

What is the Probability of a Live Birth after a New IVF/ICSI -ET in Patients with History of Unexplained Recurrent Implantation Failure?

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Abstract

Background and Objective: The main objective of this study was to determine pregnancy & live birth rates after a new IVF/ICSI and fresh embryo transfer in patients with history of unexplained recurrent implantation failure (RIF).

Method: In this prospective cohort study, 50 unexplained RIF patients who were scheduled for a new IVF/ICSI -ET treatment in Avicenna specialized and tertiary center for infertility treatment, were followed to determine pregnancy & live birth rates. All patients were assessed for inclusion and exclusion criteria also had informed consent before entering the study.

Results: The mean age of patients was 33.57 ± 4.63 years. Mean number of previous unsuccessful IVF/ICSI -ET cycles was 2.72 ± 1 . The average number of oocytes picked up via ovarian puncture was 11.2 ± 6.5 and mean number of grown embryos was 5 ± 6 . Four of 50 patients were excluded from the study, 10 of 46 (21.7%) patients had positive pregnancy tests, clinical pregnancy also live birth rates per ICSI cycle was 8/46 (17.3%). one case of ectopic pregnancy, one chemical and two clinical pregnancy losses also two twin pregnancies, one of them resulted in preterm labor in 34th week, happened. Sides effects such as infection, hemorrhage and fetal anomaly didn't occur in patients.

Conclusion: This study showed that pregnancy and live birth rates per new ICSI- ET cycle for unexplained RIF patients were 21.7% and 17.3% respectively. These rates are less than success rates among the general population scheduled for IVF/ICSI -ET with no history of unexplained recurrent implantation failure. Therefore, unexplained RIF patients may need to undergo a greater number of ART cycles to gain a live birth.

Key words: unexplained recurrent implantation failure, new IVF/ICSI -ET, live birth

Background and Objective

Despite great advances in assisted reproductive techniques (ART) in recent years, live birth rate as the main ART outcome has not improved significantly¹. In 2013, mean live birth rate per embryo transfer was 30%, indicating most IVF/ICSI cycles are failed. Several factors may affect embryo implantation, such as technique of embryo transfer, endometrial receptivity, embryo invasion to implant in the endometrium. Increased female age is also considered as a key factor for implantation failure²⁻⁵. There is no net definition for recurrent implantation failure. Now days, two unsuccessful embryo transfers, each containing two embryos with descent quality and development stage is considered as recurrent implantation failure (RIF)⁶, In recent years, with a tendency to only one embryo transfer per cycle, this definition is ambiguous, so RIF is considered as at least two unsuccessful descent quality fresh or frozen embryo transfer, while the number of cleavage stage and blastocyst stage embryos are more than 4 and 2, respectively.

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Sometimes, the reason of IVF failure is found but most often no specific cause can be detected and implantation failure is considered as the main factor for unsuccessful ART cycle. Recurrent implantation failure result in anxiety and frustration in couples and impose heavy financial costs on them. Therefore, approach to RIF patients is a challenge for infertility specialists.

There are several algorithms and methods to assess RIF patients⁷, female factors (increased age, myoma, polyp, endometrial adhesion, thin endometrium, hydrosalpinx, thrombophilia, underlying disease like diabetes, hypo or hyper thyroidism, hypertension) may cause RIF⁸, if so. Proper individualized treatments are recommended to increase the probability of pregnancy. such as: egg donation, myomectomy, polypectomy, hysteroscopy to remove septum or endometrial adhesion and correction of the underlying disease⁹⁻¹⁴. Treatment of hydrosalpinx should be performed before new embryo transfer^{15,16}. when genetic disorders are the main cause of RIF karyotyping of couples, PGD and third-party parenting may help to improve the situation. Hatching, blastocyst embryo transfer, and sequential embryo transfer are sometimes used to increase the chance of implantation, while none of them are considered as the definite solution for RIF patients¹⁷⁻¹⁹. Unexplained implantation failure is occurred when no cause is found for unsuccessful implantation, in another word, female, male and embryo conditions are all acceptable but pregnancy does not happen, if this occurs at least in two IVF /ICSI-ET cycles, it is called unexplained recurrent implantation failure. As mentioned before treatment of RIF patients, especially unexplained ones is a major challenge for all infertility specialists. Because no cause is found for failures, it is associated with psychological

and financial complications, and prediction of a live birth after the next ART cycle is too difficult^{20,21}.

