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Is Rescue Intracytoplasmic Sperm Injection, an Option for Fertilization Failure? A Systematic Review

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Abstract

Rescue intracytoplasmic sperm injection (ICSI) is an attempt to overcome fertilization failure after *in vitro* fertilization (IVF) treatment and is being used in many centers. There is still controversy over the use of rescue ICSI. The aim of this systemic review was to assess the feasibility, efficacy, and safety of rescue ICSI. An electronic literature search was performed in PubMed by the term "rescue ICSI" from 2000 to 2016. The search was expanded by using listed references from the selected articles. The outcome was listed in terms of the number of embryos, fertilization rate, pregnancy rate and clinical outcomes of pregnancy. The factors that can affect the efficacy of IVF/ICSI and recommendations for the use of rescue ICSI are discussed. Altogether, 16 articles were listed with 1,554 patients and 181 pregnancies. From the review, it can be concluded that the pregnancy rate is not as good as fertilization rate, though it can result in the delivery of a healthy baby and should be used as an option to salvage IVF failed cycle.

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Introduction

Infertility is a growing problem in today's world and the prevalence of infertility is increasing every year. *In vitro* fertilization (IVF) has helped many infertile couples and plays an important role in overcoming infertility, but when IVF fails, it leads to emotional and financial burden [1, 2]. Around 3.5% to 20% of the IVF cycles are likely to have total fertilization failure [3, 4]. In 2003and 2010 incidences of total fertilization failure after conventional IVF using normal sperm were reported from 5% to 20% [3, 5]. In 2012, those were reported to be 3.5% based on a large single-center study [4].

Fertilization is the fusion of an oocyte with sperm to form an embryo. This involves complex steps from sperm penetration, extrusion of the second polar body, oocyte activation, decondensation of both nuclei and chromosome cytoplasmic migration of the pronuclear [6]. A total of 55%-92% of the fertilization failure in conventional IVF is due to lack of sperm penetration into the oocyte [6, 7]. In intracytoplasmic sperm injection (ICSI), sperm is directly inserted into the oocyte by piercing the oocyte membrane mechanically [8]. Oocytes after failed IVF are re-inseminated using the ICSI method. This is called rescue-ICSI [9]. Rescue ICSI is an attempt to overcome fertilization failure in IVF. It is of two types early ICSI which is done in one-day-old oocytes and late ICSI which is done in 2 days old oocytes. Rescue ICSI was first introduced in 1993 to salvage the 1-day old oocyte after conventional IVF failure for severe male factor infertility. It had high fertilization rate of 53% and cleavage rate of 84% [10]. However, rescue ICSI has also seen beneficial in non-male factor infertility and unexpected infertility. There have been reports that favor rescue ICSI as it showed a positive effect on fertilization rate, embryo quality, and pregnancy rate; however, some physicians do not recommend it [11, 12].

The purpose of this article is to review the available knowledge about clinical outcomes and effectiveness of rescue ICSI and to discuss various factors that can cause fertilization failure.

Data collection and selection criteria

Articles for the review were selected from PubMed using search term "rescue ICSI". Articles were selected from 2000 to 2016. Additional articles were also included from the references of these articles to expand our study. In this review, only the published articles and their data have been used so no institutional review board approval was required. Articles were selected taking consideration of inclusion and exclusion criteria that are described below.

Selection criteria

The articles written in English related to the cause of infertility other than non-male factors and unexplained infertility, articles that performed rescue ICSI in the index cycle after fertilization failure and articles that mentioned female factor infertility as fallopian tube factor, ovarian function decline, endometriosis etc. were considered. While the articles involving animals, invasive tests, sperm abnormalities and abstracts used in any conference were excluded.

