JOURNAL OF TAZEEZ FOR PUBLIC HEALTH
AN OFFICIAL JOURNAL OF SAUDI HEALTH PROMOTION AND EDUCATION ASSOCIATION
Vol3; Issue2, April 2026

Original study

Women's Age as a Determinant of Pregnancy Outcomes in ICSI Treatment: A Retrospective Cohort Study

Lama Alshwairikh[1], Nora Alrazeyg[2], Tariq Wani[3], Dania Al-Jaroudi[3]

1. Reproductive Endocrine and infertility Medicine Department, King Fahad Medical City, Riyadh Second Health Cluster, Saudi Arabia
2. Obstetrics and Gyn ecology Department, King Fahad Medical City, Riyadh Second Health Cluster, Saudi Arabia
3. Research center, King Fahad Medical City, Riyadh Second Health Cluster, Saudi Arabia

ABSTRACT

Background: Female age is a major determinant of assisted reproductive technology outcomes, and data on intracytoplasmic sperm injection (ICSI) outcomes in women aged 40 years and older is limited. This study evaluated the association between maternal age and reproductive outcomes after IVF/ICSI. **Methods:** A retrospective cohort study was conducted at the Reproductive Endocrine and Infertility Medicine Department, King Fahad Medical City, Riyadh, Saudi Arabia, including IVF/ICSI cycles performed between January 2022 and December 2024. Women were grouped as ≤34 years, 35–39 years, and >39 years, with additional analysis using ≤35 and >35 years. Demographic, clinical, stimulation, embryological, and reproductive outcome data were analyzed. **Results:** A total of 2,507 cycles were included; 1,280 (51.1%) were in women aged ≤34 years, 741 (29.6%) in women aged 35–39 years, and 486 (19.4%) in women aged >39 years. Embryo transfer rates declined significantly with age (77.9%, 75.6%, and 60.3%, respectively; p<0.001). Older women had lower baseline antral follicle count, higher baseline FSH, required higher gonadotropin doses, and had fewer retrieved oocytes, mature oocytes, fertilized oocytes, and cleaved embryos (all p<0.001). Clinical pregnancy rates decreased from 28.0% to 21.3% and 14.3%, while miscarriage increased and live birth significantly decreased with age (p<0.001). **Conclusion:** Advancing maternal age was associated with reduced ovarian response and poorer reproductive outcomes after IVF/ICSI, among women older than 39 years.

Keywords: Advanced Maternal Age; Intracytoplasmic Sperm Injection; In Vitro Fertilization; Assisted Reproductive Technology; Clinical Pregnancy; Live Birth; Miscarriage

Published: April 23, 2026

https://doi.org/10.65759/wveyyz75

Introduction

Infertility is considered to be a global issue, according to a new report published by the World Health Organization (WHO), approximately 17.5% of the adult population – roughly 1 in 6 worldwide – experience infertility at least once during their reproductive lifetime [1]. Assisted reproductive technologies were developed to treat infertility and Intracytoplasmic sperm injection (ICSI) has emerged as a cornerstone of assisted reproductive technology (ART), offering a viable solution for couples facing infertility [2,3]. While ICSI has significantly improved fertilization rates, overall pregnancy and live birth rates, it remains influenced by a range of patient and treatment-related factors. Among these, female age is consistently identified as a critical determinant of reproductive outcomes [1].

Ovarian aging typically initiates around the age of 30 years and continues until the age of menopause [2]. The main causes of age-related infertility and lower IVF/ICSI success rates in aged females include declining ovarian reserve, diminished mitochondrial function, and a higher rate of aneuploidy, which contribute to incompetencies of the oocytes and/or embryos [3]. Studies found an inverse relationship between female age and pregnancy rate [4]. Additionally, advanced maternal age is associated with not only lower fertility potential, but also with a higher risk of adverse perinatal and obstetric outcomes [5].

Advanced maternal age is considered as female aged over 35 years experiencing pregnancy [1]. Both embryo implantation and live birth rates gradually decrease with age in case of IVF/ICSI, with a marked and sharp decline observed after the age of 40 years [6]. Among this population undergoing IVF/ICSI, live birth rates per embryo transfer drop to 5.9% – 6.7% and drops even further to 0.7% in those aged 45 years and above [7]. In contrast, females aged 35 years or younger have a live birth rate of about 40-50%. Moreover, advanced maternal age is associated with an increased cycle cancellation and higher miscarriage rates [1]. The cycle cancellation rate is around 19% at the age of 40 years and rises steadily, reaching 55% at the age of 45 years or older [8] Miscarriage rates also increase significantly with age, reported at 44.8% for those aged 40 years and older, ranging from 39% at age of 40 years to 67% at age of 45 years or older [8]. In the context of a global trend toward delayed childbearing, the demand for assisted reproductive technologies among women aged 40 and older has risen significantly. Intracytoplasmic sperm injection (ICSI) is widely used in this age group; however, reproductive outcomes remain a subject of concern due to age-related declines in oocyte quality, ovarian reserve, and embryo viability.