So far in Iran, no study has been conducted on the possibility of pregnancy and live birth in patients with recurrent implantation failure after the new ART cycle. This study is designed to determine the probability of live birth after a new IVF /ICSI-ET cycle in unexplained RIF patients.

Methods

This research is a prospective cohort study. This study was approved by the ethics committee of Avicenna Research Institute, the approved number was No. 326/91. Fifty couples scheduled for new ICSI cycle, in Avicenna Infertility Treatment Center, known as a referral infertility treatment center in Iran, were included in this study.

All 50 patients had a history of at least two failed IVF / ICSI-ETs with no apparent reason (repeated unexplained implant failure). Sampling of this project was done between December 2015 and September 2018. To select these 50 patients, initially 230 patients with a history of at least two previous implantation failures were examined.

Of these, 87 were excluded after reviewing the inclusion and exclusion criteria. Forty were reluctant to participate in the study, and 53 did not participate in the study due to request in order to use various accessory methods such as hysteroscopy (endometrial scratch), immunomodulators or drugs such as prednisolone, IVIG, GCSF, heparin, hydroxychloroquine, etc. Because these agents were considered as confounding factors in the results, these 53 patients were also excluded from the study (Figure 1).

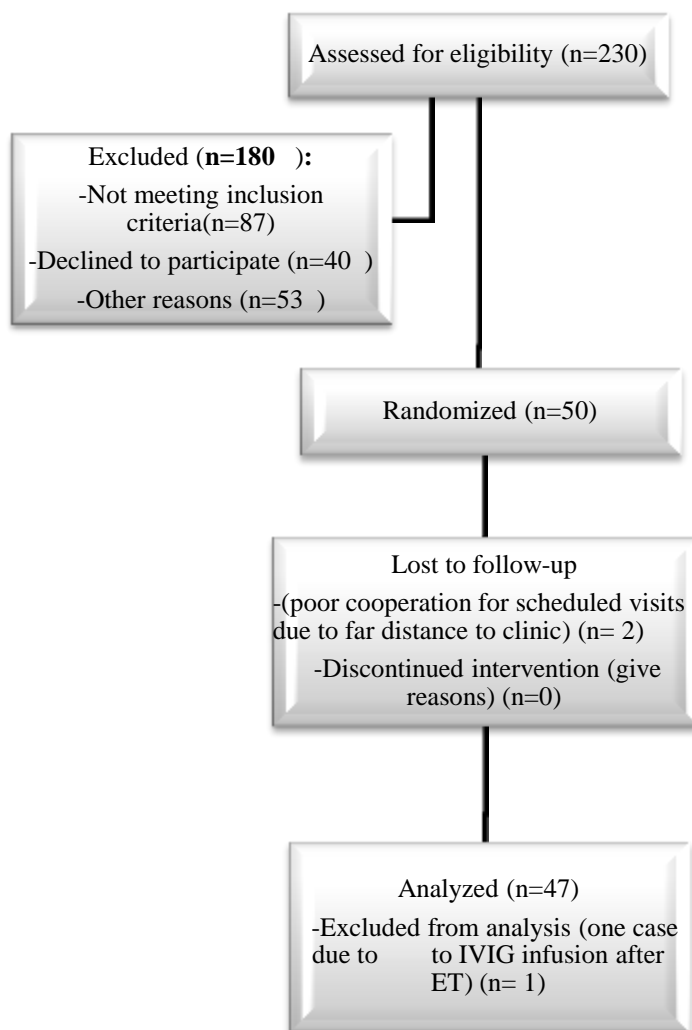


Figure 1. Diagram for Patient's eligibility& admission to the study

All women were less than 39 years old. In order to confirm the diagnosis of unexplained RIF, karyotype examination was performed for all couples and cases with karyotype disorder (were not included in the study). Routine, infectious (CBC Prolactin, FBS, HbA1C, TSH, FT4, TPO, ...), and hormonal tests on 3th day of menstrual cycle (FSH, LH, Estradiol), Also necessary tests for thrombophilia and immune system assessment such as prtC, prtS, Homocysteine, APCR, Antithrombin III, ANA, B2 glycoprotien (IgG-IgM), Anticardiolipin (IgG-IgM), DRVVT (LAC), and Antithyroglobulin antibody were requested.

