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Comparing fertilization rates from intracytoplasmic sperm injection to conventional in vitro fertilization among women of advanced age with non — male factor infertility: a meta-analysis

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Abstract

Objective: To evaluate the effectiveness of intracytoplasmic sperm injection (ICSI) in improving fertilization rates compared to conventional in vitro fertilization rates (IVF) among women aged ≥38 years with a non–male factor diagnosis.

Design: Systematic review and meta-analysis.

Setting: Not applicable.

Patient(s): Women aged ≥38 years with a non–male factor diagnosis receiving IVF or ICSI.

Intervention(s): A systematic review of databases including PubMed and Embase was performed. Study protocol was registered at the International Prospective Register of Systematic Reviews. Studies were selected if they compared fertilization rates from ICSI with those from conventional IVF among women aged ≥38 years with a non–male factor infertility diagnosis. A random effects model was used. Meta-analysis of Observational Studies in Epidemiology guidelines were applied.

Main Outcome Measure(s): Fertilization rate.

Results: Seven studies including 8796 retrieved oocytes (ICSI: 4,369; IVF: 4,427) with mean female age ≥38 years met the inclusion criteria. There was no significant difference in fertilization rates between ICSI and conventional IVF (relative risk [RR] 0.99, 95% confidence interval [CI] 0.93–1.06; P – .8). Heterogeneity was observed between studies (I^2 = 58.2; $P < .05$). Heterogeneity was significant (I^2 = 57.1; $P < .05$) when cycles with prior fertilization failure were

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excluded; however, when analysis was restricted to poor responders (RR 1.01, 95% CI 0.97–1.05; $P = .6$), heterogeneity was no longer significant ($I^2 = 0.0$; $P = .5$).

Conclusions: No difference was found in fertilization rates between conventional IVF and ICSI. Further studies are needed to assess the impact of ICSI in this population, controlling for other indications such as preimplantation genetic testing.

Abstract

Evaluar la efectividad de la microinyección espermática (ICSI) para mejorar las tasas de fecundación comparado con las tasas de fecundación in vitro (FIV) entre mujeres ≥ 38 años sin diagnóstico de factor masculino.

Revisión sistemática y metaanálisis.

No aplica.

Mujeres ≥ 38 años, sin diagnóstico de factor masculino que hayan recibido FIV o ICSI.

Se realizó una revisión sistemática de las bases de datos incluidas en PubMed y Embase. El protocolo de estudio fue registrado en el Registro Internacional Prospectivo de Revisiones Sistemáticas. Los estudios fueron seleccionados si se comparaban las tasas de fecundación de ICSI con la conseguida con FIV convencional en mujeres ≥ 38 años sin diagnóstico de factor masculino. Se utilizó un modelo de efectos aleatorios. Se aplicaron las pautas de meta análisis de estudios observacionales en epidemiología.

Tasa de fecundación.

Cumplieron con los criterios de inclusión 7 estudios con 8796 ovocitos (ICSI: 4,369; FIV: 4,427) con una edad media de la mujer de ≥ 38 años. No hubo diferencias significativas en la tasa de fecundación entre ICSI y el FIV convencional (riesgo relativo [RR] 0.99, 95% intervalo de confianza [CI] 0.93-1.06; P=.8). Se observó heterogeneidad entre estudios ($I^2 = 58.2$; $P < .05$). La heterogeneidad fue significativa ($I^2 = 57.1$; $P < .05$) cuando los ciclos con fallo de fecundación previo fueron excluidos; sin embargo, cuando el análisis fue restringido a baja respondedoras (RR 1.01, 95% CI 0.97-1.05; P=.6), la heterogeneidad ya no fue significativa ($I^2 = 0.0$; $P = .5$).

No se encontró diferencia en las tasas de fecundación entre FIV convencional e ICSI. Se necesitan más estudios para valorar el impacto del ICSI en esta población, controlando otras indicaciones como el test diagnóstico preimplantacional.

Keywords

Intracytoplasmic sperm injection; fertilization rates; non–male factor infertility; conventional IVF; advanced age

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Although the initial purpose of intracytoplasmic sperm injection (ICSI) was to treat patients with severe male factor infertility, in the past few decades the use of ICSI among patients with non–male factor infertility diagnoses has increased dramatically worldwide (1). Some clinics in the United States and other countries report using ICSI in all in vitro fertilization (IVF) cycles (2, 3). In the United States, overall ICSI use increased from 34% in 1996 to 76% in 2012 (4). The increase in use was greater in patients with non–male factor infertility than in those patients with a diagnosis of male factor infertility. Furthermore, among women aged ≥38 years with non–male factor infertility diagnosis, ICSI use increased from 16.0% to 69.7% in the United States (4).