Some organizations have restricted the use of IVF and ICSI for women in their forties, resulting in a limited body of literature on the subject. This study aims to fill the current gap in literature by evaluating ICSI outcomes in women aged 40 and older without an upper limit for age, thereby contributing valuable data to improve clinical decision-making, patient counselling, and management strategies in this growing patient population.

Materials and Methods

Study design and setting

A retrospective cohort study was conducted in the Reproductive Endocrine and Infertility Medicine Department, Women's Specialized Hospital, King

Fahad Medical City (KFMC), Riyadh Second Health Cluster (R2), Riyadh, Saudi Arabia. The study period extended from January 2022 to December 2024.

Study participants

The study included all female patients undergoing IVF/ICSI cycles. The exclusion criteria were cycles managed with the long protocol, cycles with no fresh embryo transfer (freeze-all), cycles canceled because the patient was COVID-19 positive, cycles canceled because of patient cancellation or failure to attend follow-up, cycles canceled because no sperm was obtained from ejaculate sample or TESA, and cycles converted to intrauterine insemination during stimulation follow-up. Women who underwent IVF/ICSI cycles for fertility preservation were also excluded. The control group included all female patients undergoing IVF/ICSI cycles who were aged less than 40 years, and these controls were further divided into two groups: 35–39 years and less than 35 years. All participants were followed to identify reproductive outcomes.

Treatment protocol

Patients underwent controlled ovarian hyperstimulation using a standard GnRH antagonist protocol. Ovarian stimulation was carried out using either a single gonadotropin or combined gonadotropins, including recombinant FSH (GonalF, Serono, Inc., Rockland, MA, USA), recombinant LH (Luveris, EMD Serono, Rockland, MA, USA), hMG (Merional, IBSA Institut Biochimique SA, Switzerland), and hMG (Menopur, IBSA Institut Biochimique SA, Switzerland). During the initial visit, between day 2 and day 4 of the menstrual cycle, each patient underwent transvaginal ultrasonography to confirm the absence of ovarian cysts and an endometrial thickness of less than 7 mm. Blood investigations were also performed to confirm plasma E2 levels of less than 250 mmol/L and FSH levels of less than 20 IU/L. Gonadotropins were then started at varying doses, with dose adjustment by either a step-up or step-down approach after 5 or 6 days of stimulation according to ovarian response as assessed by estradiol levels and follicular recruitment on transvaginal ultrasound. Daily injections of 0.25 mg GnRH antagonist (Cetrotide w, Serono, Inc., Rockland, MA, USA) were started on either day 5 or day 6 of the menstrual cycle or when the leading follicle reached 13–14 mm in diameter. Treatment was continued until two or more leading follicles reached a mean diameter of 17 mm, after which final follicular maturation was triggered using human chorionic gonadotrophin (hCG) (Choriomon, IBSA Institut Biochimique S.A., Switzerland) or recombinant hCG (Ovitrelle; Merck, Kenilworth, NJ). Transvaginal oocyte retrieval was performed 36 hours after hCG administration. All patients underwent ICSI, as this had become the standard practice in the institution. One or two fresh embryos were transferred on days 2 to 5 after fertilization. For luteal phase support, patients received a 400 mg vaginal progesterone pessary twice daily (Cyclogest, Actavis, Barnstaple, UK), which was continued for 12 weeks if pregnancy occurred.

Data collection and outcomes

Data were collected using a standardized data collection form consisting of four sections. The first section included demographic and clinical characteristics, namely age, body mass index (BMI) in kg/m², duration of infertility, obstetric history, baseline FSH (IU/L), and estradiol (E2). The second section addressed the causes of infertility, including anovulation, polycystic ovary syndrome, tubal factors, endometriosis, male factors, multiple causes, and unexplained causes. The third section

included treatment-related clinical results, including the dose and duration of gonadotropin stimulation, final E2 level, LH level, endometrial thickness on the day of hCG administration, number of oocytes collected, number of mature oocytes, number of injected oocytes, number of fertilized oocytes, number and grade of transferred embryos, and number of frozen embryos. The fourth section included reproductive outcomes, namely biochemical pregnancy, defined as HCG ≥10 mIU/ml 14 days after embryo transfer, clinical pregnancy, defined as visualization of a gestational sac on transvaginal ultrasound, ectopic pregnancy, miscarriage, and live birth.

