Original Investigation

Conventional IVF at the age of fourties

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Gelecek IVF, Antalya, Türkiye

Abstract

Objective: Contrary to international guidelines, intracytoplasmic injection (ICSI) has increasingly been applied to a widening range of indications. The aim of this study is to present our experience with conventional in vitro fertilization (C-IVF) in women in their forties and to contribute to the ongoing debate on whether advanced maternal age should be considered an indication for preferring ICSI.

Material and Methods: We analyzed cases of non-male factor infertility in women aged ≥40 years. The primary outcome measures were fertilization rate, implantation rate, live birth rate, and miscarriage rate.

Results: The cohort included 204 patients with a mean age of 42.30±1.97 years, a mean antral follicle count of 4.65±2.60, body mass index of 25.80±4.54 kg/m^2 and a mean duration of infertility of 4.12±4.03 years. The mean duration of stimulation was 8.73±2.22 days, with a mean gonadotropin dose of 261.82±65.25 IU. The fertilisation rate was 74.69%. A mean of 1.77±0.60 embryos were transferred resulting in an implantation rate, clinical pregnancy rate and live birth rate of 10.44%, 18.62%, 12.25% respectively.

Conclusion: Fertilisation, implantation, live birth and miscarriage rates after C-IVF are satisfactory for women ≥40 years of age. Given its lower cost, ease of application and comparable clinical outcomes, C-IVF should be considered the preferred method of fertilisation in advanced-age patients. [J Turk Ger Gynecol Assoc.]

Keywords: IVF, ICSI, advanced reproductive age, implantation rate, clinical pregnancy rate, live birth rate

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Introduction

Although medical practice should ideally be grounded in evidence-based principles, it is undeniable that the field of medically assisted reproduction (MAR) has advanced in a predominantly technology-driven manner. When we look back at the nearly a half-century after the report of the first successful in vitro fertilization (IVF) delivery, we can recognize a list of adjunct treatments or interventions exemplifying this reality. Among these clinical, laboratory and complementary interventions, intracytoplasmic injection (ICSI) can be defined as an add-on procedure when performed in non-male factor infertility cases (1). There has been an ongoing debate for the last three decades about this widely used procedure for non-male infertility cases. Nevertheless, ICSI is the *de facto* routine insemination technique for all etiologic subgroups of infertility in many countries.

After its first introduction as a remedy in order to overcome severe male factor infertility in 1992, the use of ICSI has steadily increased, primarily to address fertilisation concerns, contributing to nearly 65% of all MAR cycles worldwide across different regions (2). Contradictory to the recommendations of the current practice guidelines of the international societies which recommend reserving ICSI for severe male factor infertility or couples with a history of total fertilisation failure (TFF) (3), the fear of fertilisation failure often drives both embryologists and clinicians to favor ICSI. As a result, ICSI has at times been portrayed as the “state of the art” in human

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reproduction (4) and has been misleadingly promoted for an ever-expanding range of indications, even in the absence of clear justification.

In one of our previous studies, we demonstrated that the lower cost, ease of application, and comparable laboratory and clinical outcomes make conventional-IVF (C-IVF) the preferred fertilisation method in non-male factor infertility cases (5). After this publication, we recently reported our data comparing ICSI and C-IVF in non-male factor patients with fewer than four oocytes. The data of this particular subgroup showed that in the presence of normal semen parameters, low oocyte number should not be considered an indication to perform ICSI (6). Following these publications, we extended our analysis to another challenging subgroup: women aged ≥40 years with non-male factor infertility. The aim of the present study was therefore to investigate if C-IVF yielded satisfactory clinical outcomes in women at the limit of the age spectrum and to contribute to the ongoing debate over whether advanced reproductive age *per se* can justify the use of ICSI.

