

Assisted reproductive technology in India: A 3 year retrospective data analysis

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Received: 11.12.2013
Review completed: 11.12.2013
Accepted: 02.01.2014

ABSTRACT

Assisted reproductive technology (ART) has grown by leaps and bounds in the last few years. India has one of the highest growths in the ART centers and the number of ART cycles performed every year. Very soon India will be the leader in the world of ART in terms of a number of cycles. With the advances of technology and availability of techniques even in tier II and tier III cities our country, the results still vary dramatically. There is no standardization of protocols and reporting is very inadequate. Furthermore, there are only ART guidelines and no law still exists. Our first and the biggest challenge is to document the tremendous work being done in India and on the basis of analysis of this work, a proper registry can be made and guidance given to all on standardization and improvement. This is the 8th edition of National ART Registry of India being presented and analyzed.

KEY WORDS: Assisted reproduction techniques, data collection and analysis, egg sharing, National Assisted Reproductive Technology Registry of India, National Registry, oocyte retrieval, surrogacy

INTRODUCTION

Assisted reproductive technology (ART) has grown by leaps and bounds in the last few years. It is now being increasingly available to infertile couples in both developed and developing countries. Furthermore, as the economy has expanded, many infertile couples can now afford and the sophisticated ART treatment. This has led to an enormous increase in the number of ART clinics providing care to these couples all over the world. India has probably recorded the biggest growth in ART centers and the number of ART cycles being performed in our country has steadily risen over the last decade. In a latest survey, based on the number of applications received for National ART Registry, Indian Council of Medical Research (ICMR) puts the number of such clinics as 125 in the capital city of India. Officials however believe that the actual figures are around 250-300.^[1]

Correspondingly, the sophisticated treatment regimens associated with assisted reproduction are now being applied to an expanding population of otherwise healthy infertile people.

As a result, questions have been raised on the effectiveness, safety, availability and costs of these procedures, as well as many ethical and legal aspects of their use. It is therefore understandable that the practice of assisted reproduction and its clinical outcomes have been reported extensively in the literature. However, most of these previous reports have come from individual clinical centers and are based on relatively small numbers of patients. Individual clinical experiences are shared through these scientific publications, international conferences or informal communication among the known clinicians. However, the applicability of specific results and outcomes from a small group of patients to the general populations seeking treatment is obviously limited.

Hence there is a need for more rigorous data collection and formation of a central national data collection registry in each country has become necessary. This central data collection system allows the sharing of experiences between various centers and helps to define the best treatment modalities for improving the ART outcomes. It is also important for the ART programs to share information about access, effectiveness and safety of ART, so that all

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DOI:

10.4103/0974-1208.126286

stakeholders can maximize the benefits of the rapidly evolving techniques. It also forms the basis for formulating various guidelines and regulations which are needed to standardize various techniques and also to avoid the misuse of technology.

World data on the availability, effectiveness and safety of ART have been published since 1989.^[2] The number of countries reporting and analyzing their ART data is steadily increasing. Many countries now have registers of assisted reproduction that were initially set up to evaluate the effectiveness of treatment and to monitor pregnancy outcomes and health of treated women. World report based on information from these national registers is analyzed and the international comparisons are made regarding the extent of use of these techniques and pregnancy outcomes in different countries.^[3] It is believed that the data presented to the International Committee for Monitoring Assisted Reproductive Technologies (ICMART) by individual countries represents only 70% of the world's *in-vitro* fertilization (IVF) activity. The other 30% are estimations and India is reporting to ICMART.

In order to regulate the ART practices and treatment by different centers in India, the Union health ministry and the Indian Society of Assisted Reproduction (ISAR) have set up a registry "National ART Registry of India (NARI)" with a view to providing appropriate help and assistance to all those who are engaged in taking care of infertility problems in the country.

