ESHRE 2021 Virtual (26 June – 1 July 2021)

Questions for the speakers

PCC14: How national IVF-registries are built up and should work - using data to improve clinical care

20 years of data collection in Europe – what have we learned? - Christian De Geyter (Switzerland)

Q: So much emphasis on IVF that we have lost sight of the basics. IUI is now giving good results (where practiced). What is done to overcome interest groups?

A: Data on IUI are collected by EIM of ESHRE, but not by other registers. For lack of comparison we did not show any data on IUI.

Q: Concerning Cancellations, don't you think that if less than 3-5% reported there is a strong suspicion of underreporting?

A: Might be. Cancellation rates are prone to underreporting, also the level of cancellation strongly depends on reimbursement.

Q: Does the quality improve due to an increase of registries based on individual cycles?

A: Online reporting cycle by cycle will certainly improve data quality.

Q: In Australia etc more babies occur after frozen cycles than after fresh cycles. Not yet Europe: why? better freezing/lab techniques? Less embryos per transfer?

A: Freeze all is not yet adopted by all institutions, some institutions do not even offer today cryopreservation at all. For that reason Europe is still lagging behind.

Q: What about multiples in IUI?

A: The results on IUI in the EIM ESHRE report are seriously underreported.

Q: How does one overcome the heterogeneity of data submissions? Of course some countries are mindful of marketing. This is not possible in the UK HFEA submission!

A: We need more emphasis on data reporting in ART. This is part of surveillance and vigilance. Prospective cycle by cycle reporting would be optimal, but legal regulations are important, together with ongoing controls of the reported data, for example with an external auditing system imposed on the ART-services offering institutions.

Variation in access and outcomes of fertility treatment by ethnicity in the UK - Amanda Evans (United Kingdom)

Q: Does HFEA promote IVF over alternatives given it too has interest in collecting fees?

A: The HFEA is responsible for regulating fertility treatment in the UK, not promoting it. In our most recent annual report it was shown that IVF treatments account for over 90% of treatment cycles we record on our register, with the remainder being donor insemination (DI) cycles. DI cycles have been increasing in use over the last five years, due in part to increasing use by single patients and patients in female same-sex relationships.

Q: In London it's hard to have a clear ethnic group but more of a mixed group. How do you collect data on these mixed ethnicities? Any idea why more multiple embryo transfers are performed in black population?

A: We used broad ethnic groups (Asian, Black, Mixed, Other and White) for this publication in order to maintain high enough numbers to draw comparisons throughout the publication. More specific information on ethnicities is available for some information within the underlying dataset along with a page outlining the ethnicity groupings. Ethnicity groups used in this report are based on those used by the UK government.

It is unclear why Black patients received higher rates of multiple embryo transfers, but it may relate to advanced age and reduced embryo quality due to delayed treatment. The use of multiple embryo transfers may also relate to cost, as some US studies have suggested that patients choose elective single-embryo transfer more frequently when cost pressure is reduced.

Q: Did you try to control sociologic / educational, economic variables in your ethnic comparisons ?

A: Sadly we do not collect any socioeconomic information on our register so we were unable to analyse this. It is possible for UK researchers, however, to link our register data to other healthcare datasets and analyse this data for specific research purposes by submitting an application to our Register Research Panel.

Q: when you publish annual report do you practice to inform journalist or do something to increase visibility of your work?

A: Our Communications team informs journalists and relevant organisations in the UK about upcoming HFEA data releases and prepares a press release to accompany the report. Our data reports are official UK statistics, requiring us to release data to all external bodies only at the time of publication.

Q: What about the data of foreign patients/cross border fertility treatment. Eg: Is it compulsory for private clinics to gather foreign outcome parameters as well?

A: Clinics are required to submit data to us on the outcome of all fertility treatment that occurs in UK licensed fertility clinics.

Q: How do you collect children's data directly from the IVF clinics or also pediatricians are involved?

A: We collect data from the fertility clinics. It is required that clinics follow-up on treatment outcomes and report these as well to the HFEA register.

Q: Is the fee equal for all clinics (big and small)? Does the patient or the clinic pay for the registration cost?