Material and Methods

Study population

This retrospective study was conducted at a private assisted reproduction center, with protocol approval obtained from the Gelecek Center for Human Reproduction – Institutional Review Board (approval number: GTB 270622, date: 27.06.2022). After the standard work up of the couple at the initial visit to the clinic, detailed signed informed consent was routinely obtained prior to enrollment in the MAR program. Patient records from all couples undergoing MAR between January 2019 and March 2022 were thoroughly reviewed and cases of non-male factor infertility in women aged ≥40 years were analysed, irrespective of the number of collected cumulus oocyte complexes (COC). Exclusion criteria included a history of TFF in a previous MAR cycle, severe male factor infertility (defined as a total progressively motile sperm count with normal morphology <100,000), prenatal genetic testing (PGT) cycles, and couples undergoing cryopreservation of embryos for any indication. C-IVF was used as the insemination method in all cases (Figure1). Data of one cycle for each patient was included for analysis.

Controlled ovarion stimulation

Controlled ovarion stimulation (COS), pituitary suppression, fertilisation, embryo transfer, and pregnancy assessment were performed as previously described (5). Briefly, after exclusion of any ovarian cyst and endometrial lesion with a baseline ultrasound scan within the first three days of the menstrual cycle, COS with human menopausal gonadotropin (hMG, Menopur®, Ferring, Denmark) was commenced with

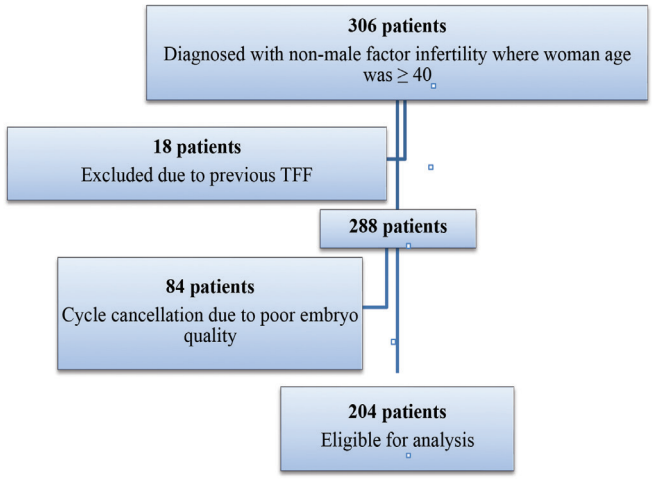

Figure 1. Flowchart showing enrollment and exclusion of the patients
TFF: Total fertilisation failure

a fixed dose of 225 IU/day, irrespective of ovarian reserve. For documentation purposes, ovarian reserve was routinely assessed on cycle day 2 or 3 of the preceding menstrual cycle using antral follicle count. Serum anti-Müllerian hormone levels were assessed in selected cases, depending on clinician preference and insurance coverage. Daily gonadotropin releasing hormone antagonist (Cetrotide® 0,25mg, Merck/Germany) injections were started using flexible protocol once the leading follicle reached 14mm. Final oocyte maturation was triggered with 250 µg recombinant human chorionic gonadotropin (hCG, Ovitrelle®, Merck, Germany) injection when the leading follicle(s) measured ≥17 mm. Ultrasound-guided oocyte pick-up (OPU) was performed under sedation anesthesia 36 hours after hCG administration, using a single-lumen 17-gauge needle.

Fertilisation, embryo transfer and pregnancy assessment

The density gradient technique has been used as the standard method for semen preparation in our clinic. Eligibility to be enrolled in C-IVF was based on our clinical cut-off for semen quality (namely "C-IVF index" defined as total progressively motile sperm count with normal morphology ≥100,000) as previously described (6). C-IVF was used as the method of insemination in all cases achieving this threshold and ICSI was reserved only for the patients with a history of prior TFF or for couples with an index <100,000.

In the C-IVF procedure, up to three COCs were placed in each well of a four-well dish with Fertilisation Medium® (Cook, Australia) and inseminated with sperm suspension containing 100,000/mL motile spermatozoa per/COC. Maturation status of the oocytes and fertilisation, i.e. existence of two pronuclei were checked after stripping the inseminated COCs from the cumulus cells 18-20 hours after insemination.