As ISAR is now a part of International Federation of Fertility Societies, all the Indian medical practitioners practicing ART should participate in providing data for NARI and hence that each unit in the country can compare the quality of its results within the country itself and also with current international statistics. ISAR has been successfully bringing out the NARI registry with the compilation of data received from many participating centers since 2001. The number of ART centers sharing their data have been increasing with time. Development of such national registries like NARI in India, is also considered as an essential component of the global registries like ICMART.

Collection of data allows us to review and analyze the annual performance of various clinics all over India and explore the trends in ART activities in detail. It is important not only to report and analyze the positive reproductive performance indicators like pregnancy rates, live birth rates etc., but also the percentage of ART cycles associated with complications such as ovarian hyperstimulation syndrome, abortions, multiple pregnancy, still births, congenital malformations etc.

ART still has some safety problems and risks that need to be described and evaluated so that current clinical policies and laboratory procedures can be revised, if necessary.

Confidence, Credibility or trust in ART is needed, not only for couples who need to undergo treatment but also for professionals who provide treatment and for the society at large, as well as for legislators and resource allocators.

Collection and analysis of these data allows us to improvise and modify our techniques and provide the best possible care to the patient.

NEED FOR A REGISTRY

Having a national registry helps us to understand better the scope and impact of assisted reproduction on the health of infertile couples. A registry is like a national surveillance system for ART technology. The collection of data on the outcomes and possible adverse effects of assisted reproductive techniques can assist:

1. Patients seeking medical assistance for their infertility by allowing them to make informed and appropriate decisions concerning their own treatment options
2. The medical and the laboratory professionals in providing optimal patient care with the best available and scientifically documented treatment modality
3. Public health authorities responsible for assuring public safety, developing health care delivery policies and ensuring cost reimbursement
4. The public in understanding better the ART and their role and value in helping people with infertility and other medical problems.

NARI in India is such a registry that enables the country to summarize the cumulative experiences of all identified clinics performing ART treatment. Such registry programs avoid the difficulties in interpreting the results of a small number of clinics performing, limited forms of assisted reproduction procedures on a relatively small numbers of patients. Furthermore, an individual clinic can compare its practice and treatment outcomes with others within its country.

DATA COLLECTION METHODOLOGY

We in India have a centralized method of collection of data from all treatment cycles started in all centers within our country. No doubt, it is a difficult and expensive approach requiring a larger staff of professionals centrally for data handling. It also requires that the individual centers agree to use a uniform data system. The information needs to be interpreted and presented with relevant professional comments to avoid misinterpretation.

Publication of crude (unadjusted) pregnancy rates from individual centers alone cannot be the primary goal of a national or an international registry. Indeed, such presentations may not be in the best interest of the public. A major task for any working group, therefore,

should be to define standard definitions and methods for presenting information, thereby facilitating interpretation and inference. ICMART has done this most recently in cooperation with the World Health Organization and this has been published in *Fertility and Sterility Journal*, vol. 92, November 2009. The use of these internationally accepted set of definitions has helped us to standardize and harmonize the data collection to monitor the availability, efficacy and safety of various ART interventions.

The centralized method of data collection has considerable advantages since it provides us with opportunities for research on multiple factors influencing selected outcomes of interest. It also enlightens us with new personal experiences by different clinicians in various parts of the country. The data in this way helps us formulating the newer guidelines and also provides us with the background for research methodology on required subject.

As of now, the data is collected from various clinics by providing them with forms which include all the necessary information required. Various ART centers, voluntarily contribute to submitting their data to ISAR. It is expected that in the near future, ICMR will provide us with software for registry for all ICMR accredited centers. This will ease out the data collection procedure and their analysis. The data which is collected from various clinics is then interpreted by a group of experts and is included in NARI. Indian data provided by NARI has also been included in the world report published by ICMART. This paper has been brought out to interpret and present the data for 3 years (2007, 2008 and 2009) included in the 8th edition of NARI.

