Success Rate of Assisted Reproductive Technology Treatment at a Tertiary Fertility Centre in Nepal

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ABSTRACT

Aims: To determine the success rate of various Assisted Reproductive Technology (ART) treatments at a tertiary fertility centre in Nepal.

Methods: This study was a retrospective study conducted at Creator's IVF Nepal Pvt. Ltd. (CIVF) from November 2015 till April 2020. The success rates of ART treatment were preclinical pregnancy rate, clinical pregnancy rate, and live birth rate. Anonymised information about demographic and clinical characteristics of the patients, ART treatment related variables, and ART outcome related variables were collected from the medical records. Descriptive analysis was performed using SPSS (Statistical Package for the Social Sciences) version 20.

Results: Overall, 768 ART cycles leading up to embryo transfer were analysed. About 69.6% of all ART treatments were autologous cycles followed by oocyte recipient cycles (22.0%), and embryo recipient cycles (8.4%). About 88.7% were fresh embryo transfers whereas 11.3% were frozen embryo transfers. Overall the preclinical pregnancy rate, clinical pregnancy rate and live birth rate were 48.4 %, 43.3%, and 33.3% respectively.

Conclusions: The success rates of ART treatment in this study were comparable to the international estimates. More research on treatment outcomes by all ART service providers in Nepal is needed to provide better evidence on utilization and efficacy of ART treatment in fertility centres across the country.

Keywords: assisted reproductive technology; clinical pregnancy; in-vitro fertilization; live birth; success rate

INTRODUCTION

Infertility is one of the major yet neglected components of reproductive health.[1] It affects up to 15% of world's reproductive aged women.[2] The inability to have a child is a source of agony to millions of infertile couples worldwide, which is often accompanied by social stigma, discrimination and isolation.[1,2] Numerous advancements in the field of Assisted Reproductive Technology (ART) have helped to relieve the burden of infertility.

In fact, approximately 8 million births have been achieved till 2018 worldwide through ART services.[3] ART encompasses all treatments and procedures that involve in-vitro handling of both human oocytes and sperm, or embryo to establish a pregnancy.[4]

Collection and analysis of data on ART outcome allows generating evidence from various centres and help improve the techniques to provide the best possible result.[5] While many private ART centres do exist in Nepal, the evidence on the effectiveness of their services remain scarce. Therefore, this study was undertaken to determine the outcome of ART services in terms of success rate in a fertility centre in Nepal

METHODS

This was a retrospective study conducted at Creator's IVF Nepal Pvt. Ltd (CIVF), a fertility centre at Lalitpur, Nepal. The medical records of 768 ART treatment cycles that were performed at CIVF over four and half years from November 2015 to April 2020 were retrieved and analysed. Ethical approval was obtained from Nepal Health Research Council (ref no: 346).

All types of ART treatment cycles reaching up to embryo transfer were included. ART treatment cycles that were cancelled prior to oocyte aspiration or embryo transfer due to reasons such as inadequate follicular development, increased risk of ovarian hyper stimulation syndrome (OHSS), or failed fertilization were excluded. Similarly, freeze-all cycles and oocyte donation cycles were also excluded.

Information of demographic and clinical variables, ART treatment-related variables, and ART outcome-related variables were collected from the ART record books in the medical record section.

Variables under study are primary and secondary type of infertility; and female factor, male factor, unexplained and combined male-female factor as the indication. ART treatment-related variables included type of ART treatment, technique of fertilization, stimulation protocol, cycle number, number of oocytes retrieved on ovum pick up (OPU), and number of embryos transferred. The type of ART treatment was categorised as autologous cycles, oocyte recipient cycles, and embryo recipient cycles. Type of embryo transfer (ET) was categorised as fresh ET and frozen ET. Technique of fertilization were categorized as IVF (In-Vitro Fertilization) and ICSI (Intracytoplasmic Sperm Injection).[3]

The stimulation protocol was categorized as GnRH (Gonadotropin Releasing Hormone) agonist long protocol, GnRH agonist short protocol, and GnRH antagonist protocol. ART outcome-related variables included preclinical pregnancy, clinical pregnancy, livebirth, number of gestational sacs seen in the first scan, multiple gestation pregnancy, type of pregnancy loss, embryo reduction, type of embryo reduction (induced or spontaneous), embryo reduction status, method of induced embryo reduction, birth by plurality (singleton, twins and triplets), and multiple birth.