If there was an immunological problem or thrombophilia, the patient was excluded from the study. Also, the evaluation of the uterine cavity for each patient was done in a personalized based approach by various methods such as (hysterosalpingography, sonohysterography, three-dimensional sonography). Müllerian anomalies or acquired factors such as endometrial adhesion (Asherman syndrome), myomas and polyps were diagnosed and treated, so that the patient was not included in the study if the uterine factor caused recurrent implant failure.

Also, during vaginal ultrasound on days 8-12 of the ICSI cycle, the endometrium was evaluated by the infertility fellowship in

terms of thickness and 3 linearity. If the endometrium was inadequate, the patient would not be included in the study.

Also, patients with history of polycystic ovarian syndrome and ovarian hyperstimulation syndrome in previous cycles (so that all fetuses were frozen) were not included in the study because this study examined the fresh embryo transfer cycle. On the other hand, severe OHSS is one of the causes of implantation failure, so this confounding factor was also eliminated.

In this study, we tried to evaluate patients in terms of entry and exit criteria, the following visits during the ICSI cycle and ovarian puncture and embryo transfer, all by only one infertility fellowship to provide maximum uniformity for patients, and the conclusion of the study could be more reliable. Also, all men were visited by an endourology fellowship, if the cause of RIF was male factors such as azoospermia, etc., the patient would be excluded from the study. All men, had at least one million sperm per milliliter (1×10^6 / ml) with at least 4% normal morphology in the sperm analysis test.

Ovarian stimulation

Patients underwent a long agonist cycle (24 patients) or an antagonist ovarian stimulation cycle (22 patients). Based on AMH, antral follicle count and age, adjusted doses of Gonal-F (Merck Serno) or Fostimon (IBSA) or Merional (IBSA) was prescribed for patients since 3th day of menstrual cycle.

After 5 days, vaginal ultrasound was performed again to check the size of the ovarian follicles. The dose of gonadotropins was again adjusted based on the size and number of follicles. In the next following days, if there were at least two 18-20mm follicles, 10000 IU Choriomon (IBSA) was injected intramuscularly and 36 hours later, in the operating room under general anesthesia

and under the guidance of vaginal ultrasound and Vallas puncture needle, oocyte retrieval was performed and follicular fluid was transferred to the embryology laboratory.

Embryos with more than six cells on the third day after ICSI and less than 10% of their space was occupied by Cell Fragment and their blastomer size was similar, were selected as good quality embryos for transfer. Embryo Transfer was done with a Cook catheter (Queensland, Australia) and through the cervix. In each transfer, one or two embryos were transferred, and if more embryos formed, the rest were frozen.

Our study only involved fresh embryos transfer (ET). All patients were monitored up to 14 and 16 days after ET. If the pregnancy test was positive, vaginal ultrasound was done in 5-7th week to detect clinical pregnancy (presence of gestational sac with fetal heart activity) also another ultrasound at 12th week was performed to follow ongoing pregnancies and first stage of fetal screening scanning. All pregnant women were followed meticulously in all necessary visits and screenings during pregnancy and finally until delivery.

In this study, the birth of a baby by cesarean section or normal vaginal delivery (NVD), which occurred after 27th weeks of pregnancy (after fetal viability), was considered as a live birth.

Results:

Four of 50 patients, were excluded from the study. Two of them due to lack of proper cooperation to go to the treatment center because of long distance and the other two patients due to IVIG infusion after embryo transfer (Figure 1).

Patients were evaluated for demographic characteristics, number of oocytes and fetuses, fetal quality, pregnancy, and live birth rates. The mean age of patients was 33.57 ± 4.63 years. The mean number of

previous unexplained failed ICSI cycles was 2.72 ± 1 cycles (Table 1).