OBSERVATION AND RESULTS

ISAR has attempted to facilitate collection of data from all programs providing ART services in India. Unfortunately, the online web based system of collecting data did not succeed and ISAR had to revert back to retrospective collection of data from various ART clinics. The number of centres providing ART services and the number of clinics reporting their cycle outcomes to ISAR has risen over the 3 year period. Whereas, 113 centres were not providing but reporting IVF services in 2007, this number rose to 132 in the year 2009 i.e., a 16% increase in the number of clinics. For intra-cytoplasmic sperm injection (ICSI), the number rose from 101 in the year 2007 to 121 in 2009. The number of clinics providing other services like surrogacy and cryopreservation also have risen over the 3 year study period. In 2009, the number of clinics providing gamete intrafallopian transfer cycles decreased by 11.1% when compared to the year 2007. The number of clinics providing pre-implantation genetic diagnosis (PGD) services has remained stable over the 3 year period.

Fresh ovarian stimulation cycles

With respect to the number of fresh ovarian stimulation IVF cycles, year 2009 showed a 27.9% increase when compared to year 2007. This is due to the increase in the number of clinics reporting the ART cycles and it is expected that this number will continue to increase in future as more and more clinics start to be report. The number of ICSI cycles performed remained almost stable between 45,516 in the year 2007 and 45,543 in the year 2009. The absolute number of ICSI cycles were higher as compared to IVF cycles in all the 3 years. As has been reviewed from other reports, the trend toward increased use of ICSI is seen throughout the world. The increased use of ICSI cannot be solely explained by increasing male factor infertility but also because of its use in other indications such as unexplained infertility, mixed causes of infertility and also importantly because of different professional approaches.^[4,5]

Indications

Tubal factor infertility was the main indication for performing IVF in all the 3 years, contributing to 33.73% of all IVF cycles in the year 2007 and 35.54% in the year 2009. While in ICSI cycles, male factor infertility was the main indication, contributing to 52% of all the ICSI cycles. The percentage of ICSI cycles performed in view of male factor infertility, polycystic ovarian syndrome, endometriosis, failed IVF remained constant at 52%, 13%, 7.3%, 7.6% respectively in all the 3 years.

Stimulation protocols

Regarding the stimulation protocols, long protocol has been the preferred protocol in the 3 year period. Around 65% of the cycles in all the 3 years were based on long protocol regimes, suggesting it as the preferred protocol by most of the clinicians.

Number of embryos transferred (ET) per ET

With regard to the number of ET, the percentage of cycles associated with transfer of three embryos decreased from 47.3% in the year 2007 to 43.09% in the year 2009. This in turn is reflected in the decrease in the rate of triplet gestation from 3.8% to 2.9% in the corresponding years. Single embryo transfer was done in 10% of all the cycles and remained same in all the 3 years. However, the double embryo transfer rates increased from 21.4% to 24.78% between 2007 and 2009.

Pregnancy outcomes

In terms of pregnancies per embryo transfer, the success rates of fresh embryo transfers (both IVF, ICSI cycles) increased from 33.3% in the year 2007 to 36.5% in the year 2009. The abortion rate per transfer stable 5.3% in 2007-2009.

The incidence of ectopic pregnancy for all fresh embryo transfers (IVF and ICSI) was 0.9% per transfer and 2.5%

per pregnancy. This figure remained constant throughout the 3 year study period. The incidence of ectopic pregnancy compares favorably to an estimated overall incidence of ectopic pregnancy of 2% per reported pregnancy.

The incidence of multiple gestation was also determined. Around 74% of all the pregnancies in the 3 year period were singleton gestations and twins represented 22% of all the pregnancies reported. The incidence of term and pre-term deliveries and the perinatal morbidity and mortality rates were not reported.

