

EDITORIAL



Towards the global coverage of a unified registry of IVF outcomes



IVF is generally considered one of the best-registered procedures in medicine. Today, 40 years after its heavily criticized clinical introduction, IVF is available as a successful treatment for infertility almost all over the world. Over 8 million IVF children have been born, and over 2.5 million cycles are being performed every year, resulting in over 500,000 deliveries annually. There is much to be proud of in such distinct achievements, yet many challenges remain.

CURRENT REGIONAL IVF REGISTRIES

Regional outcomes for IVF and intracytoplasmic injection (ICSI) – together often referred to as assisted reproductive technology (ART) – have been reported annually for many years for Europe in *Human Reproduction*, the journal of the European Society of Human Reproduction and Embryology (ESHRE) (de Geyter *et al.*, 2018), for the United States by the Centers for Disease Control and Prevention (CDC)

on their website (<https://www.cdc.gov/art/artdata/index.html>), and for some years for Latin America in our journal *RBMO* (Zegers-Hochschild *et al.*, 2018). It is with great pleasure that we are publishing the initiation of the annual African IVF registry in this issue of *RBMO* (Dyer *et al.*, 2019). Dr Dyer and her entire team are to be congratulated for this major achievement, and for their drive and persistence to motivate the many countries and centres to participate in this registry on a voluntary basis. *RBMO* is proud to be able to act as the platform of important developments in global IVF.

The main outcomes reported by the registries mentioned above are outlined in TABLE 1. It is clear that there is considerable variability in reported outcomes, both in terms of the numerator (clinical pregnancy, delivery, live birth) and the denominator (per started cycle, or per oocyte retrieval). This lack of a global consensus regarding crucial unified outcome measures renders the data reported by different registries difficult to compare.

Moreover, comparing results between continents remains extremely complicated for a variety of other reasons, such as huge differences in the cost of treatment (FIGURE 1) and associated differences in access to care (TABLE 2), along with differences in the characteristics of the patients being treated (especially in relation to lifestyle differences, possible inherent ethnic differences, diverse underlying disease conditions, previous treatments and duration of infertility, and most importantly differences in the age of patients undergoing IVF). A way to address at least some of these difficulties would be to also report outcomes in a standard subset of patients.

Unfortunately, what remains absent from a more comprehensive global coverage of IVF outcomes is data from the important Asian Pacific region, where a substantial number of IVF cycles is performed every year (estimated at more than 400,000 cycles annually). The current chair of the Asian Pacific Initiative on Reproduction (ASPIRE) has provided assurances, however, that they are currently working on

TABLE 1 SUMMARY OF GLOBAL REGIONAL IVF REGISTRIES

Area, date (Reference)	No. of countries No. of centers	No. of cycles	Success rate	Mean no. embryos/ET	Multiple births
Europe, 2014 (de Geyter <i>et al.</i> , 2018)	39 1279	508,433	30% IVF 28% ICSI clin pregn/asp	–	83% singleton 17% twin 0.5% triplet Frozen embryo transfer reported separately
USA, 2015 (CDC, 2015)	NA 464 (93% of total)	231,936	24% live birth/started cycle	–	19% singleton live birth
Latin America, 2015 (Zegers-Hochschild, 2018)	15 175 (70% of total)	75,121	24% IVF 21% ICSI delivery rate/OPU	–	20% twin 1% triplet and higher
Africa, 2013 (Dyer <i>et al.</i> , 2019)	13 40	25,770	28% IVF 36% ICSI clin pregn/asp	2.4 (27% multiple deliveries)	Low access to care
Global, 2008–2010 (Dyer <i>et al.</i> , 2016)	60 2500	4.5 million	20% ART delivery rate/ fresh asp	1.9 (30% SET in 2010)	21% multiple delivery rate
Worldwide, 2004–2013 (Kushnir <i>et al.</i> , 2017)	Australia, New Zealand, Canada, Europe, USA, Japan, Latin America	7 million	5–29% live birth rate/fresh ART cycle	Varies	4–27% multiple delivery rates

Cycles performed in Asia (presumed to be > 400,000 annually) are not included.

asp = aspiration of oocytes; clin pregn = clinical pregnancy; ET = embryo transfer; OPU = oocyte retrieval; SET = single embryo transfer