Sample size estimates

The required sample size was estimated using G*Power software. Based on a priori assumptions of 80% power, a 95% confidence interval, a medium effect size of 0.27, and three population groups, the total required sample size was calculated as 156 to test whether there were statistically significant differences between the means of outcome variables across more than two random variables with equal variance.

Statistical analysis

Data were stored and managed using Microsoft Excel and the Statistical Package for Social Sciences (SPSS), version 25.0 (SPSS, Chicago, IL). The Kolmogorov–Smirnov test was used to assess the assumption of normal distribution. If the data were biased, nonparametric tests were applied. Categorical variables were presented as frequencies and percentages, whereas continuous data were summarized as median and interquartile range. The nonparametric Kruskal–Wallis test was used to compare continuous variables. Cross-tabulation, chi-square test, and Fisher's exact test were used to compare categorical variables. All tests were two-sided, and a p-value of less than 0.05 was considered statistically significant.

Ethical considerations

This was a retrospective cohort study based on review of existing medical records, the requirement for informed consent was waived by the Institutional Review Board. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki for medical research involving human participants, including respect for patient privacy, confidentiality, and data protection. All collected data were anonymized and used only for research purposes.

Results

A total of 2,507 IVF/ICSI cycles were included in the analysis. 1,280 cycles (51.1%) were in women aged ≤34 years, 741 (29.6%) were in those aged 35–39 years, and 486 (19.4%) were in women aged >39 years. Embryo transfer (ET) was performed in 1,850 cycles (73.8%), whereas 657 cycles (26.2%) had no ET. The ET rate decreased in age categories, from 77.9% in women aged ≤34 years to 75.6% in those aged 35–39 years and 60.3% in those aged >39 years, while the proportion with no ET increased from 22.1% to 24.4% and 39.7%, respectively ($p<0.001$). Mean BMI and infertility duration increased significantly with age. Women aged >39 years also had lower baseline antral follicle count and higher baseline FSH than younger age groups ($p<0.001$ for both).

Treatment characteristics varied by age, the total starting gonadotropin dose and total gonadotropin dose increased significantly with advancing age, while final estradiol levels decreased ($p<0.001$). The mean number of retrieved oocytes declined from 8.3±5.2 in women aged ≤34 years to 6.2±4.4 in

those aged 35–39 years and 5.0±3.9 in women aged >39 years. A similar decline was observed for mature oocytes, fertilized oocytes, and cleaved embryos (all p<0.001). In contrast, total stimulation days and the number of embryos transferred did not differ significantly among the 3 age groups (p=0.566 and p=0.196, respectively). The mean day of embryo transfer became earlier with increasing age (3.1±1.0, 2.9±1.0, and 2.7±0.9 days; p<0.001).

Pregnancy outcomes showed a progressive decline with age. Clinical pregnancy rates were 28.0% in women aged ≤34 years, 21.3% in those aged 35–39 years, and 14.3% in women aged >39 years, while negative pregnancy outcomes increased from 67.5% to 75.0% and 80.9%, respectively (p<0.001). Live birth rates decreased from 62.7% in women aged ≤34 years to 56.3% in those aged 35–39 years and 26.2% in women aged >39 years, whereas miscarriage rates increased from 37.3% to 43.7% and 73.8%, respectively (p<0.001). In the secondary analysis, women aged >35 years similarly had lower ET rates, lower oocyte yield, lower clinical pregnancy and live birth rates, and higher miscarriage rates than women aged ≤35 years (all p<0.001). The main reasons for no ET were no fertilization (47.3%), no oocytes (17.0%), and no response (13.7%).