Frozen thawed embryo transfers

Protocol

With regard to the thawed embryo transfers, period from 2007 to 2009 saw an increase in the number of artificially prepared cycles, using hormones, for frozen thawed embryo transfers. The numbers for the corresponding years increased from 1525 to 2678. Accordingly, the number of natural cycles used for endometrial preparation for frozen embryo transfer (FET) decreased from 401 in the year 2007 to 227 in the year 2009. This is because of a better control over the cycle in which artificial preparation of the endometrium is done using exogenous hormones than over the natural cycle, hence making clinicians more comfortable and confident with the use of artificial cycles.

Number of ET per ET

The period from 2007 to 2009 saw an absolute increase in the number of FET cycles performed, from 1954 to 3087 cycles. The percentage of FET cycles where single embryos were transferred per cycle decreased from 9.46% in the year 2007 to 7.87% in the year 2009. However, the percentage of the cycles where three embryos were transferred increased from 42.4% in the year 2007 to 45.8% in 2009. Around 47.1% of the FET cycles in the year 2008 had transfer of three embryos per cycle. This correlates well with the increase in multiple pregnancies rates which rose from 20.6% in the year 2007 to 25.3% in the year 2009.

Outcome

Clinical pregnancy rates in FET cycles increased from 26.8% per transfer in 2007 to 29.92% per transfer in 2009. This could be explained by an increase in the total number of FET cycles does not improve the clinical pregnancy rate performed in the listed years, from 2006 in the year 2007 to 3242 in the year 2009, an absolute increase of 1216 cycles. The abortion rate per transfer in these cycles decreased from 10.5% in 2007 to 4.8% in the year 2009. The lower abortion rates could be due to better freezing protocols and a greater adoption of vitrification technique instead of slow freezing protocol. Over the 3 year study period, rates of ectopic pregnancy per FET also declined from 2.1% to 0.4%.

Egg donation

Type of donor

In relation to egg donation cycles, the period from 2007 to 2009 saw an absolute doubling in the number of donor egg cycles where the oocytes were taken from anonymous donors. The numbers increased from 1047 to 2130. In contrast, egg donations from the related/known donors increased by only 20%. This could be due to the preferential acceptance of the anonymous donors by the patients themselves due to the potential risk of conflicts that may later on arise with the use of due to the increase in mass media facilities that popularize this field of ART, thereby bringing out many women who may serve as professional donor and get financial compensation for their service provided. The number of cases in which one donor's oocytes were used for multiple recipients is unknown.

Age of recipient

The majority of the egg donation cycles were performed in women who were less than 45 years old. The trend remained the same in all the 3 years. The percentage of donor egg recipients of more than 55 years of age was around 1-1.8% in the 3 year period. This is due to the better recognition of the fact that pregnancy in menopausal age group may be unphysiological and a better screening of patients for risk factors such as hypertension, diabetes mellitus, heart disease, all of which may exacerbate with pregnancy and put the patient at undue risk. This has made many clinicians discouraging pregnancy in females of more than 50 years of age.

Indication

The main indication of egg donation was poor ovarian reserve in all the 3 years.

Number of ET per ET

In the majority of embryo transfer cycles in all the 3 years, three embryos were transferred per cycle.

Outcome

Clinical pregnancies were reported in 920 cycles, for a rate of 41.9% per embryo transfer in the year 2007. Totally 25 ectopic pregnancies were reported in the same year, making an ectopic pregnancy rate of 1.14% per transfer. Abortion rate during the same period was 7.84%. The year 2008 showed a similar trend as 2007, except for the abortion rate, which was 6.44% per transfer, i.e. 1.4% lower than the year 2007. Pregnancy rates in the year 2009 were higher by 3.24% when compared to the previous 2 years.

The multiple pregnancy rates were between 26.03% and 30.36% in the 3 years, which were comparable to the multiple pregnancy rates in the general IVF population.

The delivery rates and the perinatal outcomes were not mentioned in the data provided.