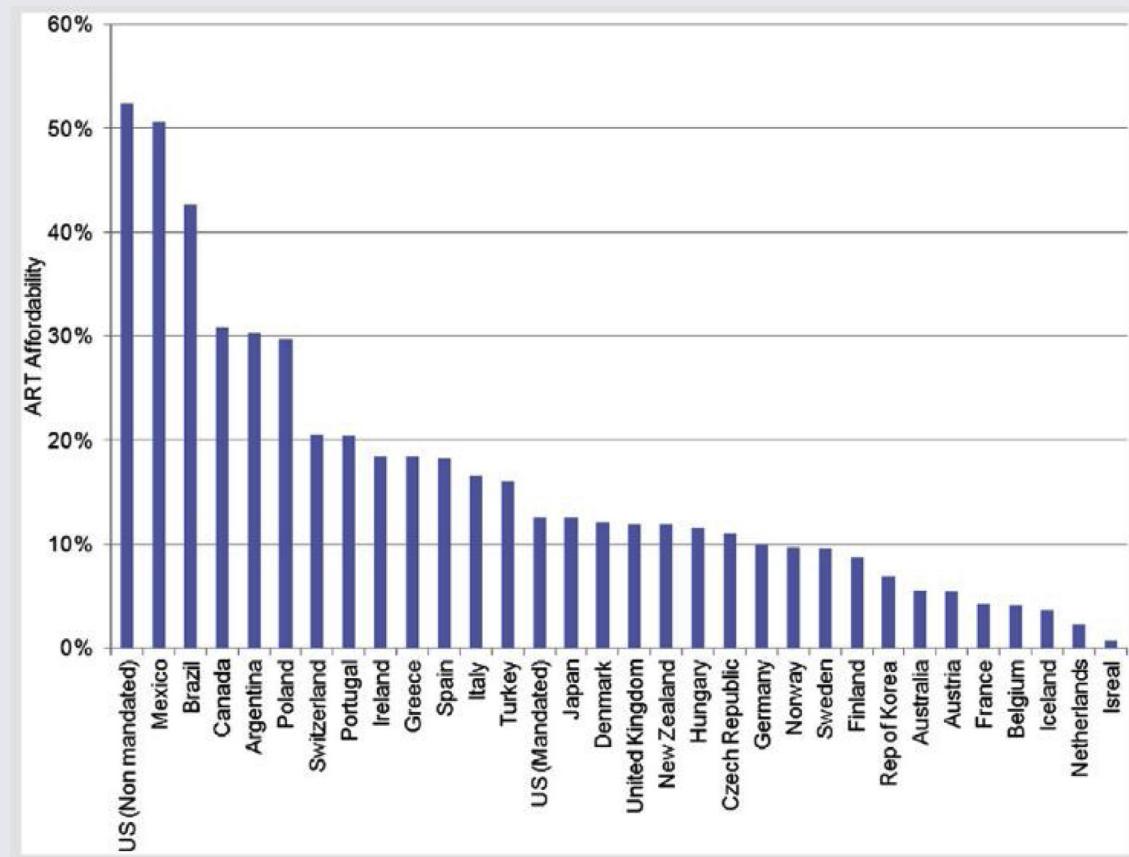


FIGURE 1 Affordability of IVF in the years 2006/2007 (reproduced from *Chambers et al., 2013*).

TABLE 2 WORLDWIDE DISPARITY IN ACCESS TO ART CARE IN 2008 (ADAPTED FROM *DYER ET AL., 2016*)

Country	No. of ART cycles/million inhabitants
Belgium	2747
Australia	2603
Greece	1903
Japan	1501
Netherlands	1292
France	1209
Germany	844
UK	827
Italy	766
Egypt	698
USA	590
Russia	295
Brasil	149
Mexico	126
India	79
Africa	55 ^a

^a Based on currently available data, but the true figure may be estimated as 275 cycles/million population (*Dyer et al., 2019*).

such a registry as a high priority (Professor Wiweko, personal communication).

In addition, considerable attempts have been made in the past by the International Committee Monitoring ART (ICMART) to summarize global IVF data based on existing registries. ART data for the years 2008–2010 from approximately 60 countries and 2500 centres (collectively representing approximately 4.5 million IVF cycles) have been reported recently (*Dyer et al., 2016*), also outlined in **TABLE 1**. Finally, worldwide trends for the period 2004–2013 have been described in the greatest ART data set available so far, involving national and regional registries representing over 7 million ART cycles (*Kushnir et al., 2017*). Live birth rates per fresh ART cycle vary greatly, in part due to the widespread introduction of natural cycle or minimal stimulation IVF in some parts of the world, along with distinct differences in the number of embryos transferred in fresh IVF cycles (for further details see **TABLE 1**).

HOW ABOUT THE AFRICAN REGISTRY?

The current first report of the African ART registry (ANARA) involves 40 centres in 13 countries (Benin, Cameroon, Egypt, Ghana, Ivory Coast, Mali, Mauritius, Morocco, Nigeria, Senegal, South Africa, Togo, Tunisia), and a total of 25,770 initiated ART cycles, resulting in a very low overall ART utilisation rate of 55 cycles per million population. ART utilization may be considered a proxy for overall access to infertility care, which is clearly very low in Africa. The true degree of access to ART care may be substantially higher, but many barriers to treatment remain, especially financial burden and the complete lack of external funding systems. To date, participation in the registry in the majority of the countries listed above has been low, resulting in an overall participation rate of only 19%. Hence, inclusion bias of data reported remains a realistic possibility.