Previous studies have found ICSI to be effective in improving fertilization rates or even embryo quality among patients with non–male factor infertility having other specific diagnoses such as unexplained infertility and polycystic ovarian syndrome (PCOS) (5-7). However, most have studies focused on younger women and found very few differences in overall clinical outcomes (5, 7).

The comparative benefits of ICSI over conventional IVF (i.e., standard insemination) are unclear among older women with a non–male factor infertility diagnosis. ICSI is recommended in cycles in which preimplantation genetic testing (PGT) is planned to reduce the risk of sperm DNA contamination (8); over the past 10 years, use of PGT, which may be more commonly performed among older women, has also increased, possibly contributing to some of the increase in ICSI (8, 9). ICSI is also recommended in cycles following prior total failed fertilization, as it may decrease the risk of subsequent fertilization failure (8). In a study using sibling oocytes, subsequent conventional insemination after total fertilization failure resulted in 11% oocytes fertilized by IVF/conventional insemination and 48% fertilized with IVF/ICSI (8, 10).

Although very few studies on ICSI use have focused on older women, some earlier studies have indicated that ICSI may be effective for improving fertilization in patients with low ovarian response (11-13). However, more recent studies have suggested that the benefits of ICSI are limited in this population (14). In 2012, the Practice Committee of the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology reported that ICSI may not be effective in improving fertilization rates in women of advanced maternal age (age >35 years), and that oocyte fertilization rates in women over 35 years of age using conventional insemination are similar to fertilization rates in younger women. However, this recommendation was based on the findings of one study with a mean female patient age of ≤38 years (mean age: 37.8 years [IVF] and 38.0 years [ICSI]) and with a high mean number of oocytes retrieved (mean number of oocytes retrieved: 9 [IVF] and 8 [ICSI]) (8). The Practice Committee also noted a lack of sufficient data to support the routine use of ICSI in non–male factor diagnosis patients, especially in women of advanced ages.

Moreover, ICSI is an invasive procedure that incurs additional costs, and the potential risks from ICSI in the absence of any clear advantage in improving live birth outcomes should be considered. Safety concerns associated with ICSI still persist, ranging from chromosomal abnormalities, birth defects, and developmental concerns in infants born from ICSI procedures, compared to infants conceived with conventional IVF (15). Understanding the relative effectiveness of ICSI compared with conventional IVF cycles can help providers and patients to make informed decisions about its use.

To date, no meta-analysis has summarized the effectiveness of ICSI among women aged ≥38 years with non–male factor infertility in improving fertilization. Older women (aged ≥

38 years) account for a substantial and increasing proportion of patients who seek assisted reproduction (~40% in the United States in 2016) (16). Few studies have focused on this age group (3). Older women are more likely to have fewer oocytes that may indicate the use of ICSI for improving the likelihood of fertilization. Older women are also more likely to undergo PGT, as it allows selection of a euploid embryo for transfer, which would increase the likelihood of pregnancy and minimize the risk of multiples.

The purpose of this study was to compare fertilization rates between ICSI and conventional IVF cycles among women aged ≥ 38 years with a non–male factor diagnosis.

MATERIALS AND METHODS

Search Strategy

A librarian-assisted search of Medline, Embase, Cochrane Database of Systematic Reviews, CINAHL, and ClinicalTrials databases was conducted from January 1988, when the first paper on ICSI was published (17), to December 2018. Medical subject headings related to the population, intervention, comparator, and outcomes (PICO) were used for the search. Additional key word search was also conducted on PubMed using key words such as ICSI, non–male factor, fertilization, advanced age. Search was restricted to English-only publications.

The terms in the search were (ovarian reserve* OR ovarian response OR ovarian responder* OR ovarian insufficiency OR ovarian function OR ovary syndrome OR ovarian failure OR low oocyte OR maternal age* OR (mother* ADJ2 age*) OR (women* ADJ2 age*) OR (woman* ADJ2 age*) OR (female* ADJ2 age*) OR (women ADJ2 old*) OR (woman ADJ2 old*) OR (female* ADJ2 old*) OR non–male factor* OR female factor* OR maternal factor*) AND intracytoplasmic sperm injections/OR (intracytoplasmic sperm injection* OR intra-cytoplasmic sperm injection* OR ICSI OR (sperm ADJ2 microinjection*) OR micro-insemination).ti,ab. NOT exp animal/ not exp human*/limit Exclude Medline Journals* ; limit English ; 1988.