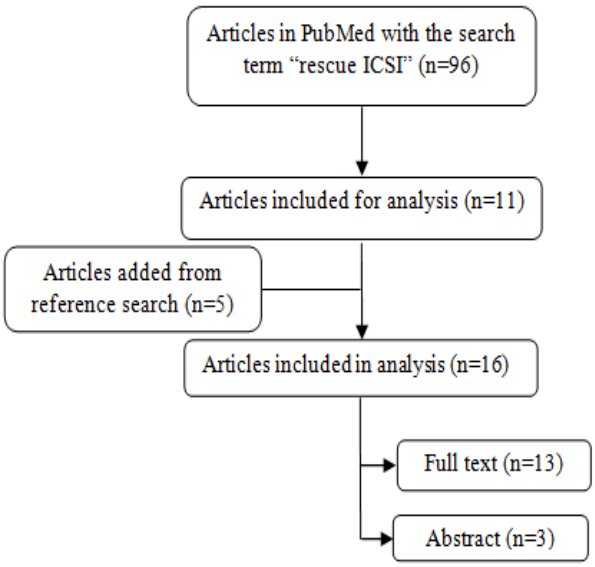

Fig. 1 Flow chart of the selection process of studies.

Outcome measures

The primary outcome of the review was pregnancy while the secondary outcomes were the number of embryos, number of pregnancies, fertilization rate, and pregnancy rate.

Data analysis

Using the search term “rescue ICSI” in PubMed, 96 articles were retrieved. According to the selection criteria, 11 articles were selected. 5 additional articles were also included from the references of these articles to expand the study. Altogether, 16 articles were included in this systemic review. The complete selection process of articles is shown in Fig. 1.Out of 16 articles, 13 are full-text articles and 3 are abstracts (only abstracts available are from Systemic Biology in Reproductive Medicals, The Journal of Reproductive Medicine and Saudi Medical Journal). There are 4 prospective studies, 9 retrospective studies, and 3 case reports. Total fertilization failure is present in 10 articles. The characteristics of the included studies in this review are mentioned in Table 1.

The data describes 1554 patients, 11,313 oocytes used for rescue ICSI, more than 4,318 embryos derived after rescue ICSI and only 2,539 embryos were transferred leading to 181 pregnancies. 127 babies were born out of which 17 were twins, one triplet, 90 singletons, 8 ongoing pregnancies, 27 abortions, two ectopic pregnancies, five chemical pregnancies and two late terminations due to chromosomal abnormality were found. Total fertilization failure was seen in 1,088 patients, 8,276 oocytes were used for rescue ICSI, out of 2,284 embryos 1,779 embryos were transferred and a total of 138 pregnancies were reported with 90 babies born. There were 69 singletons, 18 twins, one triplet, four ongoing pregnancies, 23 abortions, one ectopic, five chemical pregnancies and two late terminations [4, 12-26]. Though abnormal pregnancies are high in total fertilization, yet the outcome was good.

Two articles, one retrospective study [22] and one prospective study [25] compared early ICSI with late ICSI. In these articles, early ICSI was performed in 6 hours and 24 hours whereas late ICSI was performed in 22 hours and 48 hours after initial insemination, respectively. Fertilization rate of early ICSI in both the articles were 70.3% and 47.1% which were higher than late ICSI that were 48.6% and 40%, respectively. Both the studies recommended early ICSI to be better than late ICSI.

All three case reports [14, 20, 23] and four prospective studies [12, 16, 19, 25] recommend the use of rescue ICSI for IVF failed cycles. One prospective study [19] showed that six hours insemination of oocytes gave good result and another prospective study mentioned the increase in fertilization rate and embryonic development after rescue ICSI. Out of nine retrospective studies, six studies [4, 13, 17, 18, 22, 26] recommend the use of rescue ICSI. One retrospective study [13] commented that rescue ICSI is helpful for patients with IVF rate <25% and is not recommended for patients with IVF rate >25%. Another retrospective study [4] preferred rescue ICSI as embryos derived from it can be cryopreserved and subsequently can be used in frozen-thawed cycles. One retrospective study [17] showed the success rate to be associated with young age and high-quality embryos and it is cost effective in terms of total fertilization failure and is, therefore, worthwhile. An overview of the included studies is shown in Table 2.