Table 1. Summarized age categories (≤34, 35–39, >39) and studied parameters

Characteristic	Description	≤34 N=1280 (51.1%)	35–39 N=741 (29.6%)	>39 N=486 (19.4%)	Total N=2507 (100.0%)	p-value
Criteria	ET	997 (77.9%)	560 (75.6%)	293 (60.3%)	1850 (73.8%)	<0.001
Criteria	No ET	283 (22.1%)	181 (24.4%)	193 (39.7%)	657 (26.2%)	<0.001
BMI (kg/m2)	Mean ± SD	27.7 ± 5.1	29 ± 4.9	30.1 ± 5	28.53 ± 5.13	<0.001
Infertility duration (year)	Mean ± SD	5 ± 2.1	7.3 ± 2.8	8.4 ± 4.4	6 ± 3	<0.001
Cause of infertility	Endometriosis	14 (1.1%)	18 (2.4%)	5 (1.0%)	37 (1.5%)	<0.001
Cause of infertility	Male	492 (38.4%)	212 (28.6%)	136 (28.0%)	840 (33.5%)	<0.001
Cause of infertility	Multiple	103 (8.0%)	71 (9.6%)	61 (12.6%)	235 (9.4%)	<0.001
Cause of infertility	ovulatory	337 (26.3%)	259 (35.0%)	195 (40.1%)	791 (31.6%)	<0.001
Cause of infertility	tubal	68 (5.3%)	28 (3.8%)	10 (2.1%)	106 (4.2%)	<0.001
Cause of infertility	unexplained	266 (20.8%)	153 (20.6%)	79 (16.3%)	498 (19.9%)	<0.001
Previous ART cycles	No	839 (65.5%)	469 (63.3%)	237 (48.8%)	1545 (61.6%)	<0.001
Previous ART cycles	Yes	441 (34.5%)	272 (36.7%)	249 (51.2%)	962 (38.4%)	<0.001
Previous miscariage	No	1212 (94.7%)	664 (89.6%)	375 (77.2%)	2251 (89.8%)	<0.001
Previous miscariage	Yes	68 (5.3%)	77 (10.4%)	111 (22.8%)	256 (10.2%)	<0.001
Baseline AFC	Mean ± SD	25 ± 14.2	16 ± 9.7	8.5 ± 6.2	19 ± 13	<0.001
Baseline FSH	Mean ± SD	6.5 ± 2.6	7.4 ± 3.1	8.2 ± 3.8	7.1 ± 3.1	<0.001
Total start dose	Mean ± SD	270.2 ± 131.3	372.4 ± 134.9	475.6 ± 111.6	340 ± 151	<0.001
Total stimulation days	Mean ± SD	10.5 ± 1.9	10.6 ± 2.1	10.5 ± 2.2	10 ± 2	0.566
Total gonadotropins dose	Mean ± SD	2877.3 ± 1603.2	3929.8 ± 1701.8	4991.6 ± 1629.5	3598 ± 1832	<0.001
Final E2	Mean ± SD	6631.2 ± 4210.9	5273.9 ± 3941.5	4160.1 ± 3894.2	5751 ± 4186	<0.001
Final LH	Mean ± SD	2.1 ± 2	2.6 ± 2.8	3 ± 3.5	2.4 ± 2.6	<0.001
Final ET	Mean ± SD	9.1 ± 1.4	9.2 ± 1.5	8.7 ± 1.8	9 ± 2	<0.001
Number of oocytes retrived	Mean ± SD	8.3 ± 5.2	6.2 ± 4.4	5 ± 3.9	7 ± 5	<0.001
MII	Mean ± SD	6.3 ± 3.9	4.7 ± 3.5	3.6 ± 2.8	5 ± 4	<0.001
Number of fertilized	Mean ± SD	4.3 ± 3	3.5 ± 2.7	2.8 ± 1.9	4 ± 3	<0.001

Characteristic	Description	≤34 N=1280 (51.1%)	35–39 N=741 (29.6%)	>39 N=486 (19.4%)	Total N=2507 (100.0%)	p-value
Number of cleaved	Mean ± SD	4.2 ± 2.9	3.3 ± 2.3	2.7 ± 1.7	4 ± 3	<0.001
Number of embryos transferred	Mean ± SD	1.6 ± 0.5	1.6 ± 0.5	1.7 ± 0.6	2 ± 1	0.196
Day of ET	Mean ± SD	3.1 ± 1	2.9 ± 1	2.7 ± 0.9	3 ± 1	<0.001
Pregnant (clinical, biochemical, ectopic)	Biochemical	44 (4.4%)	21 (3.8%)	14 (4.8%)	79 (4.3%)	<0.001
Pregnant (clinical, biochemical, ectopic)	clinical	279 (28.0%)	119 (21.3%)	42 (14.3%)	440 (23.8%)	<0.001
Pregnant (clinical, biochemical, ectopic)	ectopic	1 (0.1%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	<0.001
Pregnant (clinical, biochemical, ectopic)	negative	673 (67.5%)	420 (75.0%)	237 (80.9%)	1330 (71.9%)	<0.001
Miscarriage/Livebirth	Livebirth	175 (62.7%)	67 (56.3%)	11 (26.2%)	253 (57.5%)	<0.001
Miscarriage/Livebirth	Miscariage	104 (37.3%)	52 (43.7%)	31 (73.8%)	187 (42.5%)	<0.001
Single/twins	Single	271 (97.1%)	115 (96.6%)	40 (95.2%)	426 (96.8%)	0.802
Single/twins	Twins	8 (2.9%)	4 (3.4%)	2 (4.8%)	14 (3.2%)	0.802

