable [15].

Conclusions

As in other medical fields, improvement of both surveillance of all ART activities and vigilance of occurring complications and adverse events is becoming mandatory. National registers have been organizing and high levels of completeness have been reached in many countries, but the current trend towards a higher diversity in treatment modalities demand changes in the setting of our data collection. ART surveillance should now develop from cross-sectional data analysis towards prospective surveillance of cumulative data.

Practice points

- Surveillance in ART is defined by the continuous and systematic collection of health data needed for the analysis and interpretation of trends in medical care including their safety.
- Vigilance in ART is defined by the detection, analysis and communication of complications, errors and adverse events occurring during or after ART, including infant health.
- ART is developing from a cycle-dependent treatment protocol towards a segmented longitudinal approach, in which single therapeutic steps may be spread over prolonged time intervals.
- Surveillance and vigilance in ART should now be organized from a crosssectional approach to a cumulative-based analysis.

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