A: The HFEA charges clinics per cycle performed. This means that larger clinics will pay more as they are performing more cycles in a year.

Q: In Asian origin, do you mix middle-East, India, & Far east ? Infertility & many characteristics may be very different.

A: Yes, in the main body of the report South Asian and East Asian ethnicities are combined. Around 87% of the UK identifies with White ethnicities, which required us using broad ethnic categories and grouping five years of data to draw any reasonable comparisons. We do mention in the body of the report some major differences within the Asian and Black ethnic groups when it is notable and have provided more specific ethnic groups in the underlying dataset of the report whenever possible.

Tools to build up a registry: Choosing the relevant indicators for editing a proper core dataset - Markus S. Kupka (Germany)

Q: There may be another question: What for use: surveillance only ? some research ? a mix ?

A: From my point of view it could/should e a mixture.

Q: Can you suggest examples of software on market for collecting data or you suggest make a software by IT professional.

A: Meditex is one, Redshift Technologies, www.dynasolutions.com, www.browser.pt
but this is a very personal list

Q: There is a lot of costs with optimal IVF software. For instance, do you think the databases need to be CE marked, that requires so much expenses?

A: It's very sensitive data. Under no circumstances should there be access for uninvolved third parties.So all aspects of data-safety have to be implemented.

Q: How important are data sets used for amendments in national and European legislation e.g. reimbursement or changes in transfer freezing policy?

A: There are some initiatives of the EU to create an own data collecting system but it is not easy to reflect the huge variety of legal settings and requirement in all 40 European countries.

As shown for Austria the data collecting system is directly connected to the reimbursement system.

How can we use data to improve clinical care? - Christine Wyns (Belgium)

Q: Don't you think that clinics comparison needs to be made & published on similar patients characteristics & clinic policies, including multiple rate?

A: Indeed. The optimal situation is to define the "ideal patient/procedure" for comparison. EIM is looking into criteria that could be useful. However, differences in clinical practices, namely routine use of PGT in some clinics complicates the identification and comparison. In addition, the socioeconomic context may also play a role e.g. more embryos transferred when there is no social security,…

Q: Freeze-all approach resulted that PR and LBR per cycle dropped. Cumulative LBRs are not available in EIM. Comparisons are not possible. How to solve this issue?

A: The solution is a prospective cycle-by-cycle data collection but this implies that a uniform system for European countries should be made available with linked expenses. It is the future but not in the short term, unfortunately.

Q: Don't you think that we might include a set of questions on cumulative rates to registries that are able to make it?

A: Indeed. An optional module could be added to EIM modules.

Money meets data - The Austrian link of an IVF-registry and reimbursement - Heinz Strohmer (Austria)

Q: What would happen in Austria if all performed cycles would be recorded in the registry - not only the governmental payed cycles?

A: There is an obligation to report all cycles irrespective whether they are supported financially or not. But there is a difference regarding the quality of the report. All cycles covered by the "IVF – Fonds" have to be reported more in detail and case – by – case. All other cycles are reported once a year as a summary report. There have been initiatives to include the "private" cycles in the reporting system of the "Fonds" cycles, but the motivation of the centers is low as this would increase the workload without incentive.

Q: Are rules on age for all practice (ART forbidden outside) or only for money aspects if yes, are outside cycles reported to the register ?

A: Age ist only a limiting factor regarding access to the IVF Fonds. Female patients are accepted only until the 40th birthday, male patients unitl the 50th birthday. In general, egg donation recipients need to be younger than 45, the donor has to be younger than 30 years. Regarding the report see above.

Q: Is it possible to use IVF service in Austria with 100% private base? In that case, the reports from clinics are still mandatory with potential penalty, right?

A: Yes, for sure patients may pay the service 100% by themselves and some couples (see age limits above) are forced to do so anyway. As already stated the reports regarding these patients are summary reports and not case – by – case. The reporting of the Funds-cycles is highly linked to the money issue mentioned in the title of the lecture. The detailed reporting is mandatory to finally receive the money when the cycle is completed.

Q.In routine 3, you have recommended "the number of transferred embryos based on algorithm''. Please share about this?