At the cleavage stage, embryos were graded from 1 to 4 based on morphological criteria, including blastomere number, degree of fragmentation, and cell symmetry. Grade I and II embryos were deemed suitable for either transfer or cryopreservation. Single or dual cleavage-stage embryo transfers were performed on day 3 post-OPU, depending on availability.

Luteal phase support was initiated the day after OPU with daily intramuscular injections of 50 mg progesterone (Progestan 50 mg®, Koçak Farma, Türkiye). Following embryo transfer, administration was switched to the vaginal route using 200 mg progesterone capsules three times daily (Progestan 200 mg®, Koçak Farma, Türkiye) and continued until either a negative β-hCG test or the eighth week of pregnancy. The route of progesterone administration was based on convenience; using injectable preparation up to the embryo transfer ensures a clean intervention site, while switching to the vaginal form thereafter is both patient-friendly and cost-effective. The daily doses for both intramuscular and vaginal formulations were determined in accordance with the ESHRE Ovarian Stimulation Guideline.

Fertilisation rate, implantation rate, live birth rate (LBR) and miscarriage rate were the main outcome parameters.

Statistical analysis

Continuous variables are reported as mean ± standard deviation or median (quartiles), and compared between the groups with Independent Sample t-test (if the data size was sufficient in each group) or Mann-Whitney U test (if the data size was insufficient or the data was non-normally distributed in each group) based on distribution characteristics. Categorical variables are reported as numbers and percentages and compared with chi square test or derivatives, as appropriate. A two-sided $p<0.05$ was considered significant.

Results

A total of 306 cases diagnosed with non-male factor infertility where the woman's age was ≥40 years were analyzed. After excluding eighteen (5.88%) cases with a history of TFF and eighty-four cycles cancelled due to fertilisation failure or poor embryo quality, a total of 204 cases were deemed eligible for the final analysis.

Mean age of the patients was 42.30±1.97 years, mean duration of infertility was 4.12±4.03 years and mean antral follicle count was 4.65±2.60. Ninety-three (45.68%) patients had a history of previous pregnancy. Baseline characteristics of the cohort are depicted in Table 1.

Etiological reasons for infertility (Table 2) and stimulation characteristics (Table 3) are also tabulated below respectively. The mean fertilisation rate per collected COC was 74.69%. The implantation rate, LBR and miscarriage rate were 10.44%, 12.25% and 47.16% respectively (Table 4).

Table 1. Baseline characteristics of the research cohort

	C-IVF
No of patients	204
Patients' age (years)	42.30±1.97
Husbands' age (years)	42.06±6.52
Duration of infertility	4.12±4.03
Primary infertility (%)	119 (58.30%)
History of pregnancy	93 (45.68%)
Patients with previous IVF cycles	68 (33.33%)
BMI (kg/m²)	25.80±4.54
AFC	4.65±2.60

BMI: Body mass index, AFC: Antral follicle count, C-IVF: Conventional in vitro fertilization

Table 2. Etiological reasons for infertility

	C-IVF
Tubal factor	34
Ovulatory factor	107
Endometriozis	4
Unexplained	9
Male factor	12
Combined	38

C-IVF: Conventional in vitro fertilization

Table 3. Stimulation characteristics

	C-IVF
Length of stimulation	8.73±2.22
Gonadotropin units	261.82±65.25
D3 FSH	9.66±5.77
D3 LH	6.20±3.15
Peak E_2	978.47±771.44

FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, E_2: Estradiol, C-IVF: Conventional in vitro fertilization

Table 4. Laboratory and clinical outcome parameters

	C-IVF
COC#	960
Fertilisation rate/COC retrieved	74.69%
Fertilisation failure	18 (5.88%)
Cancelled cycles	84
#Embryos transferred	1.77±0.60
#Embryos frozen	18 (8.82%)
Implantation rate	10.44%
Pregnancy rate	53 (25.98%)
Clinical pregnancy	38 (18.62%)
Live birth rate	25 (12.25%)
Miscarriage rate	25 (47.16%)

#: Number sign, COC: Cumulus oocyte complex, C-IVF: Conventional in vitro fertilization

Even small time intervals can lead to a sharp decline in oocyte quality and reproductive potential in women in their forties so we further analyzed outcomes by each year of age (Table 5).