Factors that lead to fertilization failure

Maternal age

Hormonal imbalances, abnormalities in follicular development are due to the aging of the somatic cells surrounding the oocytes and impaired perifollicular microcirculation [27]. The decline of fertility increases with age as the ovarian reserve, endometrial receptivity and oocyte quality are impaired. This can also be explained by telomerase shorting that occurs due to prolonged exposure of reactive oxygen species or/and telomerase deficiency [28]. Telomerase adequate length is essential for proper alignment of the chromosome during metaphase. The success rate for less than 35 years women was 38.9% deliveries per oocyte retrieval, whereas for women aged >40 years was 11.1% deliveries per oocyte retrieval [29]. According to one of the articles published in 2014 reported success rate of 47.4% for women aged 27-37 years, 30.1% for women aged 38-40 years, 20.3% for women aged 41-43 years and 10.7% for women aged 43-44 years [30]. Another article published in 2015 showed a pregnancy rate after frozen egg transplant in women aged less than 35 years was 57.7%; whereas the pregnancy rate in patients aged >35

Table 1 Characteristics of the studies included in the review.

Year	Study design	Text	TFF	No. of patients	Reference
2016	Retrospective	F	No	313	[13]
2013	Case report	F	Yes	1	[14]
2013	Retrospective	F	Yes	11	[15]
2012	Prospective	A	Not mentioned	77	[16]
2012	Retrospective	F	Yes	607	[4]
2011	Retrospective	F	Yes	92	[17]
2011	Prospective	A	Yes	112	[12]
2010	Retrospective	F	Yes	17	[18]
2006	Prospective	F	No	20	[19]
2006	Case report	F	Yes	1	[20]
2005	Retrospective	A	Yes	82	[21]
2003	Retrospective	F	Yes	Early R-ICSI 25; late R-ICSI 20	[22]
2003	Case report	F	No	1	[23]
2002	Retrospective	F	Yes	120	[24]
2000	Prospective	F	No	Early R-ICSI 25; late R-ICSI 20	[25]
2000	Retrospective	F	No	32	[26]

F= Full article available; A= only abstract available; TFF= Total fertilization failure

years was 29.2% [31]. No study has reported about maternal age with rescue ICSI. An article compared reproductive outcomes of ICSI and IVF with non-male factor infertility in women aged >40years concluded that there is no advantage of IVF/ICSI in advanced maternal age [32].

Oocyte activation

In 40-70% of failed ICSI cycles, oocyte shows the correct injection of sperm into the oocyte and that failure is due to oocyte-activation deficiency [33, 34]. Oocyte activation is a complex process in which there is an increase in intracellular calcium on sperm entry that helps in the release of cortical granules that activates membrane-bound ATPase and meiosis starts with the release of second polar body and formation of male and female pronuclei. To assist oocyte activation, there are various mechanical, physical and chemical methods. (1) Mechanical method: It consists of vigorous aspiration and re-injection of cytoplasm with spermatozoa in the oocyte. This process is repeated two times and there is a substantial amount of Ca^{2+} influx from the culture medium in which it is placed. A study conducted on 14 patients that used a mechanical method had 53% fertilization rate and 33.3% pregnancy rate [35]. (2) Physical method: It consists of electrical activation. Electric field generates micro pores in the cell membrane of gametes and somatic cells that induce sufficient calcium influx through pores to activate cytoplasm by the calcium-dependent mechanism. An article that used electrical activation on oocyte with a single square direct current pulse (91.5kV/cm, 100ms) approximately 30 minutes after ICSI concluded that these oocytes could develop into good quality embryo and competencies to establish an ongoing pregnancy. The degeneration rate was reported to be 12% [36]. Another article reported fertilization rate of 68% and the degeneration rate of 5-9% using double square direct current pulse to achieve a field strength of 2.6-2.8kV/cm approximately 20-30 minutes after ICSI [37]. (3) Chemical method: mainly used artificial chemical activating agents are strontium chloride ($SrCl_2$) and calcium ionophore. $SrCl_2$ moves inside the oocyte by the concentration gradient and releases Ca^{2+} from endoplasmic retinaculum. Commonly used an artificial chemical activating agent is calcium ionophores. It is lipid-soluble molecules that carry ions across the lipid layer of cell membrane leading extracellular calcium to move into the cell. There are various protocols for using ionophore. An article that used single exposure on oocyte within 60 minutes from the ICSI injection to 5-10µm calcium ionophore A23187 for 5 minute protocol reported fertilization rate of 41.6%, 44.4% and 12.8% and pregnancy rate of 18.8%, 31.4% and 24.1% in 3 groups that were divided on the history of no fertilization [38]. Using the same activation protocol, pregnancy outcome was studied in which