Table 2. Summarized age categories (≤35, >35) and studied parameters

Characteristic	Description	≤35 N=1049 (57.8%)	>35 N=1058 (42.2%)	Total N=2507 (100.0%)	p-value
	ET	1133 (78.2%)	717 (67.8%)	1850 (73.8%)	<0.001
	No ET	316 (21.8%)	341 (32.2%)	657 (26.2%)	<0.001
BMI (kg/m2)	Mean ± SD	27.75 ± 5.12	29.6 ± 4.94	28.53 ± 5.13	<0.001
Infertility duration (year)	Mean ± SD	5 ± 2	8 ± 4	6 ± 3	<0.001
Cause of infertility	Endometriosis	19 (1.3%)	18 (1.7%)	37 (1.5%)	<0.001
Cause of infertility	Male	550 (38.0%)	290 (27.4%)	840 (33.5%)	<0.001
Cause of infertility	Multiple	121 (8.4%)	114 (10.8%)	235 (9.4%)	<0.001
Cause of infertility	ovulatory	386 (26.6%)	405 (38.3%)	791 (31.6%)	<0.001
Cause of infertility	tubal	73 (5.0%)	33 (3.1%)	106 (4.2%)	<0.001

Characteristic	Description	≤35 N=1049 (57.8%)	>35 N=1058 (42.2%)	Total N=2507 (100.0%)	p-value
Cause of infertility	unexplained	300 (20.7%)	198 (18.7%)	498 (19.9%)	<0.001
Previous ART cycles	No	948 (65.4%)	597 (56.4%)	1545 (61.6%)	<0.001
Previous ART cycles	Yes	501 (34.6%)	461 (43.6%)	962 (38.4%)	<0.001
Previous miscarriage	No	1356 (93.6%)	895 (84.6%)	2251 (89.8%)	<0.001
Previous miscarriage	Yes	93 (6.4%)	163 (15.4%)	256 (10.2%)	<0.001
Baseline AFC	Mean ± SD	24 ± 14	12 ± 9	19 ± 13	<0.001
Baseline FSH	Mean ± SD	6.6 ± 2.7	7.8 ± 3.5	7.1 ± 3.1	<0.001
Total start dose	Mean ± SD	278 ± 133	425 ± 132	340 ± 151	<0.001
Total stimulation days	Mean ± SD	10 ± 2	11 ± 2	10 ± 2	0.796
Total gonadotropins dose	Mean ± SD	2955 ± 1609	4480 ± 1750	3598 ± 1832	<0.001
Final E2	Mean ± SD	6501 ± 4173	4723 ± 3984	5751 ± 4186	<0.001
Final LH	Mean ± SD	2.1 ± 2.1	2.8 ± 3.2	2.4 ± 2.6	<0.001
Final ET	Mean ± SD	9 ± 1	9 ± 2	9 ± 2	0.001
Number of oocytes retrieved	Mean ± SD	8 ± 5	6 ± 4	7 ± 5	<0.001
MII	Mean ± SD	6 ± 4	4 ± 3	5 ± 4	<0.001
Number of fertilized	Mean ± SD	4 ± 3	3 ± 2	4 ± 3	<0.001
Number of cleaved	Mean ± SD	4 ± 3	3 ± 2	4 ± 3	<0.001
Number of embryos transferred	Mean ± SD	2 ± 1	2 ± 1	2 ± 1	0.925
Day of ET	Mean ± SD	3 ± 1	3 ± 1	3 ± 1	<0.001
Pregnant (clinical, biochemical, ectopic)	Biochemical	48 (4.2%)	31 (4.3%)	79 (4.3%)	<0.001
Pregnant (clinical, biochemical, ectopic)	clinical	317 (28.0%)	123 (17.2%)	440 (23.8%)	<0.001
Pregnant (clinical, biochemical, ectopic)	ectopic	1 (0.1%)	0 (0.0%)	1 (0.1%)	<0.001
Pregnant (clinical, biochemical, ectopic)	negative	767 (67.7%)	563 (78.5%)	1330 (71.9%)	<0.001
Miscarriage/Livebirth	Livebirth	199 (62.8%)	54 (43.9%)	253 (57.5%)	<0.001