Studies were selected based on the PICO framework developed a priori for the study protocol. Studies were included for the review if the participants were women aged ≥ 38 years with non–male factor infertility diagnosis. Any study that examined use of ICSI for a non–male factor diagnosis in this population was included in the review. The intervention was the use of IVF with ICSI for the treatment of non–male factor infertility. The comparator was conventional IVF treatment for patients with non–male factor infertility diagnosis. The main outcome was overall fertilization rate. The secondary outcomes were fertilization rates for metaphase II (MII) mature oocytes, poor responders, and for cycles with no prior fertilization failure.

Studies were included if fertilization rates (either per oocyte inseminated or injected or per oocyte retrieved) were reported for both conventional IVF and ICSI for women aged ≥38 years with non–male factor infertility diagnosis. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram shows the results of the search and the number of included and excluded studies (Figure 1). The reasons for excluding studies identified by the search from the meta-analysis were documented in the flow diagram.

Outcome Measure

In the included studies, fertilization rate was defined as the number of two pronuclei (2PN) zygotes observed divided by the number of oocytes injected or inseminated multiplied by 100. A few studies reported fertilization rate as the number of 2PN zygotes observed divided by the number of oocytes retrieved multiplied by 100.

Study Identification

Two authors (S.S., S.L.B.) independently screened the articles for inclusion and exclusion in the study. Discrepancies were resolved by discussion and mutual agreement and, if needed, by reaching a consensus with other authors (J.F.K. or D.M.K.).

Risk of Bias Assessment

Two authors (S.S., S.L.B.) independently assessed manuscript eligibility and quality using the National Institute of Health/National Heart, Lung, and Blood Institute (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools) criteria to determine whether the study had a high, moderate, or low risk of bias. These series of quality assessment tools were based on methods, concepts, and other tools developed by researchers in the Agency for Healthcare Research and Quality (AHRQ) Evidence-Based Practice Centers, the Cochrane Collaboration, the U.S. Preventive Service Task Force, the Scottish Intercollegiate Guidelines Network, and the National Health Service Centre for Reviews and Dissemination, as well as by consulting epidemiologists and others working in evidence-based medicine. Fourteen key questions are designed to help evaluate the internal validity of a study. In general terms, a "good"-quality study has the least risk of bias, and results are valid. A "fair"-quality study is susceptible to some bias deemed not sufficient to invalidate its results. A "poor"-quality rating indicates significant risk of bias.

Meta-analyses

Meta-analysis of Observational Studies in Epidemiology guidelines were followed for reporting the results of this review (18). Random effects models were used to calculate pooled relative risks (RR) and 95% confidence intervals (CI) for fertilization in cycles using ICSI vs. conventional IVF. Pooled RRs were estimated for all studies. Sensitivity analysis was conducted to assess whether underlying causes of heterogeneity could be eliminated by pooling results of studies reporting only mature oocytes (which have better chances of fertilization), or from pooling results of only poor responders in women with three or fewer oocytes retrieved (who have lower chances of fertilization) or by excluding studies with prior documented fertilization failure (which is considered an indication for ICSI). Heterogeneity was assessed with the use of the I^2 test. Comprehensive Meta-Analysis Software Version 3.0 was used for the analyses (19).

Data Extraction

The data were extracted from the text, tables, and graphs in the manuscripts (Table 1). The following data were reported: name of author, year of publication, period of study, study design, size of study, country, patient characteristics, female age (years), mean number of oocytes retrieved (conventional IVF), mean number of oocytes retrieved (ICSI), fertilization rate (conventional IVF), fertilization rate (ICSI), fertilization rates for MII mature oocytes, and quality rating.

Protocol Registration

The protocol of this review was registered at the International Prospective Register of Systematic Reviews website (PROS-PERO, http://www.crd.york.ac.uk/prospero/) on July 7, 2017. The registration number is CRD42017072725.

Ethical Approval

As this study was a systematic review and meta-analysis of aggregated published data, institutional review board approval was not required.

RESULTS

Study Selection

Database searches yielded 3077 citations with an additional five identified through a keyword search in PubMed. Six duplicate publications were excluded. The remaining 3076 citations were assessed for eligibility by screening titles and abstracts. The PRISMA flow chart of study selection is illustrated in Figure 1. Of the 3076 titles and abstracts screened, 3030 were excluded for not meeting the PICO criteria. A total of 45 full text articles and one abstract were further assessed for eligibility by full review of the papers. Of these, 39 studies were excluded after the full text review, of which 37 studies did not meet the PICO criteria and two studies were excluded because they did not report original data. In total, seven articles met the inclusion criteria (3, 14, 20–24); one of these was an abstract (21) (Figure 1).