Discussion

Our results demonstrate that C-IVF provided a clinically acceptable fertilization rate, implantation rate and clinical outcome in fresh embryo transfer cycles for patients enrolling in MAR in their forties. The rationale for not including frozen embryo replacement cycles was to avoid the confounding effect of the freezing/thawing process.

Analysis of the MAR timeline shows that since the first successful delivery via C-IVF nearly fifty years ago, numerous adjunct procedures, spanning clinical, laboratory, and complementary treatments, have been introduced in efforts to improve treatment protocols and optimize fertilisation rates, embryo quality, and implantation rates. Amongst this pool of adjunct therapies and treatments, ICSI is worth being highlighted as the only prominent one so far to have been proven to contribute to the clinical outcome, albeit in male factor infertility only (1,7). Indeed, well designed randomized prospective studies and guidelines of international IVF societies have long suggested that with non-male factor infertility, C-IVF is associated with better fertilisation and implantation rates and similar LBRs when compared to ICSI (3). Hence, ICSI should actually be the insemination technique only in severe male factor infertility or reserved for patients with a history of TFF. However, during the following thirty years after the first introduction of ICSI, its use has steadily increased globally for all infertility etiologies, even accounting for 98% of all MAR cycles in certain geographical regions (8).

This increase in ICSI use may initially be attributed to some early studies claiming higher fertilisation and better clinical outcome via ICSI. Although the following well designed studies clearly showed the advantages of C-IVF over ICSI, recently factors such as patient and media-driven social pressure along with competitive dynamics within the IVF sector, have also contributed to this trend. In his article criticising liberal use of ICSI, with an analytic approach, Hans Evers ironically described IVF practitioners as Santa Claus in the fertility clinic and drew attention to the concept of therapeutic illusion, suggesting that in many cases the women who conceived with ICSI actually would also do so with C-IVF (8).

Despite the existence of robust and convincing data in favor of C-IVF, practitioners often hesitate to proceed to C-IVF in non-male factor cases for two basic reasons, both related to fertilisation. The first is the misconception that ICSI provides higher fertilisation rates, and the second and more significant concern, in our opinion, is the fear of TFF. It is therefore prudent to address these two issues separately and analyze them individually.

Fertilisation rate

When fertilisation rates are compared per inseminated oocyte, ICSI appears to yield higher rates, as expected, since immature oocytes are excluded during the denudation process. However, when assessed per collected COC, which is a more meaningful index reflecting the total number of embryos obtained, fertilisation rates are reported to be similar or even higher with C-IVF (9).

This critical point underlies the misconception that ICSI yields superior fertilisation rates (Figure 2). In fact, higher fertilisation per collected COC observed with C-IVF is quite understandable since immaturely harvested oocytes may have the chance of continuing their final maturation process in *in vitro* conditions during co-insemination with sperm suspension with their cumulus cells intact. Indeed cumulus cells are essential for supporting the growth of the oocyte, providing it with essential nutrients, hormones, and other factors crucial for proper development, maturation, fertilization, and subsequent embryonic growth.

In other words, it could be claimed that ICSI may have a detrimental effect on cycle outcomes by excluding immature oocytes from the cohort at the outset, rather than allowing them to undergo further maturation and potentially achieve fertilization in the subsequent hours. Since ICSI is an invasive procedure, another theoretical reason for better fertilisation via C-IVF is the potential degeneration of the oocytes resulting