Characteristic	Description	≤35 N=1049 (57.8%)	>35 N=1058 (42.2%)	Total N=2507 (100.0%)	p-value
Miscarriage/Livebirth	Miscarriage	118 (37.2%)	69 (56.1%)	187 (42.5%)	<0.001
Single/twins	Single	307 (96.8%)	119 (96.7%)	426 (96.8%)	>0.999
Single/twins	Twins	10 (3.2%)	4 (3.3%)	14 (3.2%)	>0.999

Table 3. Summarized characteristics according to ET versus No ET

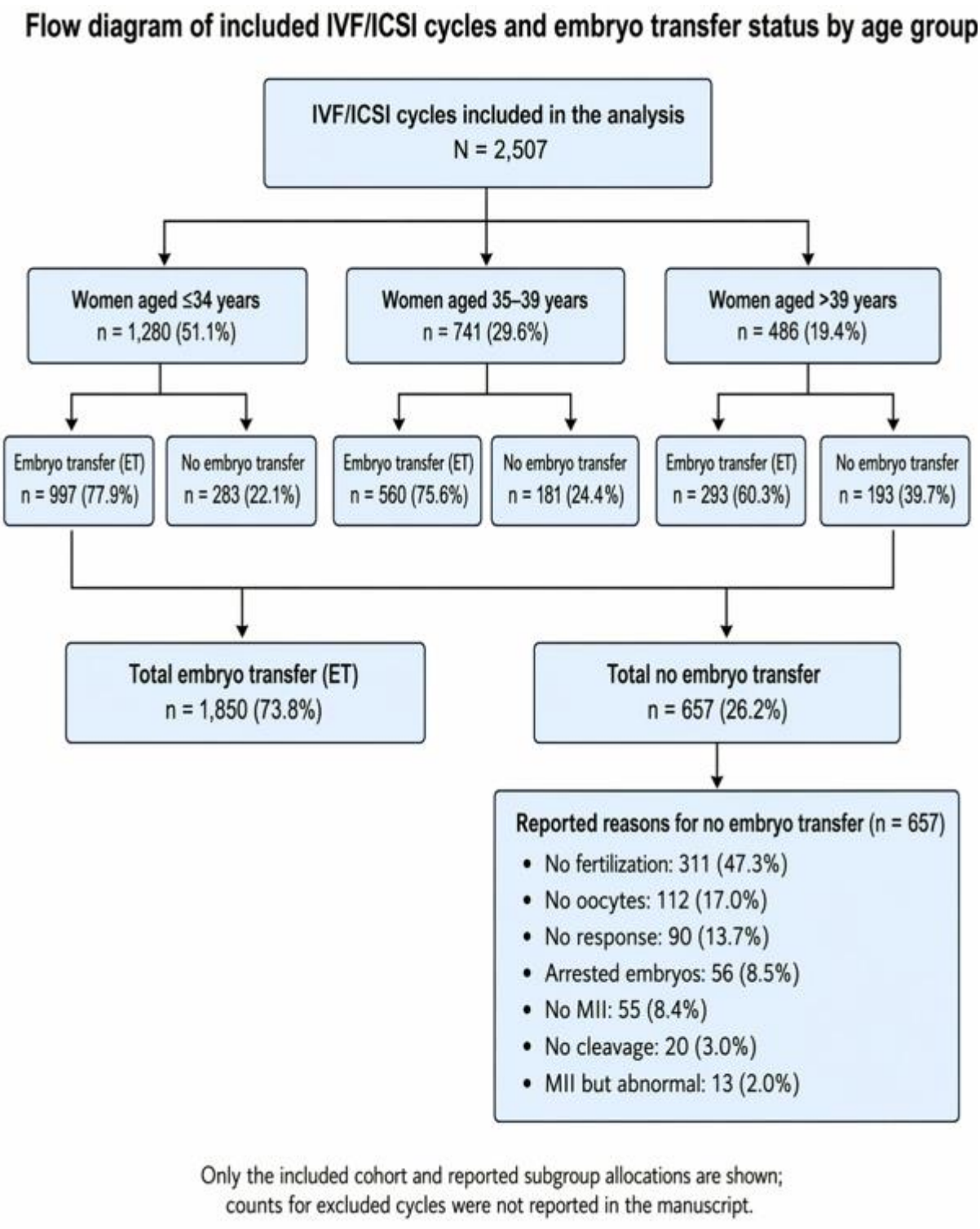
Characteristic	Description / Statistic	ET N=1850 (73.8%)	No ET N=657 (26.2%)	Total N=2507 (100.0%)
Age (year)	Mean ± SD	33.7 ± 5.2	35.3 ± 5.6	34.2 ± 5.3
BMI (kg/m2)	Mean ± SD	28.4 ± 5.1	28.8 ± 5.1	28.5 ± 5.1
Infertility duration (year)	Mean ± SD	6.2 ± 3.3	6.7 ± 3	6.4 ± 3.2
Cause of infertility	Endometriosis	30 (1.6%)	7 (1.1%)	37 (1.5%)
Cause of infertility	Male	646 (34.9%)	194 (29.5%)	840 (33.5%)
Cause of infertility	Multiple	173 (9.4%)	62 (9.4%)	235 (9.4%)
Cause of infertility	ovulatory	527 (28.5%)	264 (40.2%)	791 (31.6%)
Cause of infertility	tubal	81 (4.4%)	25 (3.8%)	106 (4.2%)
Cause of infertility	unexplained	393 (21.2%)	105 (16.0%)	498 (19.9%)
Previous ART cycles	No	1142 (61.7%)	403 (61.3%)	1545 (61.6%)
Previous ART cycles	Yes	708 (38.3%)	254 (38.7%)	962 (38.4%)
Baseline AFC	Mean ± SD	20.8 ± 13.1	14.5 ± 13.2	19.2 ± 13.4
Baseline FSH	Mean ± SD	6.7 ± 2.5	8.4 ± 4.1	7.1 ± 3.1
Total start dose	Mean ± SD	319.7 ± 144.6	398 ± 155.4	340.2 ± 151.5
Total stimulation days	Mean ± SD	10.5 ± 1.9	10.5 ± 2.4	10.5 ± 2
Total gonadotropins dose	Mean ± SD	3381.3 ± 1704	4209.4 ± 2031.6	3598.3 ± 1831.8
Final E2	Mean ± SD	6296 ± 3992.6	4216.3 ± 4338.8	5751 ± 4186.4
Final LH	Mean ± SD	2 ± 1.7	3.4 ± 4.1	2.4 ± 2.6
Final ET	Mean ± SD	9.3 ± 1.3	8.6 ± 1.8	9.1 ± 1.5
Number of oocytes retrived	Mean ± SD	7.4 ± 4.8	5.8 ± 5.5	7.1 ± 5