Table 1. patients' Demographic characteristics

Variables	Control Group (n=46)
Age	33.57 ± 4.63
BMI	25.25 ± 3.24
Infertility Duration	7.22 ± 4.36
Number of previous IVF/ICSI cycles	2.72 ± 1.00
Baseline FSH	7.63 ± 2.56
Baseline AMH	2.81 ± 2.43
Sperm Count (count/ml)	$(43 \pm 42) \times 10^6$

Patients were also evaluated in terms of treatment cycle characteristics. Twenty-four patients with antagonist and 22 with long agonist ovarian stimulation cycles were treated. There was no significant difference in number of patients between antagonist and long protocol groups

(ANOVA test $0.989 = P$ -value). Mean number of oocytes picked up was 11.2 ± 6.5 . The average number of embryos grown up was 5 ± 6 . The mean endometrial thickness on the day of HCG injection was 7.9 ± 1.7 mm (Table 2).

Table 2. patient's ICSI cycle characteristics

Variables		Control Group (n=46)	Chi-Square
Cycle Protocol*	Antagonist(n=24)	52.2%	P-value: 0.989 (N.S) ¹
	Long agonist (n=22)	47.8%	
Mean Gonadotropin dosage		$(28.7 \pm 12.7) \times 75$ IU	
Mean Duration (days) of Gonadotropin Administration		9.54 ± 2.3	
Mean E2 before OPU		2845 ± 2025	
Mean Endometrial Thickness**		7.9 ± 1.7	
Mean Number of Oocytes		11.2 ± 6.5	
Mean Number of*** Embryos		5 ± 6	
Percentage of Mean Good Quality Embryos*		64.3%	
Mean Number of Frozen Embryos**		2.35 ± 3.77	
Mean Number of Transferred Embryos***		2 ± 1	

*Data are presented as percentage

**Data are presented as (Mean \pm SD)

*** Data are presented as (Median \pm IQR)

1-N. S: Not Significant Chi-Square test

Ten patients had positive pregnancy test 10/46 (21.7%). There were 8 cases of clinical pregnancy 8/46 (17.3%), two cases of abortion 2/10 (20%), six progressive pregnancies 6/10 (60%), two cases of twin pregnancies and 8 live births (two cases of

twin births). These 46 new microinjection cycles, resulted in 8 live births 8/46 (17.3%). 4 babies from two cases of twin pregnancies plus 4 babies from four singleton pregnancies (Table 3).

Table 3. Pregnancy outcome

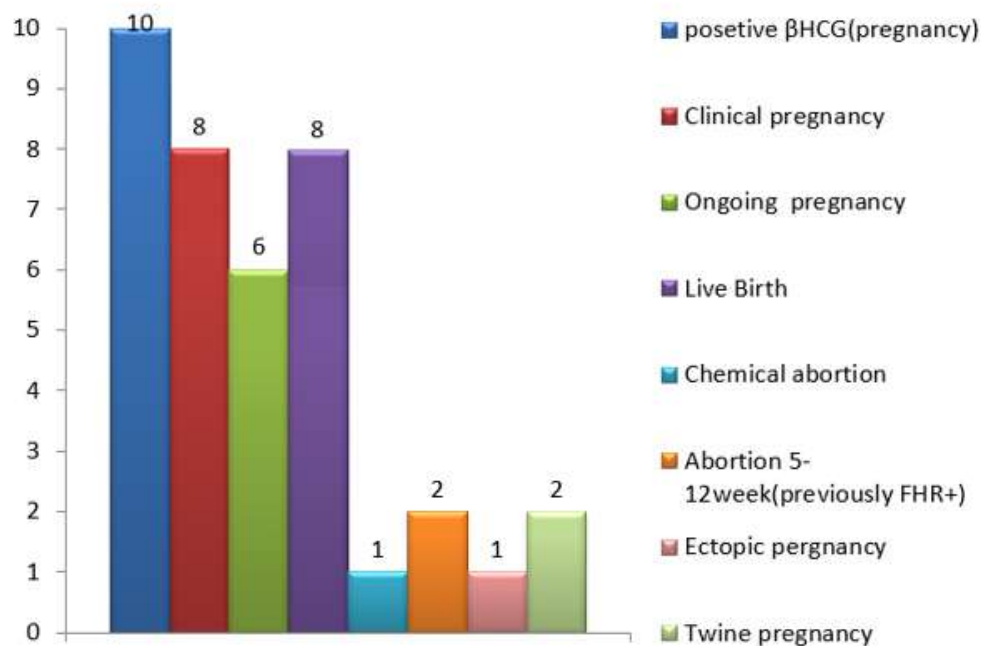
Variables	Control Group (n=46)
β HCG+	10/46 (21.7%)
Clinical pregnancy rate	8/46 (17.3%)
Live Birth Rate	8*/46 (17.3%)
Clinical pregnancy rate (per HCG+)	8/10 (80%)
Ongoing pregnancy per HCG+(12 th week)	6/10 (60%)
Abortion before 12 th week ^B	2/10 (20%)
Twin pregnancy	2/10 (20%)