Characteristics of the Included Studies

The studies were conducted at fertility centers in six countries: Canada, China (two), Greece, Israel, Italy, and the United States (Table 1). The period of study ranged from 2001 to 2016. All seven studies were cohort studies.

All sevem studies included male partners who had normal semen parameters according to the World Health Organization (WHO) criteria of sperm concentration, motility, and morphology (25, 26). In four studies, no statistical differences were found in any patient characteristics and patient diagnosis between the ICSI and conventional IVF group (20, 22–24). One study noted a significantly higher previous number of IVF cycles in the ICSI group (3); another study reported significantly higher primary infertility in the ICSI group (14); and one study examined the use of ICSI for poor-quality oocytes with zona pellucida abnormalities (21). Only one study reported the presence of two types of infertility diagnoses, unexplained infertility and PCOS, in both groups of patients, but found no significant difference in the prevalence (3). This study also excluded all PGT cycles. Two studies included cycles with prior fertilization failure (3, 20). However, one of these two studies excluded these cycles from the study population, as prior fertilization failure may be an indication for the use of ICSI (3).

The search yielded seven studies with female patients aged ≥38 years. Among the five studies reporting mean age, no difference in mean age was observed between patients using conventional IVF (41.3 years) and those using ICSI (41.4 years).

Six of the seven studies included patients characterized by poor ovarian response to ovarian stimulation with three or fewer oocytes available after retrieval. Of these, two focused only on women with a single oocyte retrieved (20, 23). Only one study included older women with a high number of oocytes retrieved (7.2 ± 5.5 in the conventional IVF group and 6.5 ± 5.7 in the ICSI group) (3). The ICSI group had more previous IVF cycles than the conventional IVF group in this study, suggesting that ICSI patients had more severe infertility compared to conventional IVF patients (3). This study also included a subanalysis of cycle outcomes in poor responders with three or fewer oocytes retrieved. Another study included total number of oocytes, both mature and immature, in the conventional IVF group, whereas the ICSI group included only MII phase oocytes (14).

Overall, the mean number of oocytes retrieved per cycle was 2.8 oocytes in patients receiving conventional IVF compared with 2.7 oocytes in patients receiving ICSI. No study reported significant difference in the mean number of oocytes retrieved between the conventional IVF and ICSI group. Five studies reported fertilization rates for MII mature oocytes.

Fertilization rates between conventional IVF and ICSI groups were not significantly different in six studies. Only one study, which included cycles with a high number of oocytes retrieved, reported significantly higher fertilization rate in the IVF group compared to the ICSI group (57% vs. 52%, $P<.05$); however, no difference in fertilization rate per MII mature oocytes was observed (64% vs. 67%, $P=.25$) (3). Furthermore, the subanalysis of this study, which restricted analysis to cycles with three or fewer MII mature oocytes, did not show any difference in fertilization rate between conventional IVF and ICSI (57% vs. 58%, $P=.91$) (3).

Risk of bias was low in four studies (rated as good quality) (3, 20, 22, 23), moderate in two studies (rated as fair quality) (14, 24), and high in one study (rated as poor quality) (21).

Results of Meta-analysis

All seven studies were included in the meta-analysis with a total of 8796 retrieved oocytes (ICSI: 4369; IVF: 4427). The pooled RR indicated no significant difference in fertilization rates between conventional IVF and ICSI (RR 0.99, 95% CI 0.93 – 1.06; $P=.8$) (Figure 2). Significant heterogeneity was observed between the studies ($I^2 = 58.2$; $P<.05$). Sensitivity analyses were performed to determine the underlying causes of heterogeneity. The study population was restricted to patients who were poor responders, defined as having three or fewer oocytes retrieved. All seven studies were included in this sensitivity analysis. The resulting pooled RR of an oocyte fertilizing after conventional IVF and ICSI remained similar (RR 1.01, 95% CI 0.97–1.05; P=.6), but heterogeneity was no longer significant (I^2 = 0.0; P=.5) (Figure 3).