A: The algorithm is based on international guidelines and the number of transferred embryos is based on age, number of previous attempts and further risk factors (e.g. previous cesarean section, preoperation on the uterus …). Theoretically the patient may opt out of this algorithm but then she will lose any financial support of the Fonds. Anyway this algorithm should be the basis for decision also in patients paying by themselvers.

Q: How much fetal reduction occurs to manage the multiple births?

A: We do not have any registry covering these procedures. From my point of view and experience with our patients it is a topic in cases of double transfer ending as a triplet pregnancy with one monochorionic twin pregnancy plus a single pregnancy.

Q: I was surprised by the difference public/private in success rates, that we never observed in France. Could you detail hypotheses

A: There is a certain competition between the private centers and as we all know pregnancy rate is one of the core marketing messages transported to the public. Initially the treatment cycle ended when a clinical pregnancy was reported. There was no obligation to follow up the patient until delivery or any complication during later stages of pregnancy. As the system has been changed that the patients have to report the delivery in order not to be forced to take over the 70% Fonds support, the two lines (private versus public centers) approached during one year. One may assume that private centers had the tendency to report some clinical pregnancies rather generously before this change.

The only statistics you can trust are those you falsified yourself - From basics statistics to interpretation - René Eijkemans (The Netherlands)

Q: Why the 95% CI is usually used instead of 99%. Any trade-off?

A: Indeed, other levels of confidence could be used. In fact, when comparing clinics usually a higher than 95% level of confidence is often used, such as 99%, because you do want to reduce the risk of a false alarm for clinics.

Q: Lies, true lies, statistics.. comparing clinics seems so complicated that marketing claims of 'the best clinic' seem questionable and should be abandoned?

A: Many people would agree, and the best use of comparing clinics is in benchmarking and quality improvement, not in commercial marketing. In a country with many commercial clinics there obviously will be an incentive to have ranking for marketing purposes, but a disclaimer should always be made about the inherent statistical uncertainty.

Q: Don't you think that a real ranking is useful or may be misleading when differences are short?

A: The message of papers on ranking is that ranking often is very uncertain and unstable. A clinic that ends up high in ranking in one year may be average the next year. Therefore, the ranking should always be presented in a document with guidance on how to interpret the differences.

Q: What can be the maximum loss to follow-up of cycle outcomes that we can consider the results of clinic as credible?

A: In principle, results should be reported with the patient perspective in mind. Usually, that would be results per started cycle, and the outcome of all started cycles should be available. A loss to follow-up of 10% already could lead to a difference in success rate of 5%, so definitely the loss to follow-up rate should be much lower than 10%.

From ANARA (Africa) to ANZARD (Australia) - How to condense data of different registries - Geoffrey David Adamson (U.S.A.)

Q: Thank you Adam for the wonderful presentation. Is there an Asian register besides the national ones?

A: Currently there are only national registries in Asia. ICMART would like to help countries currently without registries develop one. You can contact us at ICMART@icsevents.com if you are interested.

Q: Excellent presentation, David. Are you looking to link your registry or encouraging national registries to link IVF interventions to child health outcomes?

A: Yes, we definitely think this is important. Some countries do not allow this for regulatory and privacy reasons and others have not yet done this because of the logistical complexities and financial reasons. Some registries are performing linkage through using statistical methods to link. We hope in the future more countries can find ways to link ART registries with birth registries and also other childhood registries.

Q: Don't you think that a way for the future is to make the various registries more compatible, to increase the value & to improve easiness?

A: Yes, we think compatible registries would be a very positive development. We are trying to encourage that with our International Glossary of Infertility and Fertility Care so that terminology is

used consistently, and by the current forms and information documents to help collect the data in a consistent fashion. The next big step is to encourage as many registries as possible to develop case-based registries, and preferably with a way to identify cases-from the same patient also. But this has not yet happened in many countries, including developed ones, that still have aggregated data reporting by clinic. Once all registries are case-based it will be easier to standardize the data for collection, aggregation of countries/regions and analysis.

Q: Is there a lot of interstate fertility care migration in the United States and is it being monitored?