all 35 children born were healthy except for one with anal atresia [39]. Another reported twin pregnancy using *in vitro*-matured oocyte [40]. The neonatal behavior and neurological development of 21 children till the age of 3 years who were born by artificial oocyte activation were reported. It used calcium ionophore within 30 minutes of incubation in 5-6% CO_2 atmosphere by two exposures to ionomycin, 10 µm for 10 minutes, 30 minutes apart. The results were reassuring and outcomes of all the tests were within the expected range [34]. A review that used 14 articles to study the reproductive outcome using ICSI by artificial oocyte activation in couples with previous fertilization failure stated that evidence is not sufficient to determine the efficacy and safety of artificial oocyte activation in ICSI [41].

Low ovarian response

It is an important factor in predicting fertilization failure. Plan of rescue ICSI can be made if there is a low ovarian response. The condition that occurs in the process of IVF treatment when ovarian stimulation is suboptimal i.e. there are less number of eggs/oocytes available that can be retrieved is called low ovarian response. This condition leads to low fertilization rate and pregnancy rate. A patient with the low ovarian response can have an intact ovarian function [42]. It was first reported in 1983 soon after the introduction of *in vitro* fertilization technique [42]. Eggs are formed in the female before her birth. At the time of birth, there are around one to two million eggs. As the age increases the number of eggs decreases, at puberty 250,000 to 500,00 eggs, at 35 years of age, 25,000 eggs and at menopause <1000 eggs are present. Eggs present in the ovary are of three types: immature eggs that remain in a dormant stage, eggs that get mature for ovulation and eggs that atrophy or dies. A decrease in the available number of eggs is called low ovarian response. Causes of low ovarian response are: (1) by age, there is a decline of ovarian reserve, which also indicates a decline in the quality of primordial follicle [43-45]. (2) Chromosome abnormality; as Turner syndrome that lacks one X chromosome or gene abnormality like fragile X syndrome. Fragile X primary ovarian insufficiency is experienced by approximately 28% of females with an FMR1 permutation. Another 23% of females experience menopause before the age of 45 years. (3) Iatrogenic; e.g., past surgical treatment, pelvic infection, radiation and chemotherapy for cancer treatment, ovarian cyst and ovarian scarring caused by endometriosis, laser treatment on the surface of the ovary to treat endometriosis. For the treatment of polycystic ovarian disease, sometimes excessive laparoscopic ovarian drilling can cause premature ovarian failure as the follicles are present in the thin one-millimeter outer layer of the ovary [46]. (4) Others are adrenal gland impairment, autoimmune disorder, ovarian tissue destroyed by torsion, pelvic adhesion, high body mass index, smoking. Criteria to diagnose low ovarian response are: estradiol level <500 pg/ml during stimulation, estradiol level <200 pg/ml on day 5 of stimulation, FSH level ≥15mlU/ml on day 3, low number of oocytes retrieved, past history of stimulation cycle that required additional days of stimulation with high dosage of gonadotropins [47] .

Follicular stimulating hormone (FSH) is the hormone released by the pituitary gland. FSH stimulates the ovary to produce an egg. A good quality egg releases hormone-like inhibin and estradiol (E). E2 gives negative feedback to lower the FSH level. High levels of FSH shows compromised egg quality. At the age of a female increases number of egg decreases, which results in low levels of E2. Low level of estradiol signals the pituitary to produce more FSH hormone to stimulate ovaries to produce a good follicle. When a female approaches menopause the baseline FSH level (day 3 of her cycle) will tend to increase gradually over the years and then it is called premature ovarian failure or primary ovarian insufficiency. Thus a high level of serum FSH on the early part of the menstrual cycle is a predictor of reproductive aging. FSH level >10IU/ml predicts poor response to various stimulations [45, 48]whereas FSH level >18IU/ml predicts poor pregnancy outcome [49]. In women age >35 years old, high FSH level strongly predicts poor IVF response and pregnancy rate [50]. Fetal aneuploidy is reported in elevated day three serum FSH [51]. Similarly, another article reported higher miscarriage rate with elevated serum FSH level [52]. In the presence of cyst elevated E2 level can be seen.