Data are presented as ratio (percentage)

*4 Babies from two cases of twin pregnancies plus 4 babies from four singleton pregnancies

Out of 10 pregnancies, one case of chemical abortion, one case of ectopic pregnancy, and 8 cases of clinical pregnancy were confirmed in sonographic examinations, of which 8 in case of clinical pregnancy, two abortions (one in

the 7th week and the second in 10th week) occurred, six on-going pregnancies, two of which were twins and the other four were singleton pregnancies, which eventually led to eight live births (Figure 2 and Table 3).

**Figure 2.** pergnancy outcom in 46 unexplained RIF patients

four cases of singleton pregnancies resulted in live births at 39-39th weeks of gestation. Two cases of twin pregnancies occurred, one of them terminated by elective cesarean section at 38th weeks and two female babies were born. In another

twin pregnancy, the mother underwent an emergency cesarean section at 34th weeks due to preterm labor pain. The result was a female and a male baby. Both the infants did not need to be hospitalized (Table 4)

Table 4. Progressive pregnancies leading to childbirth

Row	Progressive pregnancies	Delivery week	Delivery	weight	Apgar score	congenital anomaly	sex
1	Twin pregnancy	34	Emergency cesarean section	2500gr	9/10	–	Female
				2600 gr	9/10	–	female
2	Twin pregnancy	38	Elective cesarean section	2000 gr	9/10	–	Female
				2100 gr	9/10	–	Male
3	singleton pregnancy	39 ^w +3 ^d	Elective cesarean section	2700gr	9/10	–	Male
4	singleton pregnancy	39 ^w	Elective cesarean section	3200gr	9/10	–	female
5	singleton pregnancy	38 ^w	Elective cesarean section	4000gr	9/10	–	female
6	singleton pregnancy	39 ^w +2 ^d	Elective cesarean section	3700gr	9/10	–	Male

Complications

Since patients with PCOD and history of severe OHSS in previous cycles were not entered to the study due to exclusion criteria, the role of PCOD, as a confounding factor in recurrent implant failure, has been omitted in this study. No case of OHSS occurred among patients. Patients with suspected mild OHSS were evaluated with lower HCG doses (5000 IU) for trigger injection and ultrasound to examine ovaries and pelvis before embryo transfer.

There were no complications such as bleeding or infection after ovarian puncture in this study.

One case of ectopic pregnancy due to small size (1.5 × 2 cm), lack of fetal heart activity in the ectopic pregnancy sac and the stability of the patient's vital signs was treated by injection of methotrexate without surgery.

In both cases of abortions at 7th and 10th weeks, patients spontaneously suffered

from vaginal bleeding and pregnancy products were expelled, but in abortion at 10 weeks, uterine curettage was performed due to some retained pregnancy tissues and no other complication occurred.

There have been two cases of twin pregnancies:

One of them was terminated by elective cesarean section at 38th week and two babies were both born with 9-10 Apgar score and weighing 2500 gr and 2600 gr.

The next case of twin pregnancy, the mother underwent emergency cesarean section in the 34th week of pregnancy due to preterm labor pains. The result was a female and a male baby, both with 9-10 Apgar score, weighing 2000 gr and 2100 gr respectively. Both infants did not need to be hospitalized.