Characteristic	Description / Statistic	ET N=1850 (73.8%)	No ET N=657 (26.2%)	Total N=2507 (100.0%)
MII	Mean ± SD	5.6 ± 3.7	4 ± 4.1	5.3 ± 3.8
Number of fertilized	Mean ± SD	3.8 ± 2.8	3.8 ± 3.3	3.8 ± 2.9
Number of cleaved	Mean ± SD	3.7 ± 2.6	3.6 ± 2.7	3.7 ± 2.6

Table 4. Reasons for no ET

Reason	No ET N=657 (26.2%)	Total N=2507 (100.0%)
Arrested embryos	56 (8.5%)	56 (2.2%)
MII but abnormal	13 (2.0%)	13 (0.5%)
No cleavage	20 (3.0%)	20 (0.8%)
No fertilization	311 (47.3%)	311 (12.4%)
No MII	55 (8.4%)	55 (2.2%)
No oocytes	112 (17.0%)	112 (4.5%)
No response	90 (13.7%)	90 (3.6%)

Figure 1: Flow diagram



Discussion

This study examined ICSI outcomes in women aged ≥40 years compared with a younger control group and found a clear, clinical decline in reproductive outcomes with advancing maternal age. Specifically, women aged 40 and older had lower oocyte yield, lower fertilization-to-embryo conversion, reduced clinical pregnancy and ongoing pregnancy rates, higher early pregnancy loss, and lower live-birth rates per started cycle and per transfer. These findings are consistent with the established effect of maternal age on ovarian reserve and embryo competence and underline the persistent challenge of achieving live birth with autologous oocytes in advanced-age patients.

Biological explanations for the age-associated drop in success are multifactorial. The quantity of recruitable oocytes declines with age, producing fewer mature oocytes at retrieval and therefore fewer embryos available for transfer or cryopreservation. More importantly, oocyte quality — particularly the rate of chromosomal aneuploidy — rises sharply with maternal age, causing lower implantation potential and higher miscarriage rates even when embryos reach the blastocyst stage. Several large cohort analyses and practice-guidance statements report substantially higher aneuploidy rates and progressively lower per-embryo live-birth potential after age 35–38, with further decline past age 40. These mechanisms likely explain why cumulative live-birth rates per cycle are markedly lower in the ≥40 group despite modern laboratory practices.