Recipients of egg sharing

Age of recipient

Egg sharing continues to be an effective method for egg donation, whereby a patient who is herself undergoing ovarian stimulation for her own IVF cycle, shares her excess eggs with other infertile couple in need for ovum donation. As was the case with donor egg cycles, the maximum number of recipients of egg sharing cycles were below 45 years of age and the main indication of donor egg sharing continued to be poor ovarian reserve in all the 3 years. In the majority of these cycles, 4-5 eggs were shared between the donor and recipient.

Outcome

The clinical pregnancy rates per transfer were between 32.4% and 35.17% during the 3 year period. This rate was lower than the pregnancy rates in the donor egg cycles where the oocytes were retrieved from healthy young donors with no infertility factors. The lower rates in the egg sharing cycles could also be due to the underlying ovarian problem which was causing infertility in the donor female. However, such cycles continue to be used in all ART clinics as it does not require a special preparation and ovarian stimulation of another woman (donor), which may pose an extra risk to her health.

Embryo donation cycles

Embryo donation cycles are an option for those couples where both partners have untreatable cause of infertility. The number of embryo donation cycles increased from 1213 transfers in the year 2007 to 1773 transfers in the year 2009. This is due to the increased affordability, awareness and access to treatment among such couples in need for embryo donation cycles. This is also made possible because of the improved embryo vitrification techniques which have led to the increased survival of the thawed for use in such couples. The majority of the embryo donation cycles were performed using three embryos per transfer in all the 3 years. However, the percentages of ED cycles where three embryos were transferred, decreased from 55.1% in 2007 to 38.8% in 2009. There was a corresponding increase in the number of double embryo transfers during the same years, which increased from 18.5% in 2007 to 25.8% in 2009. This downward trend in the number of embryo transferred was reflected in the rates of multiple pregnancy which showed a decline by 4.6% between the year 2007 and 2009.

Pregnancy rates per embryo transfer were 40.8%, 40.3% and 38.47% in the years 2007, 2008 and 2009 respectively. The ectopic pregnancy rates declined from 0.91% in the year 2007 to 0.73% in 2008 and further lowered to 0.56% in 2009.

Surrogacy

Between the year 2007 and 2009, there was more than 3 times increase in the number of cycles performed using host uterus for transfer, in which the embryos generated from the gametes of the commissioning couple were placed into a gestational carrier. The major indication of cycles utilizing a surrogate was repeated implantation failure in all the 3 years. The pregnancy rates increased to 53.60% per embryo transfer in the year 2009 from a previous figure of 40.8% per transfer in 2007. However, the abortion rates in 2009 were higher by 3.44% per transfer as compared to the rates in 2007. The rates of multiple pregnancy also doubled between the years 2007 and 2009. The delivery rates, the perinatal outcomes and the maternal morbidity rates were not outlined in the data provided.

CONCLUSIONS

The number of clinics reporting their data to ISAR has increased from 2007 to 2009, as did the number of ART cycles with an increased overall probability of success. The increase in number of cycles reported is largely attributed to the increase in number of clinics combined with increase in numbers of treatment cycles at many high load clinics. The rise in the number of clinics and the number of ART cycles performed every year has been exponential. In the year 2000, only 5500 cycles of IVF-ICSI were performed in our country, this number rose to 21,500 in the year 2006, the number projected for 2011 is 110,000.^[6]

The increased reporting rate is also attributable to the increased awareness among the concerned clinicians about the necessity to report their data. It is this combined data from various national registries that forms the basis of various recommendations by the expert authorities. The combined experience from various clinicians is also utilized for the research work in the desired field.

It is seen from this report that the ART practice has changed with an increasing prevalence of the use of ICSI rather than conventional IVF. ART is generally safe but multiple pregnancy remains a particular concern. The change in practice to single embryo transfer and cessation of the transfer of three or more embryos can result in a decrease in the rates of multiple pregnancy and the associated perinatal mortality and morbidity.