In four cases of singleton pregnancies, resulted in live births at 38-39th weeks of gestation. Only in one case, the mother had gestational diabetes (controlled by diet) and the weight of the newborn was

4000gr, but after birth there was no need to hospitalize the infant and the blood sugar of the baby and mother was normal (Table 4).

There were no complications such as bleeding and postpartum infection in mothers. Congenital anomalies were not seen in newborns.

Discussion

The live birth rate in population undergoing IVF / ICSI cycle is about 35% per treatment cycle in infertility centers, worldwide. Infertility centers use pre- and post-infertility treatment models to predict the chances of live birth in ART.

Variables such as the woman's age, ovarian reserve, Sperm analysis test, duration of infertility, couple's previous pregnancy status and type of treatment protocol, are used in pre-treatment models, while, variables related to the ART cycle (number of oocytes, number and stage of embryos, number of frozen embryos) are considered in post-treatment models. Then, by combining pre- and post-treatment models, the cumulative probability of live birth (taking into account the sum of fresh and frozen cycles is predicted).

However, some models predict the likelihood of live birth only after a single fresh embryo transfer, without considering the significant contribution of the frozen embryo transfer cycle to the cumulative rate of live birth²¹⁻²³.

In a study conducted by Metello et al, 2019 in Portugal, 739 IVF / ICSI cycles were examined in the period 2012 to 2016, positive pregnancy test and live birth rates were 46% and 31.4% respectively. These 739 ART cycles included all patients during this period and the focus of the study was not on unexplained RIF patients²⁴.

Another study by Khalife et al, 2020, In Beirut, examined fresh embryo transfer cycles. The live birth rate after the first

IVF / ICSI cycle was 33.0%. But in women with at least two previous failed IVF / ICSI treatments, the rate of live births in the third, fourth, fifth and sixth cycles of IVF / ICSI and subsequent fresh embryo transfer was, respectively 26.5%, 25%, 20.5%, and 26.8% per cycle²⁵.

Koot et al., 2019 in the Netherlands, studied 118 women under the age of 39 with a history of unexplained recurrent implantation failure in a retrospective cohort, from January 2008 to December 2012 at two university centers. In this study, the researchers had communicated with unexplained RIF patients by e-mailing a questionnaire and receiving answers from patients. live birth rate was about 15% per new IVF / ICSI cycle²⁶.

In Iran, no study has been conducted on the rate of live births in unexplained RIF patients. This study is the first study conducted in this field.

In this study, a prospective cohort was performed at Avicenna Infertility Treatment clinic as a referral tertiary center in Iran. The focus of the study was on unexplained RIF patients.

Fifty patients with history of at least two unexplained unsuccessful IVF / ICSI -ET, formed our study population. Also, all patients were examined in terms of genetics, immunology, underlying diseases, uterine anomalies, and endometrial suitability, if there was a specific factor for implantation failure, the patient would not be included in the study.

In addition, all patients have been visited since the first visit and then in subsequent visits and visits during the ART cycle and ovarian puncture and embryo transfer by one infertility fellowship to provide more uniform conditions for the patients.

In our study, after the new ICSI cycle and new embryo transfer, the pregnancy rate was 21.7% and the live birth rate was 17.3% which is lower than the average success rate (approximately 33% of live

births) of the population undergoing IVF / ICSI in general. But the results were close to a study by Koot et al. Conducted on people with recurrent failure.

The results of our study differ from those of Khalife et al, with live birth rate of more than 20% in unexplained RIF patients.

Conclusion

This study shows, unexplained RIF patients, compared with the general population undergo ART for a variety of infertility reasons are less likely to become pregnant and have live birth following their new IVF / ICSI cycle.

Therefore, couples with unexplained recurrent implantation failures need to repeat more IVF / ICSI cycles to achieve a live birth. psychological and financial support for couples, with recurrent failed IVF / ICSI treatments, seems to be absolutely necessary. For example, using health insurance coverage for a greater number of IVF / ICSI cycles can be helpful. Psychological counseling and couple therapy are also recommended in this group of patients.

Of course, more studies with larger sample size should be done in order to obtain more accurate results and suggest more appropriate strategies for treating couples with unexplained recurrent implantation failure.

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