Preclinical pregnancy was defined as a pregnancy detected by elevated serum beta HCG level (>25 mIU/ml) on the 15th day after ET.[6] Clinical pregnancy was defined as pregnancy presented with at least one gestational sac upon visualization by transvaginal sonography (TVS) at 4 to 5 weeks of gestation.[4] Live birth referred to a delivery of at least one live baby. Any pregnancy with more than one embryo was considered as multiple gestation pregnancy.[7]

Type of pregnancy loss were biochemical pregnancy, ectopic pregnancy, induced abortion, miscarriage, and intra-uterine foetal death (IUFD).

Transvaginal Embryo Reduction (TVS-ER) and Transabdominal Embryo Reduction (TAS-ER) were the two induced embryo reduction methods performed under ultrasound guidance. TVS-ER was performed at 6 to 7 weeks of gestation whereas TAS-ER was performed at 11 to 12 weeks.[8]

Data entry was done in MS-Excel, which was then exported to IBM SPSS (Statistical Package for the Social Sciences) version 20 for further data management and analysis. Descriptive analysis was computed and continuous variables were presented as mean and standard deviation whereas categorical variables were represented in frequency and percentages. The success rates were compared across different types of ART treatment by descriptive analysis only.

RESULT

Demographic and clinical characteristics

Overall, 768 ART cycles leading up to ET were analysed. The mean age of women was 34.4±5.1 ranging from 20 to 50 years whereas mean age of husband was found to be 37.8 ±5.8 years ranging from 23 to 75 years. The proportion of primary infertility was more than secondary infertility i.e. (55.9% vs 44.1%). The average duration of infertility was 5.7±4.3 years which ranged from 1 to 25 years. Female factors contributed to almost half of all treatment cycles i.e. 46.5% [Table-1].

Overview of ART treatment

Overall, the proportion of autologous, oocyte recipient and embryo recipient cycles was 69.6%, 22.0% and 8.4% respectively. Majority were fresh autologous i.e. 63.2% whereas 6.4% were frozen autologous. One-fifth of all cycles were oocyte recipient cycles with fresh ET i.e. 20.7%. whereas only 10 ART cycles i.e. 1.3 % were oocyte recipient cycles with frozen ET. Embryo recipient cycles with fresh ET contributed to 4.8% whereas embryo recipient cycles with frozen ET contributed to 3.6% of all ART cycles.

Table-1: Indication of ART treatments (N=768)

Indication for ART	Frequency	Percent
Female factor	357	46.5
Unexplained	301	39.2
Male factor	94	12.2
Combined male-female factor	16	2.1

Majority of ET were performed in fresh cycle i.e. 88.7%. Likewise, conventional IVF was widely used technique of fertilization contributing to 68.6% of all fresh autologous and oocyte recipient cycles. Altogether, 485 fresh autologous cycles were performed in which ovum pick up (OPU) was performed. Among them, majority underwent GnRH agonist long protocol (87.0%). Donor sperm was used only in 41 (8.5%) of these cycles out of 485. The average number of oocytes retrieved were 9.7 ± 6.2. The average number of treatment cycles was 1.6±1.2 and the mean number of embryos transferred were 3.1±1.0. (Table 2)

Table-2: Fertilization methods (n=644) and stimulation protocol (n=485)

Characteristics		N	%
Technique of fertilization (n=644)	Conventional IVF	442	68.6
	ICSI	202	31.4
Stimulation protocol (n=485)	GnRH agonist long protocol	422	87.0
	GnRH agonist short protocol	16	3.3
	GnRH antagonist protocol	47	9.7

Success rate of ART treatment per ET

Almost half of the ART treatment yielded pregnancy and one-third had livebirth [Figure-1].