Additional sensitivity analyses were conducting by restricting studies reporting fertilization rates for MII mature oocytes. Only five of the seven studies reported fertilization rates for MII mature oocytes. No significant difference in fertilization rates between ICSI and conventional IVF was observed when only mature oocytes were used (RR 1.08, 95% CI 0.97–1.20; P=.16); however, heterogeneity was still significant (I^2 = 79.6; P<.001) (Supplemental Figure 1). Analysis was then restricted to studies that did not include cycles with prior fertilization failure. Only one study was excluded (20). No significant difference in fertilization rates between ICSI and conventional IVF was observed (RR 0.98, 95% CI 0.92–1.05; P=.5); however, heterogeneity was still significant (I^2 = 57.1; P<.05) (Supplemental Figure 2).

DISCUSSION

This is the first meta-analysis to compare fertilization rates resulting from conventional IVF to those resulting from ICSI in patients aged ≥38 years with non–male factor infertility. Compared with conventional IVF, fertilization rates did not differ in ICSI cycles performed among women aged ≥38 years with non–male factor infertility diagnosis. Even when restricted to MII mature oocytes or poor responders having three or fewer oocytes retrieved, fertilization rates with conventional IVF were not significantly different from those with ICSI. When cycles with prior fertilization failure were removed from the analysis, fertilization rates did not significantly vary between the two procedures.

Although older women increasingly use assisted reproduction, few studies have focused on examining the safety and efficacy of various infertility treatment methods in this age group (3). When they do seek assisted reproduction, ICSI appears to be frequently used, even though few studies have tested its advantage over conventional IVF in improving fertilization rates (3). Because fewer and poorer-quality oocytes maybe retrieved in older women compared to younger women after ovarian stimulation, the increasing use of ICSI may reflect a belief that ICSI improves the chances of fertilization. ICSI use in older women may also reflect the increasing use of PGT to screen for aneuploidy among older women undergoing assisted reproductive technology (8, 9).

Because the primary goal of the studies included in this review was to compare fertilization rates from ICSI to conventional IVF for non–male factor indications, the studies were restricted to only patients with normal sperm parameters who were aged ≥38 years. None of the included studies reported PGT or any other non–male factor indications as a reason for using ICSI except one study that included cycles with prior fertilization failure (20). One study excluded PGT cycles from analysis (3). Although this study reported having patients with unexplained infertility and PCOS in both groups, was only used only in patients with normal sperm parameters and not for any other non–male factor indications (3). However, only one of the studies in the review included normal responders as indicated by mean number of oocytes retrieved (IVF: 7.2 ± 5.5; ICSI: 6.5 ± 5.7) and did not find any differences in fertilization rates between conventional IVF and ICSI (3).

Individually and collectively, the studies that met the selection criteria for the review suggested similar fertilization rates among conventional IVF and ICSI cycles. The results of these studies also suggested that a low number of oocytes retrieved may not be a good indication for the use of ICSI, even when mature oocytes were used for ICSI. In four of the five individual studies (3, 21, 23, 24) as well as in the meta-analysis, no differences in fertilization rates was observed when MII oocytes were used. Similar results have been reported in previous studies (5). One possible explanation could be oocyte degeneration during ICSI (27, 28). The single study in the review that reported significant higher fertilization rate in the ICSI group with MII oocytes suggested that this may be due to denominator differences in the IVF group, which included both mature and immature oocytes (14). One reason for its lack of effect is that ICSI was developed primarily to overcome male infertility with the specific goal of selecting a single sperm for fertilization, and therefore was less likely to be effective in cases of low oocyte yield or poor-quality oocytes. Therefore, more studies are needed to disentangle the true effects of ICSI on fertilization rates.

This meta-analysis has several limitations. The included studies focused primarily on women of advanced maternal age who were poor responders with a non–male factor diagnosis, but most studies did not identify other non–male factor indications in these women, such as planned PGT, prior fertilization failure with conventional insemination, unexplained infertility, or PCOS. Only one study excluded PGT cycles. These effects could not be assessed, but are important for disentangling the true benefits of ICSI compared with conventional IVF. In addition, only a few studies met the eligibility criteria for the review, suggesting a need for more studies to assess the effects of ICSI among older women who have no other indications for ICSI. The results of the meta-analysis should be robust, as they included a total of 8796 oocytes retrieved.

