Rescue intracytoplasmic sperm injection: a systematic review

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Objective: To assess the feasibility, efficacy, and safety of rescue intracytoplasmic sperm injection (ICSI) in cases of fertilization failure, using a scientific literature search.
Design: Systematic review.
Setting: Centers for reproductive care.
Patient(s): Infertility patients with total or partial fertilization failure during an IVF cycle.
Intervention(s): An electronic literature search was performed in PubMed from 1992 through May 2013. The search was then expanded by using listed references from selected articles.
Main Outcome Measure(s): Pregnancy rate. The secondary outcome measures were fertilization rate, normal fertilization rate, cleavage rate, birth rate, and malformation rate.
Result(s): Thirty-eight studies including 1,863 patients were included. The pooled pregnancy rate was 14.4%; 194 babies were delivered.
Conclusion(s): Rescue ICSI can result in the delivery of a healthy newborn, although the pregnancy rates are low. The clinical evidence did not indicate an elevated rate of malformations, although the data are limited and incomplete. (Fertil Steril® 2014;101:690–8. ©2014 by American Society for Reproductive Medicine.)
Key Words: IVF, total fertilization failure, rescue ICSI

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Total fertilization failure (TFF) is frustrating to patients, adding further emotional strain and increased financial costs to an already stressful treatment. The incidence of TFF after IVF in the presence of normal sperm has been reported to be 4%–16% (1, 2). TFF leaves the medical team with limited alternatives. The first is to cancel the current treatment cycle and to offer intracytoplasmic sperm injection (ICSI) in the subsequent cycle. Since the likelihood of TFF recurrence in subsequent IVF cycles is approximately 30% (1), the use of micromanipulation techniques in a subsequent cycle is logical, although not evidenced based, and another cycle of conventional IVF might be offered as well (3). The second alternative is to attempt rescue ICSI in the present cycle. Rescue ICSI in cases of fertilization failure was first described 20 years ago (4); the frequency of its current use is unknown. The primary reasons for avoiding rescue ICSI is the concern for oocyte chromosomal abnormalities and low effectiveness. The purpose of this study is to review the available knowledge about the clinical applicability, effectiveness, and safety of rescue ICSI.

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MATERIALS AND METHODS

We used the Preferred Outcome Items for Systematic Reviews and Meta-analysis to report the results of this systematic review (5).

Search Strategy

We performed a systematic literature search in PubMed for relevant publications until May 31, 2013. We used the search term "rescue ICSI." We also used listed references from selected articles to expand the search.

Eligibility Criteria and Data Extraction

We included only articles that described cases of ICSI that were performed in the index cycle after fertilization failure was diagnosed. All the abstracts retrieved from the search were assessed (by R.B.-F.), and the full manuscripts of citations that met

eligibility criteria were obtained. The articles were evaluated and the data extracted. Data that appeared in more than one article were included once (excluding two articles, references 6 and 7).

Outcome Measures

The primary outcome of the review was the pregnancy rate. The secondary outcomes were fertilization rate, normal fertilization rate, cleavage rate, birth rate, and malformation rate.

RESULTS

Our search (last updated on May 31, 2013) retrieved 66 articles. Further evaluation resulted in the exclusion of 41 articles that did not meet the eligibility criteria. Subsequently, references of retrieved articles were screened, and 13 additional publications were included. Altogether, 38 studies were included in the analysis. The complete selection process is depicted in Figure 1.