Table 2 An overview of the results obtained after studies included in this review.

R-ICSI (hrs. after retrieval)	Oocytes injected	Fert. rate (%)	P rate (%)	No. of embryos	Embryos transferred	P	Outcome	Ref.
>5	1831	68.38	37.8	1243	573	3		[13]
24	4	-	-	3	3	1	1 healthy child delivered at 38 weeks by cesarean section	[14]
22-23	87	68.7	*-	-	-	-	-	[15]
>6	683	-	-	471	75	27	17 singleton, 7 twins, 3 abortions	[16]
19-22	4824	45	-	1416	1321	67	47singleton, 6 twins, 1 triplet, 11 missed abortion, 1 ectopic, 1 late termination	[4]
>16-18	883	56.2	21.7	470	92	20	10 healthy babies delivered, 4 miscarriage, 1 termination d/t trisomy 21, 5 chemical pregnancy	[17]
4 to 6	522	63.1	-	-	110	27	7 abortions	[12]
24	127	69	-	-	20	5	1 healthy baby delivered, 4 ongoing pregnancies	[18]
6	184	90.2	30	140	68	6	4 ongoing pregnancies, 2 early miscarriage	[19]
20	7	-	-	3	1	1	1 singleton pregnancy	[20]
-	616	-	5.1	174	-	4	-	[21]
6	245	70.3	48	145	74	12	8singleton,3 twins,1 abortion	[22]
22	182	48.5	5	73	58	1	1 healthy baby delivered	[22]
>20	12	-	-	5	5	1	1 healthy baby delivered at 33 weeks by cesarean section	[23]
>18-20	779	30.4	0	-	100	0	no pregnancy	[24]
24	68	47.1	-	25	4	0	no pregnancy	[25]
48	25	40	-	9	2	0	no pregnancy	[25]
19-22	234	60.2	20.7	141	29	6	3 singleton, 1 twin, 1 missed abortion,1 ectopic pregnancy	[26]

*The empty cells show that this information was not mentioned. R-ICSI = rescue intracytoplasmic sperm injection; Fert. = fertilization; P = pregnancies.

Screening of the cyst should be done by ultrasound and blood test as in the presence of cyst high E2 level will suppress the FSH level, which will give the false normal appearance. E2 together with FSH helps to establish baseline ovarian response. In IVF cycles E2 level determines the risk of ovarian hyperstimulation syndrome (OHSS). Most clinicians agree on the risk of OHSS with a peak E2 level, E2 level <3000 pg/ml is a low risk [45]. A clomiphene citrate challenge test is used to check ovarian reserve. It is based on the theory that the highly responsive ovaries have a good ovarian response that will have low FSH level, even after giving the fertility medication; clomiphene citrate (Clomid or Serophene). It is done by comparing the level of FSH on cycle day 3 and day 10 following the administration of 100mg clomiphene citrate on cycle day 5-9. In a low ovarian response (low quality of eggs), the pituitary gland will secrete more FSH to improve the quality of eggs both in the basal state and even after giving clomiphene citrate. Female who fails this test usually need “donor egg IVF”. Antral follicle count (AFC) provides the best estimation of ovarian response. It is the best single tool in predicting low ovarian response [53-55]. Follicles <9mm in diameter are called antral follicles. They represent primordial follicles in the ovary that contain immature egg, which can develop and ovulate in the future. Antral follicles can easily be seen, counted and measured by non-invasive methods, i.e., trans vaginal ultrasound. There is a decline of AFC with increasing age of the female. AFC can be counted at any time of menstrual cycle and indicates ovarian reserve. It can predict the success of IVF treatment. AFC: <4 very poor ovarian reserves, 4-7 low count and high dosage of FSH is required during the infertility treatment, 8-12 slightly reduced reserve, and>12 normal. In women older than 44 years of age, AFC has been reported by several studies to be more accurate than basal FSH test in predicting IVF outcome [56]. Other hormones like antimullerian hormone (AMH) are secreted by granulose cells of preantral and antral follicles in the ovary. It can be measured any time in the menstrual cycle. The value of AMC <0.7 ng/ml indicates poor response in ovarian stimulation, but it cannot predict the pregnancy. Correlations between low AMH and menopause have been reported [57]. Another hormone inhibin-B also produced by preantral and early antral follicle is measured on day 3 of the menstrual cycle. With increasing age of female with