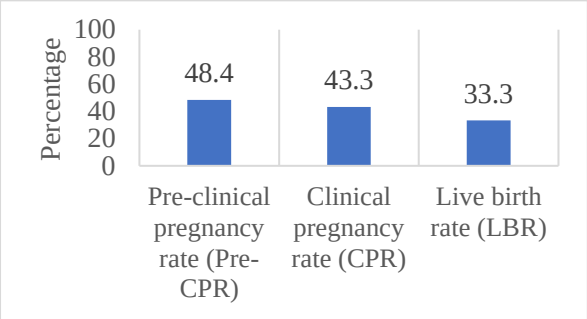

Figure-1: Success rate per ET of ART treatment (N=768)

Pregnancy loss after serum βhCG (Beta Human chorionic gonadotropin) confirmed for pregnancy

Table-3: Pregnancy loss after serum βhCG confirmed for pregnancy

Characteristics	N	%
Preclinical pregnancy loss (n=372)		
Biochemical pregnancy	40	10.8
Clinical pregnancy loss (n=332)	76	22.9
Type of clinical pregnancy loss (n=332)		
Miscarriage	69	20.8
Ectopic pregnancy	3	0.9
Induced abortion	2	0.6
IUFD (Intra-Uterine Fetal Death)	2	0.6
Type of miscarriage (n=69)		
Missed abortion	49	71.0
Anembryonic miscarriage	20	29.0

Nearly half (48.4%) of all treatment cycles i.e. 372 cycles had resulted in pre-clinical pregnancy. However, 40 of these pregnancies i.e. 10.8% turned out to be biochemical. Miscarriage was the leading contributor for loss of clinical pregnancy i.e. 20.8%. Likewise, three clinical pregnancies were ectopic. Similarly, two induced abortions and two IUFD were reported. Anembryonic miscarriage and missed abortion contributed to 29% and 71% of all miscarriages respectively. [Table-3]

Multiple pregnancy, embryo reduction and type of delivery

Table-4: Multiple pregnancy, embryo reduction and type of delivery

Characteristics	Number	Percent
*Number of gestational sacs seen in first scan (n=329)**		
One	223	67.8
Two	67	20.4
Three	32	9.7
Four	7	2.1
Type of embryo reduction (n=41)		
Spontaneous embryo reduction	23	56.1
Induced embryo reduction	18	43.9
Embryo reduction status (n=41)		
Quadruplet to triplet	1	2.4
Quadruplet to twin	5	12.2
Quadruplet to single	1	2.4
Triplet to twin	18	43.9
Triplet to single	6	14.6
Twin to single	10	24.4
Method of induced embryo reduction (n=18)		
Transvaginal embryo reduction (TVS-ER)	11	61.1
Transabdominal embryo reduction (TAS-ER)	7	38.9
Birth by plurality (n=256)		
Singleton	180	70.3
Twin	71	27.7
Triplet	5	2.0
Multiple birth rate (n=256)	76	29.7

** Intrauterine clinical pregnancies*

Single gestational sac seen in first scan was in two-third of all intrauterine clinical pregnancies. Multiple pregnancy rate accounted for 31.9% (106 out of 332) of all clinical pregnancies. Around 38.7% (41 out of 106) of all multiple gestational pregnancies resulted in embryo reduction. Altogether, there had been 256 live births. [Table-4]

Outcome by different ART treatment

The overall pre-CPR, CPR and LBR for autologous cycles (including both fresh and frozen ET) were 48.5%, 42.3% and 33.3% respectively. Among autologous cycles, frozen ET cycles reported slightly better CPR (44.9% vs 42.1%) and LBR (36.7% vs 33.0%) than fresh ET. Likewise, the overall pre-CPR, CPR and LBR for oocyte recipient cycles were 46.2%, 43.8% and 31.4% respectively. Among oocyte recipient cycles, all three measures of success rates were slightly better in fresh ET in comparison to frozen ET as shown in table 5. Similarly, the overall pre-CPR, CPR and LBR for embryo recipient cycles were 53.8%, 49.2% and 38.5% respectively. Among embryo recipient cycles, frozen ET cycles had better CPR and LBR than fresh ET i.e. (50.0% vs 48.6%) and (42.9% vs 35.1%). [Table-5]

DISCUSSION

A number of countries have set up a national ART registry that reports the outcomes and implication that helps plan more effective treatments.[5] However, no national registry administered by national authority or medical organization are evident in Nepal.[9] Although, many private ART centres provide services in Nepal, very little is known about the number and types of procedures performed along with their efficacy. In this context, this is the first study conducted to assess the outcome of different ART treatments at a private tertiary fertility centre in Nepal.