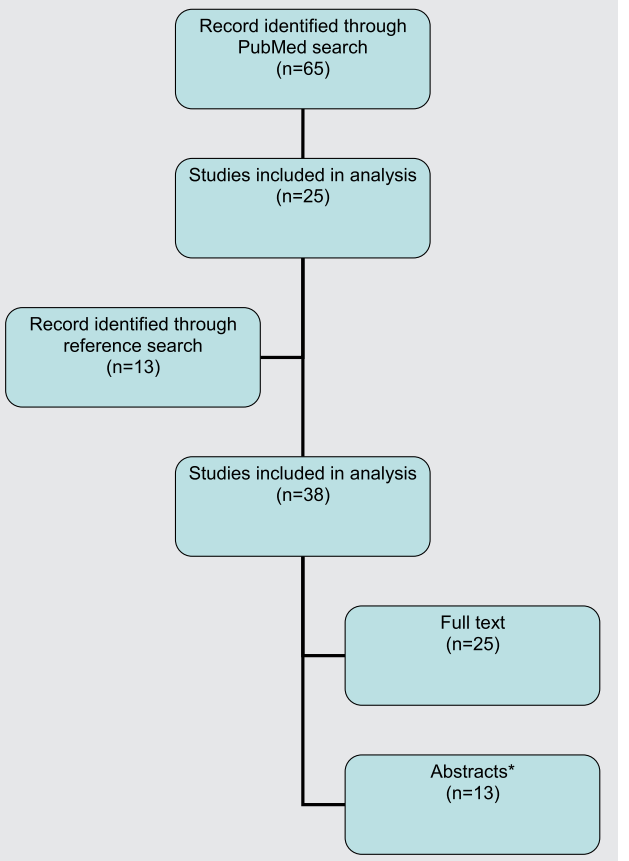
Description of Included Studies

Of the 38 studies, 25 are full-text articles and 13 are abstracts (seven from the scientific program of the annual American Society for Reproductive Medicine or European Society of Human Reproduction and Embryology conferences; five full texts in languages other than English; one full text unavailable). Owing to the paucity of published data, it was decided not to exclude the abstracts. Two studies are presented jointly since they report different data of the same population (8, 9). Ten studies are prospective, 23 are retrospective, and four are case reports. Nineteen articles describe cases of TFF; only three of them are prospective. The others include cases of low fertilization rates or do not precisely describe the study population. The characteristics of the studies included in the review are presented in Table 1.

The data describe 1,863 patients, more than 14,145 injected oocytes, 3,001 fresh embryos transferred, and 293 pregnancies. The pooled pregnancy rate is 14.4% per cycle and 17.8% per fresh ET. A total of 194 babies were delivered; of them, 102 were reported as healthy. Two pregnancies were terminated owing to fetal anomalies (trisomy 21 and an eye abnormality). Cytogenetic analysis of 42 embryos was done, but it was informative for only 16; of them, 10 were abnormal (among them haploid and tetraploid embryos, one trisomy 21 and one mosaic). TFF was described in 1,313 patients (one study contributed 40% of them [27]); 10,873 oocytes were injected, and 2,933 embryos were transferred in 1,136 fresh and 71 frozen-thawed transfers. A total of 248 pregnancies were reported, resulting in 177 live births or ongoing pregnancies. The pregnancy rate for cases of TFF was 15.6% per cycle and 17.2% per fresh ET.

Late rescue ICSI (about 24 hours after the ovum pick-up [OPU]) was carried out in 27 studies. Four studies described early rescue ICSI (about 8–10 hours after the OPU), and three compared the two. In cases of TFF, early rescue ICSI resulted in a pregnancy rate of 44%, as compared with 9.7% in late rescue ICSI (94/214 vs. 97/994). An overview of the included studies is presented in Table 2.

FIGURE 1



Seven abstracts of the scientific program of annual American Society for Reproductive Medicine or European Society of Human Reproduction and Embryology conferences; five full texts in foreign language; one full text not available.

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Owing to a lack of data and inconsistency in the reports, trustworthy calculations of birth and malformation rates are not possible.

DISCUSSION

TTF in assisted reproductive techniques (ART) is a frustrating experience for patients, with a heavy financial and emotional burden. The incidence of TFF after conventional IVF using apparently normal sperm has been reported to range from 5% to as high as 15%–20% (45). Recently, Ming et al. reported a 3.52% TFF rate in a large single-center study (27).

Fertilization is a complex process in which a single sperm nucleus is united with a pronucleus of an activated oocyte. Essential steps for successful fertilization include capacitation of the spermatozoon, binding of the spermatozoon to the zona pellucida, inducement of the acrosome reaction, penetration of the zona pellucida, fusion with the oolemma, completion of meiotic division with extrusion of the second polar body, metabolic activation of the oocyte, decondensation of the sperm nucleus and maternal chromosomes, and cytoplasmic migration of the pronuclei (46).