In addition, among the included studies, one was an abstract; in another study, the conventional IVF group included mature and immature oocytes, which could not be distinguished before fertilization, whereas the ICSI group included only MII phase oocytes. Another limitation concerns the quality of the published papers included in the meta-analyses. The search yielded only cohort studies ranging from poor to good quality and limited by a lack of randomization in selecting patients, and therefore likely to be prone to selection bias. In addition, very few studies provided justification for sample size and, in some cases, did not account for all potential confounders. Some heterogeneity between the studies included in the analyses was observed; this may be explained by the differences in the size of the studies or variations in techniques between clinics and countries in laboratory practices; therefore, the results of this review should be interpreted with caution. Heterogeneity was minimized when strict definition of poorest responders (three or fewer oocytes retrieved) was used. Nonetheless, no significant differences in patient characteristics (mean age, infertility diagnosis, and years of infertility) were observed in the individual studies between the conventional IVF and ICSI groups. Similar numbers of oocytes were retrieved in both groups in all studies, and criteria for normal sperm morphology were consistently applied across studies. Furthermore, some studies clearly stated that standard ICSI protocols were followed to reduce variability in ICSI procedures. Fertilization techniques were also similar, and standard laboratory protocols were used.

In conclusion, the evidence to support the use of ICSI to improve fertilization rates among those with non–male factor infertility in the absence of specific indications for ICSI is lacking. Given the added costs of performing ICSI, as well as possible negative associations among offspring resulting from ICSI, additional large randomized trials that control for indicated use may be useful to see if ICSI has any significant advantage over conventional IVF in improving fertilization rates in older women with non–male factor infertility diagnosis. This may inform patient education and clinical guidelines regarding the use of ICSI as it pertains to this population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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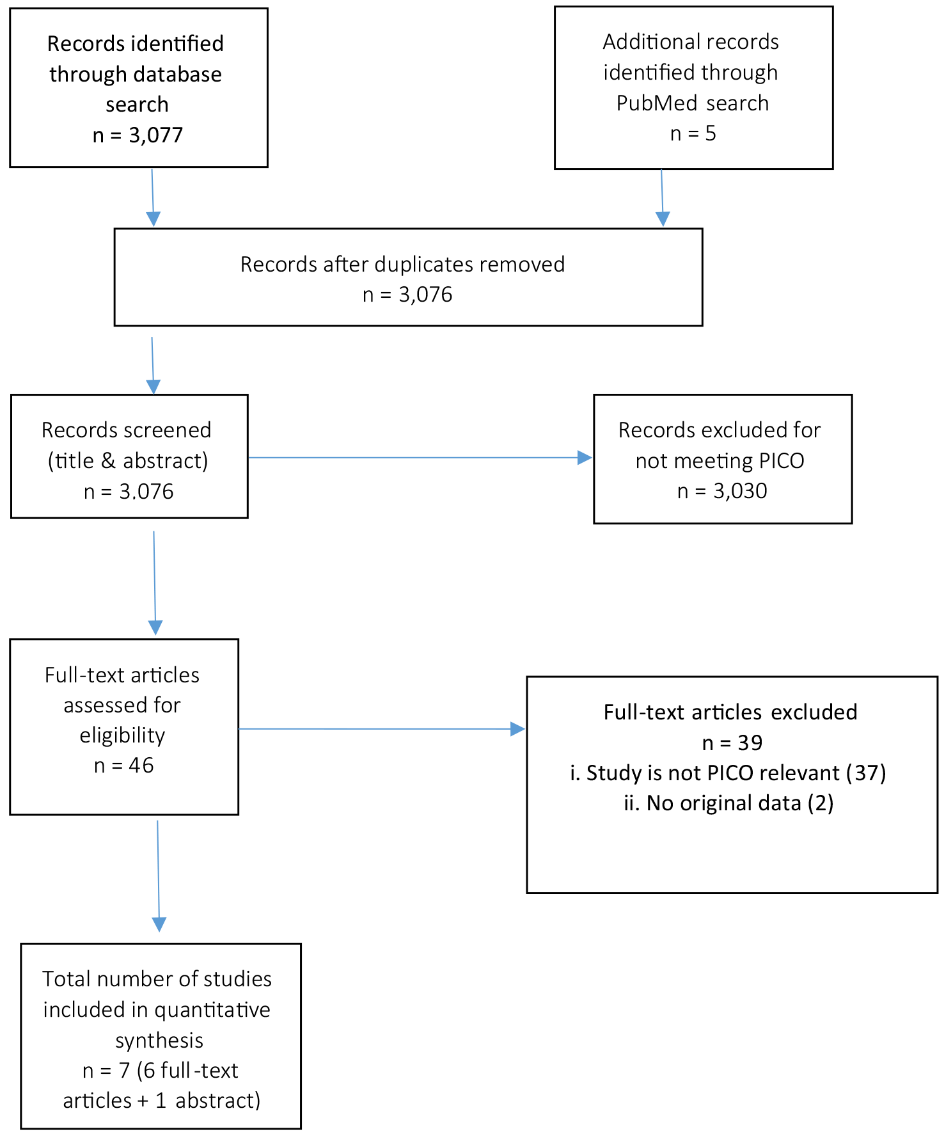

FIGURE 1.