It should also be noted that most patients treated in Africa are under 35 years old and therefore may present with favourable IVF outcomes. On average, 2.4 embryos have been transferred, which may be related to a favourable overall pregnancy rate reported per fresh embryo transfer. Unsurprisingly, such an embryo transfer policy has given rise to a high multiple delivery rate of 27%. Some preliminary results regarding pregnancy follow-up are also reported, again with a great margin of uncertainty due to major inter-country differences in those lost to follow up.

Of course, there remains much to be done to improve the African registry, since – due to under-reporting – data currently reported may not be representative of all IVF performed in Africa. This position, however, takes nothing away from the greatness of this first step. This first landmark report will hopefully encourage more African countries and centres to include their prospectively collected data in future annual reports of this registry, allowing the provision of more robust data that better represents ART in Africa. Setting a clear standard for the way IVF should be practiced in Africa would create a point of reference for individual centres, would allow the monitoring of differences in outcomes over time related to policy changes and changes in applied IVF technologies, and would also provide a

useful source of information for African patients seeking ART care. In addition, such a registry may increase the visibility and transparency of ART treatment (and infertility care in general) in Africa, which may result in much-needed increased social acceptance by patients, communities, media, governments, insurers and even churches. Finally, such registries would allow for the future monitoring of both short- and long-term health outcomes in women undergoing IVF and their offspring.

CHALLENGES TOWARDS THE UNIFIED REPORTING OF IVF OUTCOMES; THE ISSUE OF 'LIVE BIRTH'

Ideally, a registry should focus on the robust reporting of a medical intervention with clearly described characteristics for patients undergoing such a treatment along with well-defined endpoints for success (or failure) of treatment. In medicine, current discussions regarding treatment outcomes centre around the so-called 'PROM' (patient-reported outcomes measures). Hence, patients should also be involved in defining the most relevant endpoints for such registries. In other areas of medicine where patients have indeed been involved in defining the most appropriate outcomes, it turns out that the views of the doctor do not necessarily always coincide with what is important for patients. I am not aware of any instances where patient preferences have been explored in a systematic fashion in the context of infertility, let alone IVF. I would assume – but of course I could be wrong – that patients would focus primarily on the chance of ending up with having a healthy child when starting ART treatment, along with time to pregnancy ('how long will it take'), and at what cost both in terms of money (affordability, especially important in the many countries where patients have to pay out-of-pocket for treatment), burden of treatment ('will I suffer, and how will it interfere with my life') and chances for serious complications. We have previously referred to this as the 'holistic approach' of assessing IVF outcomes (Heijnen *et al.*, 2004).

During the early days of IVF, individual IVF centers started reporting their chances for a positive pregnancy test following the transfer of multiple embryos. Aiming to compensate for

suboptimal embryology laboratory performance in those early years, a clinical practice evolved that aimed to generate many oocytes, allowing for the subsequent transfer of multiple embryos. A positive pregnancy test was portrayed as a success. However, such an event could end up as just a (another) stressful experience for patients if the pregnancy ended in a miscarriage. Aiming to maximise success rates per fresh embryo transfer (that is often how national registries report IVF success rates of individual clinics), many embryos were transferred at the same time resulting in unacceptably high multiple pregnancy rates with major implications for perinatal morbidity and even mortality (Fauser *et al.*, 2006). In fact, even today, in many parts of the world – including Africa – approximately 50% of all children born following IVF are from multiple pregnancies. Evidence is accumulating that multiple (and even twin) pregnancies following IVF are associated with suboptimal perinatal outcomes and potential negative implications for future health of IVF offspring (Pinborg, 2018).

Over the years, the creation and handling of embryos in the laboratory has improved significantly, as has the cryopreservation of embryos generated but not transferred in the fresh cycle. Despite this, the current policy to continue to transfer multiple embryos simultaneously may be related to the often-used parameters for IVF success, i.e. pregnancy rates per fresh embryo transfer. This illustrates clearly that the way outcome parameters are defined in clinical registries actually dictates clinical practice. Wouldn't it be much better to first define best clinical practice and for outcome registries to be designed accordingly, rather than the other way around?