both inhibin-B and AMH level decreases. The lower level of inhibin-B can be used as a marker to predict low ovarian reserve [58]. Low level of inhibin-B on day 3 is associated with poor IVF outcome. Serum level <45pg/ml is correlated with poor response to gonadotropins. The level of progesterone is measured one week prior to the expected menses. Its value <3ng/ml indicates an ovulation. The level of luteinizing hormone (LH) is measured in mid-follicular phase. The level of LH varies with different studies. A meta-analysis showed no associated between low LH level with decreased pregnancy rate in IVF treatment [59].

Oocyte maturity

Oocytes are prepared for retrieval in IVF treatment by the administration of high dose of FHS and human chorionic gonadotropin. Mature oocytes are at metaphase II (MII) stage. However, there are also immature oocytes (MI). Approximately 15% of the oocytes obtained are at MI stage [60, 61]. Oocytes need to reach nuclear maturation and competence that include reorganization of the ribosome, mitochondria, and endoplasmic retinaculum as it is an essential requirement during early embryo development and calcium release [62, 63]. According to biological principles, generally, oocytes that are matured should only be used for ICSI and the ones that are not matured should be rejected. There have been reports of fertilization by both MI and MII oocytes. Two retrospective studies [64, 65] and one prospective study [66] used same culture medium for both rescued MI and MII oocytes showed low fertilization rate in rescued MI oocytes. Whereas, one retrospective study [67] and one randomized control study [68] showed no difference in fertilization rate, in both the reports fertilization rate was higher than 60%. An article reported 24 ICSI cycles with 36 MI oocytes mature to MII stage after *in vitro* culture for four hours. Fertilization rate was 37% and five embryos were transferred, but there was no clinical pregnancy [61]. An article reported the genetic quality of the embryo of rescue MI oocytes after various periods of time *in vitro* culture. In general, 80.6% of embryos obtained by MI oocytes had a chromosomal abnormality. When incubation was done for 24 hours, 100% aneuploidy rate was seen. As the time of incubation was reduced to 4-8 hours and 2 hours aneuploidy rate was 66.6% and 40%, respectively. Based on available reports, use of MII oocyte is preferred as the chance of chromosomal abnormality is high in using MI oocytes.

Oocytes morphology

Embryo quality and fertilization outcome can be predicted by oocyte morphology. Various reports of a relationship between oocyte morphology and embryo quality in IVF have been widely studied [69-71]. On the basis of six parameters, oocytes can be evaluated. (1) Oocytes morphology: dark color and ovoid shape show poor quality. Less dark and less ovoid shape is normal [72]. (2) Oocyte size: abnormal size is <120µ or>160µ. Normal size ranges between 130 to 150µ [73]. (3) Ooplasm: very granular or very vacuolated or the presence of several inclusions indicates poor ooplasm, good quality ooplasm has no granularity and inclusion [74-76]. (4) The structure of perivitelline space: large, absent or granular indicates poor quality. Normal size with no granules is good quality [77]. (5) Zonapellicida: very thin or thick is poor quality, between <18µ and >12µ is good quality [78]. (6) Polar body: good quality is normal size and shape. Poor quality is abnormally small or large, flat or/and multiple numbers and granular [79]. A prospective study based on these parameters on 94 patients with 594 mature oocytes concluded that higher oocyte scores result in good quality embryos that are more likely to achieve pregnancy [80].

Conclusions

Reviewing various articles, we can suggest the use of rescue ICSI to prevent fertilization failure after IVF. Even though the articles show pregnancy rate less than the fertilization rate in rescue ICSI, good quality embryos can be obtained from the oocytes that would have been discarded otherwise to give successful pregnancies. Various factors discussed in the review provide the prediction of the outcome of infertility treatment which also helps to assist the physician to plan rescue ICSI if needed.

Conflicts of interest

There are no conflicts of interest.

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