Table 5. Clinical outcomes by maternal age increment

Age	Number of patients	+ hCG	Gestational sac	Fetal heart beat	Live birth
40	52	16 (30.8%)	14 (26.9%)	13 (25.0%)	13 (25.0%)
41	34	9 (26.5%)	4 (11.8%)	3 (8.8%)	3 (8.8%)
42	31	11 (35.5%)	8 (25.8%)	5 (16.1%)	5 (16.1%)
43	31	7 (22.6%)	4 (12.9%)	1 (3.2%)	0 (0.00%)
44	24	3 (12.5%)	2 (8.3%)	2 (8.3%)	2 (8.3%)
45	18	5 (27.8%)	2 (11.1%)	1 (5.6%)	1 (5.6%)
46	14	2 (14.3%)	2 (14.3%)	1 (7.1%)	1 (7.1%)

hCG: Human chorionic gonadotropin

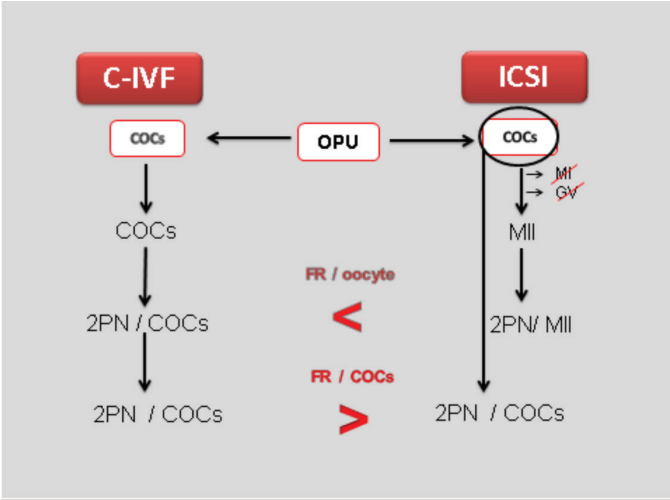

Figure 2. Fertilisation paradigm while comparing ICSI vs. C-IVF. Fertilisation rate per inseminated oocyte is better via ICSI while fertilisation rate per collected COC is better for C-IVF

COC: Cumulus oocyte complex, MI: metaphase I, MII: metaphase II, GV: Germinal vesicle, OPU: Oocyte pick-up, FR: Fertilisation rate, C-IVF: Conventional in vitro fertilization, ICSI: Intracytoplasmic injection

from mechanical damage during the denudation or ICSI procedure, which is reported to occur in 5–19% of injected oocytes. Mechanical and enzymatic removal of cumulus cells is not always simple and benign in removing all cumulus cells before ICSI, while mechanical pipetting of COCs 18-20 hours after insemination allows a faster, easier and less invasive removal of all cumulus cells.

We believe that the assumption of superior fertilisation with ICSI is more fiction than fact; the notion that "ICSI results in better fertilisation compared to C-IVF" represents a therapeutic illusion, in our opinion, in line with the suggestion of Evers. Despite the advanced age of the patients included in the present study, the fertilisation rate of nearly 75% is considered satisfactory, exceeding the 70% threshold recommended by laboratory practice guidelines.

Total fertilisation failure

Concern of encountering TFF after C-IVF is the main source of hesitancy for the practitioners preferring ICSI in cases with normal or borderline semen parameters. In fact, it is well known that ICSI does not completely exclude TFF and the literature clearly reveals similar rates of TFF with either technique (8,10). The rate of TFF observed in our advanced-age group (5.88%) was within acceptable limits and comparable to the expected TFF rates for both ICSI and C-IVF reported in international guidelines.

Beyond the misconception that ICSI yields higher fertilisation rates and the fear of TFF with C-IVF, another major reason, and perhaps the most important at present, that embryologists routinely prefer ICSI is that the young embryologists entering the field of MAR recently do not have the chance to observe or gain hands-on experience with C-IVF, resulting in limited practical knowledge of the technique. This is a growing problem which may cause the IVF team to miss a useful, time-saving, easy-to-learn and cost effective technique just because of lack of senior trainers.