The data presented in this report effectively covers the efficacy of IVF/ICSI rather than safety, which is one of the major concerns of any IVF procedure. The report clearly mentions the rates of multiple pregnancies after these procedures, however the delivery rates, low birth weights, prematurity rates, stillbirths etc., which are the indicators of safety rather than efficacy are not clearly defined. The

report also contains data on the number of ET, but not the data on fetal reduction which is practiced in some parts of the country. These data must be incorporated to provide a comprehensive and a detailed evaluation of the ART.

At the time of writing this paper, it was also realized that the outcomes of various ART techniques could not be studied with respect to female age, as no data was provided by the clinics in this regard. In a report which presented information from the UK HFEA database from 1995 to 1999, the overall live birth rates were noted to be 17.6%. The rates were more than 20% between the ages of 23 and 33 years. Above the age of 33 years, live birth rates declined to less than 10% by the age of 40. The women older than 40 years had a further decrease in the chance of a live birth.^[7] It is clear that the female age particularly influences the ART outcome and hence it becomes necessary that the future data provided to NARI by various clinics incorporates the age related outcomes of the technology.

The recommendations for various procedures like the number of embryos to be transferred can then be made in accordance with the female age. Many clinics are now successfully using the newer techniques like assisted hatching, PGD, intracytoplasmic morphologically selected sperm injection etc., in a particular subset of patients. The data provided by various ART centers should also include this aspect of ART treatment so that the cumulative results and experiences can be used to formulate the guidelines and policies for implementation of these newer techniques. Also, at present the data provided to NARI has not included long term outcomes of ART like the effect of various drugs used on the maternal health, long term outcomes on the health of babies born through ART procedures etc., Various clinics can provide these necessary details by maintaining the long-term follow-up of their patients and also by linking the ART data to other national surveillance systems like birth defect registries, cancer registries etc., while paying a close attention

to confidentiality protection. This can go a long way to provide insights into the innovations that are required to be made in the present protocols and techniques, so that the future generations can be benefitted from the previous experiences.

To conclude, work done by our national registry, NARI has helped us to compile the data of IVF centers in a systematic way since 2001. However, a further refinement of our techniques for monitoring ART efficacy and safety is still required. By doing so we are building confidence in ART for everyone involved with this wonderful, but still young, technology and especially for our patients.

ACKNOWLEDGMENTS

The authors are thankful to Dr. Parul Arora for compiling this data. Sincere thanks to all the contributing centers. Sincere thanks to ISAR and its executive committee for entrusting us with this work.

REFERENCES

1. Chandra N. When you cannot produce a baby, design it! Over 500 babies born each month in Delhi fertility clinics. Mail Today 2013.
2. Sullivan EA, Zegers-Hochschild F, Mansour R, Ishihara O, de Mouzon J, Nygren KG, *et al.* International Committee for Monitoring Assisted Reproductive Technologies (ICMART) world report: Assisted reproductive technology 2004. Hum Reprod 2013;28:1375-90.
3. Lancaster PA. Registers of *in-vitro* fertilization and assisted conception. Hum Reprod 1996;11 Suppl 4:89-104;105.
4. Ahuja K. Sir Bob Edwards: Salute to a giant. Resonance 2011;10:956-9.
5. de Mouzon J, Goossens V, Bhattacharya S, Castilla JA, Ferraretti AP, Korsak V, *et al.* Assisted reproductive technology in Europe, 2006: Results generated from European registers by ESHRE. Hum Reprod 2010;25:1851-62.
6. Pratap RK. IVF Baby Boom. Outlook Business 2011;10.
7. Fraser IS. Report of independent review of Assisted Reproductive Technologies in Australia; 2006.

How to cite this article: Malhotra N, Shah D, Pai R, Pai HD, Bankar M. Assisted reproductive technology in India: A 3 year retrospective data analysis. J Hum Reprod Sci 2013;6:235-40.

Source of Support: Nil, **Conflict of Interest:** None declared.