In our study, the overall success rate of various ART treatments in terms of pre-CPR, CPR, and LBR per ET were 48.4%, 43.3%, and 33.3% respectively. A prospective study conducted in a fertility centre in Kathmandu had reported eight clinical pregnancies (25% CPR) and four live births (12% LBR) out of 32 ETs among 68 IVF cases. However, the same study reported that 57 patients were undergoing ET, out of which seven ET cycles were cancelled.[10] Therefore, the number of ET that took place in that study was rather confusing and the results were inconclusive and inconsistent. Moreover, the sample size of the study was small. Hence, the findings

Table-5: Outcome by different ART treatment

Type of ART treatment		Number of cycles	Pre-CPR n (%)	CPR n (%)	LBR n (%)
Autologous cycle	Fresh ET	485	236 (48.7)	204 (42.1)	160 (33.0)
	Frozen ET	49	23 (46.9)	22 (44.9)	18 (36.7)
	Overall*	534	259 (48.5)	226 (42.3)	178 (33.3)
Oocyte recipient cycle	Fresh ET	159	74 (46.5)	70 (44.0)	50 (31.4)
	Frozen ET	10	4 (40.0)	4 (40.0)	3 (30.0)
	Overall*	169	78 (46.2)	74 (43.8)	53 (31.4)
Embryo recipient cycle	Fresh ET	37	20 (54.1)	18 (48.6)	13 (35.1)
	Frozen ET	28	15 (53.6)	14 (50.0)	12 (42.9)
	Overall*	65	35 (53.8)	32 (49.2)	25 (38.5)

*CPR – clinical pregnancy rate, LBR – live birth rate, *Overall ET cycles included both fresh and frozen ET cycles*

from that study and our study must be compared cautiously due to difference in types of treatment and the inconsistent results of the previous study.

A retrospective analysis of 330 IVF-ICSI cycles at a fertility centre in Karachi reported overall pregnancy rate and LBR of 35.2% and 25.1% respectively.[11] Likewise, a government set up hospital in Bangladesh reported four live births among 15 ET i.e. 26.6%.[12] The CPR among 2703 IVF/ICSI cycles performed at a private hospital in Saudi Arabia was 35.10%. [13] In a study conducted in Nairobi, the pre-CPR, CPR and LBR per treatment cycle was reported as 36.2%, 28.9% and 23.4% respectively.[14] The Australia and New Zealand Assisted Reproduction Database (ANZARD) had reported outcomes of 56401 autologous and recipient ET cycles in 2018. Among all ET cycles, 34.4% resulted in clinical pregnancy and 27.3% resulted in a live birth.[3] The CPR and LBR reported by our study are comparable to the success rates reported internationally. However, considering the differences in the clinical profiles of the patients and different types of ART treatments employed, the comparison of success rates across fertility centres are not meaningful.[15] Most of the single centre studies mentioned above only reported outcomes of autologous cycles whereas the outcomes on recipient cycles (oocyte and embryos) were missing.

The CPR for autologous fresh cycles per ET reported by NARI (National ART Registry of India) in 2009 was 36.5% [5] whereas a national study on outcomes of ART in Beijing reported 44.5% CPR in 2015.[16] Our study reported a CPR of 42.1% per ET for autologous fresh cycles which is comparable to international estimates. Globally, around one third of all ART procedures i.e. 32.5% performed were autologous thaw cycles in 2017.[17] The number and proportion of frozen ET cycles performed globally is continuing to rise. The growing preference of frozen ET can be attributed to reduced risk of ovarian hyper stimulation syndrome, cryopreservation of supernumerary embryos, easier for patients, and better understanding of endometrial and embryo synchronicity.[18] In our study, autologous thaw cycles represented 6.4% of ART cycles, whereas frozen ET(autologous and recipient cycles) accounted for 11.3% of all ART cycles. The reason behind lower proportion of frozen ET cycles performed was due to unavailability of in-house embryologists and resources to carry out frozen ET during early years of service provision in our fertility centre.

Our study reported slightly better CPR and LBR in thaw cycles compared to fresh cycle i.e. 44.9% vs. 42.1% and 36.7 % vs. 33.0% respectively. Previous studies have reported significantly higher LBR in frozen ET compared to fresh ET. i.e. 56.8% vs 44.3%. [19] In this context, future studies with robust research designs are recommended to explore the difference between the success rates of fresh and frozen ET.