Although the learning curve for C-IVF is steeper and faster than that of ICSI, there are key aspects that first-time learners must observe and practice through hands-on training, such as timing of insemination or fertilisation check, preparing the sperm suspension and calculating its volume per COC, performing rescue ICSI if the needs arise and simple manipulations at certain steps of the procedure. To support young embryologists in the field, we have prepared a freely accessible online video, "How to Do C-IVF: A Step-by-Step Guide," demonstrating each stage of the procedure in a clear and comprehensive manner (11).

Given that much of the IVF community in certain countries lacks fundamental knowledge of C-IVF, opportunities to discuss and refine the technique have been lost, including the careful selection of suitable cases, the optimal preparation of sperm suspension, and the application of alternative maneuvers (such as rescue ICSI). Focusing on the more natural and more efficient insemination technique of C-IVF should be the rationale approach instead of the fictitious belief of lower fertilisation rates or fear of TFF.

In our clinical protocol, we apply a defined metric, the "C-IVF index", both to characterize male factor infertility and to ensure the uniform use of ICSI within this group. This mathematical approach to the triage of patients for either insemination technique (ICSI or C-IVF) is helpful to the practitioners deciding the method of insemination without hesitation and also provides a standardization between practitioners. Such an index may also facilitate more meaningful comparisons between clinical and laboratory studies. To the best of our knowledge, ours is the only semen-based numerical index in the literature including all semen parameters and specifically designed to identify patients eligible for C-IVF (12).

Recently, we have published the results of a randomized controlled study comparing the laboratory and clinical outcome of ICSI with those of C-IVF in non-male factor cases (5) followed by a retrospective study comparing both techniques for patients with poor ovarian response (6) in order to clarify if lower number of oocytes would be a determinant while choosing

the insemination method. Since we found similar outcome for both C-IVF and ICSI in these two studies, we decided to further analyse our clinical data for the challenging subgroup of patiens with woman age ≥40 years to clarify if advanced age *per se* is a drawback for proceeding to C-IVF.

Demographic studies show that there is a tendency towards postponement of parenthood to late thirties and forties due to the gradual change in priorities and social life of couples in the modern era (13). Women with advanced reproductive age constitute a special group in MAR generally, with limited number of oocytes possibly with lower quality compared with the general infertility population. This raises an important question: can advanced reproductive age be considered a valid justification for preferring ICSI as the insemination method? There are a scarce number of studies in the literature directly comparing the two techniques in advanced age patients.

The first study to assess the effect of ICSI in this particular subgroup of patients was a retrospective analysis including 745 women aged 40–43 years. When C-IVF was compared with ICSI, the fertilisation rates (64% vs. 67%), fertilisation failure rates (9.0% vs. 9.7%), and LBRs (11.9% vs. 9.6%) were all comparable between the groups. Even subgroup analyses of women undergoing their first IVF cycle and women with ≤3 oocytes did not show an advantage with ICSI (13). Although this study demonstrated promising outcomes, our laboratory and clinical outcome data appear even more encouraging, considering that the patients in our cohort represent an older age population.

In another retrospective study comparing C-IVF with ICSI in 685 women aged ≥40 years with unexplained infertility, cumulative LBRs including transfers of both fresh and frozen embryo transfers were compared, with no differences observed in either cumulative live birth or abortion rates. The mean age in both groups was 41±0.8 years. Overall fertilisation rates were higher with C-IVF, while TFF tended to be more frequent in the ICSI group (6.7% vs. 9.4%) (10).

A meta-analysis evaluated the effectiveness of ICSI in improving fertilisation rates compared to C-IVF among women aged ≥38 years with a non-male factor diagnosis. A total of seven studies were included and no difference was found in fertilisation rates (14). Haas et al. (15) reported the first prospective randomized trial comparing both insemination techniques in 60 advanced age women by randomizing the ovaries of each patient prior to COS. C-IVF tended to result in a higher fertilization rate while TFF was encountered in one case from each arm (15). Taken together, all these studies support the efficiency of C-IVF with respect to both fertilization rates and subsequent clinical outcomes.