A: To my knowledge, interstate care is not being monitored. Some will occur simply because of the proximity of multiple states to single urban areas, e.g., New York area, St. Louis, Memphis, Reno, etc. In addition to geographic proximity, patients may cross interstate lines because of insurance reasons or regulatory reasons especially with respect to third party reproduction. It would be important to know how much this is occurring but only SART and/or the CDC in the US could collect these data—ICMART can only collect data that is already collected by the country. More countries are now beginning to try to collect inter-country data, especially in Europe where this occurs more often because of different regulations and services between countries, again, mostly but not entirely with respect to third-party reproduction.

Best practices of IVF registry: Linking surveillance, research, clinical practice and public health - Dmitry Kissin (U.S.A.)

Q: Don't you think that the almost only way to get 100% participation in a country is to raise a state compulsory register ?

A: Yes, I do agree that having mandatory/compulsory reporting is almost the only way to achieve complete representativeness (complete coverage) of IVF registry. Only 16% of countries with voluntary reporting have complete data, while 81% of countries with compulsory reporting have complete data. However, compulsory reporting alone may not be enough. IVF registries need to make every effort to make reporting easy and convenient, have fair and transparent reporting requirements, and make data available for researchers and policymakers.

Q: I would like to know how to link each cycle of frozen ET to a stimulated cycle or a person in U.S. registry?

A: In the U.S. National ART Surveillance System, frozen transfer cycles are linked to their corresponding retrieval cycles by using unique patient identification (ID) numbers and collecting the date of oocyte retrieval for each transferred embryo. This approach of linking fresh and frozen cycles works in most situations. However, if egg retrieval and subsequent embryo transfer occur in two different clinics, we are also asking for the name of the clinic in which egg retrieval took place for each transferred embryo. This allows linking of all egg retrievals with their corresponding transfers.

Q: Similarly, how is it possible to link the registered treatment cycle to other registry without using personal information?

A: It is possible to link ART treatment cycle information with information from other registries without knowing patient's name or other direct identifiers by utilizing a probabilistic linkage approach. For example, we were able to link U.S. National ART Surveillance System (NASS) data with several other registries with a linkage rate of >90% by primarily using these five variables: maternal date of birth,

infant date of birth, plurality, maternal residence ZIP code, and gravidity. More details can be found here: https://pubmed.ncbi.nlm.nih.gov/23829183/.

Q: Do many/any of the registers have data for lower tech treatments like IUI - is that something we are missing?

A: Several national registries collect data on IUI treatments. For example, see the latest report from the European IVF Monitoring Consortium for countries reporting information on IUI: https://pubmed.ncbi.nlm.nih.gov/34377841/. Collecting information on non-IVF fertility treatments is important because these treatments contribute as many or more multiple births than IVF.

Q: Is there a lot of interstate fertility care migration in the United States and is it being monitored?

A: U.S. National ART Surveillance System (NASS) collects information on patient residence and clinic location, which allows studying interstate fertility care migration. There has been research on receiving gestational surrogacy services in a state other than the state of residence of the intended parent: https://pubmed.ncbi.nlm.nih.gov/29774269/. However, more research is needed to describe interstate fertility care migration in the U.S. Information on how to access NASS data can be found here: https://www.cdc.gov/art/nass/accessdata.html.

Q: Which hurdles related to privacy rules when linking cycle-by-cycle registries, (e.g. ART and birth registry), risk of obtaining identifiable data ?

A: There are number of obstacles in linking ART data with other datasets, including challenges related to privacy rules and data protection requirements for each of the linked datasets. While it is not easy, many researchers have been successful in overcoming these hurdles and finding acceptable legal and technical solutions to conduct data linkages. More information about the challenges and solutions of data linkages can be found here: *Monitoring Long-Term Outcomes of ART: Linking ART Surveillance Data with Other Datasets. (2019). In D. Kissin, G. Adamson, G. Chambers, & C. De Geyter (Eds.), Assisted Reproductive Technology Surveillance (pp. 81-92). Cambridge: Cambridge University Press.*

Q: Do you think summary data registries is a more easy and feasible way to collect data, but also with more probability of false numbers?

A: IVF registries collecting summary data (versus cycle-level data) are less burdensome, but have many disadvantages, including selective reporting, reduced data quality, limited ability to conduct data validation or analytic research, inability to calculate cumulative success rates or link IVF registry data to other datasets.