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart of literature search.

Study name	Risk ratio	Lower limit	Upper limit	Fertilized/Total ICSI events	Fertilized/Total IVF events	Relative weight
Artini	0.939	0.834	1.058	119 / 161	144 / 183	15.29
Check	1.100	0.976	1.241	328 / 586	203 / 399	15.10
Gozlan	1.204	0.929	1.559	14 / 17	65 / 95	5.23
Liu	1.001	0.950	1.054	272 / 325	1451 / 1735	26.05
Sfontouris	1.010	0.791	1.290	33 / 50	66 / 101	5.75
Tannus	0.912	0.866	0.961	1656 / 3185	1047 / 1836	26.12
Xi	1.040	0.829	1.305	33 / 45	55 / 78	6.47
	0.994	0.931	1.060			

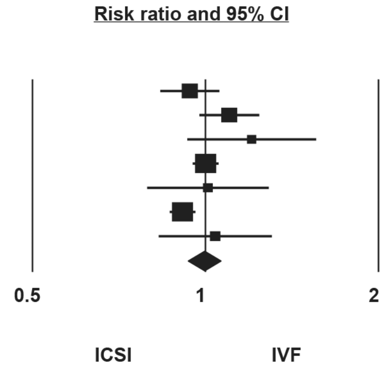

FIGURE 2.

Forest plot presenting risk ratios for fertilization with intracytoplasmic sperm injection (ICSI) compared to conventional in vitro fertilization (IVF) among women of advanced age with non–male factor infertility. Meta-analysis using random effects model. Q = 14.4, $P<.05$, $I^2 = 58.2$.

Study name	Risk ratio	Lower limit	Upper limit	Fertilized/Total: ICSI events	Fertilized/Total: IVF events	Relative weight
Artini	0.939	0.834	1.058	119 / 161	144 / 183	12.46
Check	1.100	0.976	1.241	328 / 586	203 / 399	12.16
Gozlan	1.204	0.929	1.559	14 / 17	65 / 95	2.62
Liu	1.001	0.950	1.054	272 / 325	1451 / 1735	64.22
Sfontouris	1.010	0.791	1.290	33 / 50	66 / 101	2.94
Tannus	1.016	0.766	1.349	167 / 287	23 / 41	2.19
Xi	1.040	0.829	1.305	33 / 45	55 / 78	3.40
	1.011	0.970	1.054			

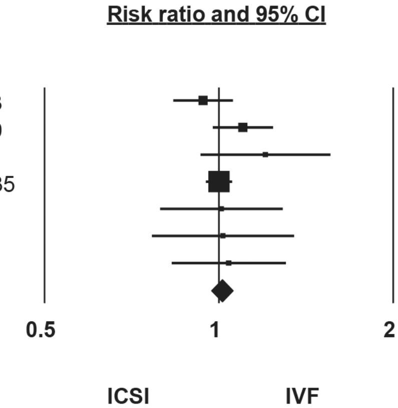

FIGURE 3.

Forest plot presenting risk ratios for fertilization with intracytoplasmic sperm injection (ICSI) compared to conventional in vitro fertilization (IVF) among women of advanced age with non–male factor infertility with three or fewer oocytes at retrieval. Meta-analysis using random effects model. Q = 5.3, P=.5, I^2 = 0.0.

TABLE 1

Characteristics of the seven included studies comparing fertilization rates achieved with ICSI to conventional IVF among women of advanced age with non–male factor infertility diagnosis