Compared with existing publications on C-IVF in advanced reproductive age, our study presents several unique findings: first, the fertilization rate per collected COC was satisfactory (74.96%); second, the rate of fertilisation failure was only slightly lower than 6%, which is acceptable given the age of the cohort; and finally, we achieved live births in women up to age 46 years, a rare and encouraging outcome. Compared to the LBR of nearly 6.5% reported by Gennarelli et al. (10), the LBR of nearly 10% of whole cohort in our study is encouraging. In our previous study, we conducted detailed comparative analyses of cost and time for both insemination techniques, demonstrating significant additional advantages of C-IVF in these respects (5). In addition to male factor infertility, there may be some relative indications for ICSI, including having a history of TFF in a previous C-IVF attempt or PGT cycles, but even these may not be strict indications.

In their well designed prospective study, De Munck et al. (16) compared the developmental competence and ploidy status in non-male factor patients undergoing PGT for aneuploidies (PGT-A) following C-IVF and ICSI on sibling oocytes and showed that ICSI is not superior to C-IVF in this regard. Hence, in cases of non-male factor infertility undergoing PGT-A, there is no strict indication to perform ICSI.

Poor oocyte quality in advanced-age women has been arbitrarily proposed as an indication for ICSI, theoretically to assist spermatozoa in bypassing some of the natural barriers. We propose the opposite analytical perspective: given that poor-quality COCs are likely more fragile, subjecting them to mechanical trauma from denudation, needle insertion, and prolonged handling outside the incubator may be detrimental. Instead, it is prudent to inseminate them via C-IVF which offers a simpler, less time-consuming approach that also avoids mechanical stress. This perspective forms the cornerstone of our strategy in managing the treatment process of infertile women of advanced age.

The present study contributes to the limited body of literature on MAR outcomes in women in their forties. By providing data on the efficacy of C-IVF from a country located in a region where ICSI is performed at an exceptionally high, and almost routine, rate (17), this study may encourage practitioners in the region to reconsider and potentially revise their standard insemination practices. Another strength of the present study is the use of a defined numerical index to characterize male factor infertility, along with the consistent application of C-IVF above a specified threshold.

Study limitations

Certain limitations, such as the retrospective design and relatively small sample size, warrant cautious interpretation of the present findings. Since C-IVF has been the default insemination method in our clinical practice for non-male factor cases for more than a decade, establishing a control group was not possible in this retrospective study. Comparison with an age-matched male factor infertility group from the same period would be inappropriate, as the adverse effects of poor sperm quality could introduce additional confounding factors.

Building on the encouraging findings of the present analysis, our next step will be to conduct a randomized study including an age-matched non-male factor infertility group undergoing ICSI as the control arm.

Conclusion

The findings of this study suggest that advanced maternal age alone should not be considered a sufficient indication for preferring ICSI over C-IVF, as C-IVF achieves satisfactory fertilization, implantation, clinical pregnancy, and miscarriage rates. Moreover, C-IVF offers advantages in terms of cost-effectiveness and time efficiency, while avoiding the potential long-term risks associated with the artificial selection of spermatozoa. Although the limited number of randomized trials makes it challenging to establish definitive conclusions regarding the superiority of either insemination method, it appears prudent to reserve ICSI primarily for cases of severe male factor infertility, in our opinion and experience.

Ethics

Ethics Committee Approval: *This retrospective study was conducted at a private assisted reproduction center, with protocol approval obtained from the Gelecek Center for Human Reproduction – Institutional Review Board (approval number: GTB 270622, date: 27.06.2022).*

Informed Consent: *After the standard work up of the couple at the initial visit to the clinic, detailed signed informed consent was routinely obtained prior to enrollment in the MAR program.*

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Footnotes

Author Contributions: *Surgical and Medical Practices: M.I., A.A., A.K.Ç., B.A., Concept: M.I., Design: M.I., Data Collection or Processing: M.I., A.A., Analysis or Interpretation: M.I., A.A., Literature Search: M.I., Writing: M.I.*

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