The use of IVF with donor oocytes has become an increasingly common treatment for women who are unable to conceive using their own oocytes.[20] In our study, the women undergoing oocyte recipient cycles received eggs either from an egg sharing program in which excess eggs from a patient undergoing ovarian stimulation for her own IVF were shared or from a healthy egg donor with no prior history of infertility. In our study, oocyte recipient cycles accounted for 22.0% of all ART treatment cycles which is higher than the global estimate i.e. 6.2% in 2017.[17] This may be explained by the fact that oocyte donation is prohibited across some parts of

the world.[21] In our study, the overall LBR for oocyte recipient cycles including both fresh and frozen ET was 31.4% which is comparable to global estimate i.e. 33.1%.[17]

In our study, excess embryos created by couples undergoing ART treatment were donated and transferred to recipient women. In 2009, NARI reported 38.5% CPR per ET for embryo recipient cycles.[5] Similarly, ANZARD and Centre for disease control and prevention (CDC) reported LBR per ET of 25.5 % [3] and 43.5%[15] respectively following transfer of donated embryos. Our study reported an overall CPR and LBR of 49.23 % and 38.46% respectively in embryo recipient cycles which are comparable to international estimates.[3,5,15]

ART is associated with multiple-gestation pregnancy and birth which may put both women and infants at risk for unfavourable health outcomes.[22] In 2011, the global multiple birth rates after fresh ET and frozen ET were 20.5% and 11.5%, respectively.[23] However, in our study the multiple birth rate was 30.5% which is higher than the global estimate. This is attributed to transfer of multiple embryos in a single ET. While limiting the number of embryos transferred might look like a straight-forward solution, the practice of ET with single embryo is rare. In lower- and middle-income countries, affected couples often bear the related financial burdens as ART treatments are extremely costly and not covered by insurance. Most patients can only afford one treatment cycle which puts pressure on both patients and providers to maximize the chances for success in a single treatment cycle. In this regard, provision of insurance coverage for ART treatment may help as an incentive to perform single ETs thereby reducing the financial burden.[23] The clinical pregnancy loss reported in our study was 22.9%. A study by Yang et al reported 19.7% pregnancy loss (excluding ectopic pregnancy and induced abortion) among 15210 pregnancies.[24] According to ANZARD, among 19409 clinical pregnancies, 19.5% had resulted in early pregnancy loss.[3] Globally, the rate of early pregnancy loss after fresh and frozen ET were 20.1% and 25.4% respectively.[23] ART conceived pregnancies are considered as high risk pregnancies and are sometimes accompanied by obstetric complications. Due to higher prevalence of tubal factor infertility, there may be an increased chance of ectopic pregnancy.[25] The ectopic pregnancy rate in our study was 0.9%. Ghimire reported the incidence of ectopic pregnancy as 0.8% in a tertiary hospital of Nepal among naturally conceived pregnancies that is comparable to ART pregnancies in our study.[26] Although the risk of spontaneous abortion from ART pregnancy appears to be higher than the risk reported by the general population, this comparison can be misleading. Pregnancies with ART are usually closely monitored, so losses in the early stages of pregnancy are usually carefully recorded and reported. In contrast, the rate of spontaneous abortion after natural conception is very difficult to measure and are likely underestimated. In addition, the increased risk of spontaneous abortion among ART conceived pregnancies may be due to the underlying genetic, chromosomal or implantation related problem of the woman receiving ART treatment and not due to the treatment itself.[14,27]

Our study is subjected to some limitations. In our study, the success rates i.e., pre-CPR, CPR and LBR were presented per ET. However, CPR and LBR per initiated cycles and per aspiration cycles could not be given. Since, this is the first observational study conducted in our fertility centre, the factors

affecting the outcome of these treatments were not studied. The obstetric and perinatal outcomes of ART conceived pregnancies were also not explored. However, future studies which explore the factors affecting the outcome of these treatments and studies investigating the obstetric and perinatal outcomes of ART conceived pregnancies will be designed and implemented.

CONCLUSIONS

In conclusion, our study found out that the success rates of ART treatment performed at CIVF were favourable and comparable to international estimates. The evidence on outcomes by all ART service providers could provide a clearer picture of utilization and efficacy of ART treatment across Nepal.

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