Author, year, period of study	Study design	Size of study (no. of oocytes inseminated or retrieved)	Country	Patient characteristics	Female age (y)	Mean no. of oocytes retrieved (conventional IVF)	Mean no. of oocytes retrieved (ICSI)[a]	Fertilization rate conventional IVF[b]	Fertilization rate ICSI[b,c]	Fertilization rates for metaphase II (MII) mature oocytes[d]	Quality rating[e]
Artini et al., 2013 January 2007 to July 2012	Retrospective cohort study	IVF: n = 183 ICSI: n = 161	Italy	Poor responders in which only 1 or 2 oocytes were retrieved	IVF: 41.4 ± 1.7 ICSI: 41.3 ± 1.3	1.58 ± 0.49	1.55 ± 0.49 (*P*=.65)	78.7	73.9 (*P*=.31)	Not reported	Good
Check et al., 2012[f]	Prospective cohort study	IVF: n = 399 ICSI: n = 586	USA	Poor responders with zona pellucida hardening	Mean age not reported. Age ≥45 y	3.1	3.1 (*P*=NS)	49.0	45.1 (*P*=NS)	56.1 (ICSI) 50.9 (IVF) (*P*=NS)	Poor
Gozlan et al., 2007, 2001 to 2005	Prospective cohort study	IVF: n = 95 ICSI: n = 17	Israel	Poor responders with single oocyte retrieved and prior fertilization failure	Mean age not reported. Age >39 y	1.0	1.0	68.4[h]	82.4[h] (*P*=.19)	Not reported	Good
Liu et al., 2018, June 2011 to May 2016	Retrospective cohort study	IVF: n = 1735 ICSI: n = 325	China	Poor responders with ≤5 oocytes retrieved, primary infertility significantly higher in ICSI vs. IVF group (*P*<.001)	IVF: 41.3 ± 1.1 ICSI: 41.3 ± 1.0	3.3 ± 1.35	3.4 ± 1.24 (*P*=.31)	83.6	83.7 (*P*=.98)	76.0 (ICSI) 62.0 (IVF)[g] (*P* <.001)	Fair
Sfontouris et al., 2015, May 2009 to December 2012	Retrospective cohort study	IVF: n = 101 ICSI: n = 50	Greece	Poor responders with single oocyte retrieved	IVF: 40.9 ± 0.7 ICSI: 41.0 ± 1.2	1.0	1.0	65.3[h]	66.0[h] (*P*=NS)	71.7 (ICSI) 81.5 (IVF) (*P*=NS)	Good
Tannus et al., 2017, January 2012 to June 2015	Retrospective cohort study	IVF: n = 1836 ICSI: n = 3185	Canada	The ICSI group had a significantly higher number of previous IVF cycles with failed fertilization (*P*<.001). These cycles were excluded from analysis; PGT cycles were excluded	IVF: 41.1 ± 0.9 ICSI: 41.2 ± 0.9	7.2 ± 5.5	6.5 ± 5.7 (*P*=.18)	57.0[h]	52.0[h] (*P*=.04)	-	Good
		IVF: n = 1556 ICSI: n = 2303		Sub- analysis with MII oocytes	—	6.1 ± 4.6	4.7 ± 3.5 (*P*<.0001)	—	—	67.0 (ICSI) 64.0 (IVF) (*P*=.25)	

Author, year, period of study	Study design	Size of study (no. of oocytes inseminated or retrieved)	Country	Patient characteristics	Female age (y)	Mean no. of oocytes retrieved (conventional IVF)	Mean no. of oocytes retrieved (ICSI)[a]	Fertilization rate conventional IVF[b]	Fertilization rate ICSI[b,c]	Fertilization rates for metaphase II (MII) mature oocytes[d]	Quality rating[e]
		IVF: n = 127 ICSI: n = 287		Sub- analysis of poor responders with ≤3 oocytes	—	1.8 ± 0.81	1.8 ± 0.74 (*P*=.90)	—	—	58.0 (ICSI) 57.0 (IVF) (*P*=.91)	
Xi et al., 2012, January 2009 to December 2010	Retrospective cohort study	IVF: n = 78 China ICSI: n = 45	China	Poor responder with ≤3 oocytes	IVF: 41.7 ± 1.8 ICSI: 42.4 ± 2.4	1.9 ± 0.86	2.1 ± 0.78 (*P*=NS)	59.8	68.8 (*P*=NS)	73.3 (ICSI) 70.5 (IVF) (*P*=NS)	Fair

Note: ICSI = intracytoplasmic sperm injection; IVF = in vitro fertilization; NS = not significant.

[a]When available, *P* values report test for significance between mean numbers of oocytes retrieved in conventional IVF group and the ICSI group.

[b][(Number of two pronuclei (2PN) observed)/(Number of oocytes injected or inseminated)*100].

[c]When available, *P* values report test for significance between fertilization rates using conventional IVF and ICS.

[d][(Number of 2PN observed)/(Number of mature oocytes injected or inseminated)*100].

[e]Quality rating derived from National Institute of Health/National Heart Lung and Blood Institute (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools) criteria.

[f]Abstract only available.

[g]Denominator of the IVF group includes total number of oocytes including mature and immature oocytes, which could not be distinguished before fertilization, whereas ICSI group has the number of only MII phase oocytes.

[h]Fertilization rate reported per oocyte retrieved.