As a matter of fact, an increasing number of IVF programs currently advocate the so called 'freeze all' strategy where no embryos are transferred at all in the fresh IVF cycle, aiming to improve embryo implantation rates by transferring cryopreserved-thawed embryos in subsequent unstimulated cycles. Although the jury is still out regarding the benefits and drawbacks of such a strategy, in the context of modern IVF and under circumstances where excellent cryopreservation facilities are available, there seems little reason to justify the transfer of more than one embryo

at a time in the majority of patients. Indeed, Northern European countries demonstrated many years ago that such a policy can be introduced at a national level without negatively affecting overall IVF success rates, and coinciding with national multiple pregnancy rates of less than 5% (Karlstrom *et al.*, 2007).

At best, current registries use 'live birth' as the numerator in the described IVF outcomes. According to a recent glossary (Zegers-Hochschild *et al.*, 2017) live birth is defined as follows:

'The complete expulsion or extraction from a woman of a product of fertilization, after 22 completed weeks of gestational age; which, after such separation, breathes or shows any other evidence of life, such as heart beat, umbilical cord pulsation or definite movement of voluntary muscles, irrespective of whether the umbilical cord has been cut or the placenta is attached. A birth weight of 500 grams or more can be used if gestational age is unknown'.

That's quite complicated. And even a successful live birth may be some way from a healthy child. Of course, it is never possible to guarantee the future health of children, and an objective definition of the word 'healthy' turns out to be problematic. It may therefore be best to define 'term live birth' (using an arbitrarily adjusted pregnancy duration beyond 32, 35, or 37 weeks amenorrhea) as the preferred endpoint, reasonably close to normal perinatal outcomes.

In the general population, it is now universally recognized that early foetal development during pregnancy has distinct implications for the future health of offspring. Even today, many mysteries remain regarding the exact content of commercially available IVF culture media used all over the world (Sunde *et al.*, 2016) and it may therefore come as no surprise that the different culture media used exert distinct long-term effects on growth and cardiovascular development of offspring (Zandstra *et al.*, 2018). It should, however, also be emphasized that described suboptimal health of children born through IVF (Meister *et al.*, 2018), may not only be related to IVF procedures, but may also depend on the suboptimal health of infertile couples.

OTHER MAJOR CHALLENGES AHEAD IN GLOBAL IVF

Even if we are able to reach a consensus on the use of 'term live birth' as the

preferred numerator of IVF outcome, we should still ask ourselves the question, 'per what?'. In other words, the denominator could be per (fresh) embryo transfer, per oocyte retrieval, or per started IVF treatment cycle. Such an approach could include data for the fresh embryo transfer only (as is usually the case in current registries), or combined (cumulative) for the fresh and frozen embryo (generated from the same ovarian stimulation oocyte harvest and transferred in subsequent cycles if pregnancy failed to occur in the fresh cycle). Finally, cumulative outcomes could even involve multiple IVF cycles (Heijnen *et al.*, 2004). The latter might be the best outcome measure from the perspective of the patient, i.e. what percentage of couples who start IVF treatment (including repeated IVF cycles if needed) will have a (healthy) baby at the end. Such a cumulative outcome measure is also frequently used for assessing effectiveness of other infertility treatments, like ovulation induction in polycystic ovary syndrome or intrauterine insemination. However, the use of life table analysis remains quite complex from a statistical point of view.

Clear recommendations have been put forward based on the so-called CONSORT statement regarding how to report outcomes of clinical IVF trials (The Harbin Consensus Conference Workshop Group, 2014), but a recent comprehensive systematic analysis convincingly demonstrated that a plethora of outcome measures are still reported in randomized controlled trials (RTC) undertaken in IVF (Wilkinson *et al.*, 2016).

It seems easy to comprehend that pregnancy chances per IVF cycle are increasing in high resource settings (availability of drugs for ovarian stimulation and proper ovarian response monitoring, better laboratory equipment and monitoring of embryo development, and so on). Affordability of IVF throughout the world varies hugely, as shown in **FIGURE 1** (Chambers, *et al.* 2013). In low resource settings, the uptake of IVF is extremely low simply because of the lack of a reimbursement system and couples who cannot afford to pay for IVF treatment out-of-pocket (Dyer *et al.*, 2016). Developing milder, simpler and more affordable IVF strategies aiming to meet these challenges represent yet another important development.

IN SUMMARY

We should celebrate the important step of the initiation of the African ART registry, as reported in the current issue of *RBMO*. We will be even more pleased if the publication of this first report encourages more African countries and IVF centers to join the registry, and if this excellent example is followed by the reporting of outcomes following ART procedures in the Asian Pacific region in the near future. Such additional endeavours would complete true worldwide coverage of ART, which would indeed represent a major achievement.

I would also like to stress the importance of reporting unified IVF treatment outcomes. Reaching a global consensus on how to report ART outcomes in terms that are relevant for patients (and presumably future children) would not only facilitate global comparison of IVF, but most importantly would induce a way to practice ART with a distinct focus on the health and wellbeing of the individual (couple) undergoing ART and also of the child to be.

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