Our data also speak to the limited capacity of ICSI to overcome age-related oocyte defects. ICSI is primarily a sperm-factor intervention that can rescue fertilization in the presence of severe male-factor infertility; it does not correct cytoplasmic or chromosomal abnormalities intrinsic to the oocyte. Comparative studies have found no consistent live-birth advantage for routine use of ICSI in non–male-factor infertility and, in some advanced-age cohorts with poor ovarian response, fertilization and pregnancy rates following ICSI may be even lower than expected. Thus, while ICSI remains appropriate when indicated for male-factor or prior fertilization failure, its routine application solely to mitigate effects of advanced maternal age is not supported by the evidence or by our findings.

Two practical implications flow from these results. First, patient counselling should emphasize realistic expectations: women aged ≥40 should be informed about lower per-cycle live-birth probabilities, increased likelihood of early pregnancy loss, and the higher chance of cycle cancellation or cycles yielding few transferable embryos. Presenting cumulative probabilities (across fresh + frozen transfers) more accurately captures the patient experience and can help with decision-making about pursuing additional cycles, donor oocytes, or alternative family-building strategies. Second, when embryo selection strategies are considered, preimplantation genetic testing for aneuploidy (PGT-A) can reduce transfer of aneuploid embryos but does not fully restore age-related declines in live birth; recent guidance and cohort data show that maternal age remains an independent predictor of outcome even after euploid selection, suggesting additional age-related uterine or embryonic factors beyond chromosomal status. Therefore, PGT-A may be useful for reducing miscarriage risk and shortening time to an euploid transfer in selected patients, but it is not a panacea for poor prognosis solely attributed to advanced maternal age.

Strengths of the present study include comparison of clinically relevant endpoints (clinical pregnancy, miscarriage, live birth), use of ICSI across groups so that differences are less likely to reflect variable insemination technique; and presenting reasons for cancelled cycles. As with most observational ART studies, patient selection and unmeasured confounders (subtle differences in ovarian stimulation protocols, cumulative embryo quality metrics, or male partner factors) may influence outcomes. Our sample size in the ≥40 subgroup limited the ability to perform granular age-stratified analyses (40–42 vs ≥43) or to robustly evaluate interactions between ovarian reserve markers (AMH, AFC) and outcomes. Finally, we did not systematically evaluate PGT-A or donor-egg cycles within the dataset, so we cannot directly quantify how often those options would have changed individual prognosis in our cohort.

For clinical practice, the data support early and frank counselling: when using autologous oocytes, women aged 40 and older should expect substantially lower success rates and higher miscarriage risk compared with younger counterparts. Clinicians should individualize treatment by integrating ovarian reserve testing, prior response, and patient goals; consider offering PGT-A when appropriate for reducing the risk of transferring aneuploid embryos; and discuss donor oocytes as a highly effective alternative when prognosis with autologous eggs is poor. Where ICSI is performed, reserve it for standard indications (male-factor infertility, prior fertilization failure, or specific laboratory reasons) rather than as an empiric strategy to overcome age-related oocyte defects.

Future research directions include prospective studies that: (1) evaluate the relative contributions of oocyte aneuploidy versus other age-related factors (mitochondrial function, spindle apparatus integrity, endometrial receptivity) to the residual reduction in live birth after euploid embryo transfer; (2) test interventions aimed at improving oocyte health or uterine receptivity in older patients; and (3) define subgroups of women ≥40 with favorable prognosis (for instance, those with good ovarian response or multiple top-quality embryos) to better individualize the offer of autologous ART versus donor egg. Continued aggregation of multicenter datasets and randomized trials where feasible will help refine counseling and optimize treatment pathways for this growing patient population.

Conclusion

Our findings align with the broader literature showing that advancing maternal age is associated with reduced ICSI success, primarily driven by lower oocyte yield and higher rates of embryo aneuploidy and miscarriage. ICSI cannot reverse the fundamental biological decline associated with reproductive aging.; therefore, clinicians should emphasize timely fertility evaluation and management should focus on realistic age-specific counselling, individualized treatment planning, and consideration of alternative reproductive options when appropriate.

Acknowledgment statement

The authors would like to thank the Research Center at King Fahd Medical City, Riyadh Second Health Cluster, Riyadh, Saudi Arabia for their assistance in the preparation of this manuscript.

Declaration of interest

The authors have nothing to declare

Conflict of interest

The authors have no conflicts of interest.

Authors 'contributions

Lama Alshwairikh and Dania AlJaroudi: Carried out the study, and participated in study design, data analysis, and drafting of the manuscript. Tariq Wani carried out the data analysis. Nora Alrazeyg participated in drafting the manuscript. All the authors have read and approved the final manuscript and have revised it critically for important intellectual content.

Funding

None

Availability of data and materials

Data are available upon request from the corresponding author.

Reference

1. Organization, W.H., 2023. Infertility prevalence estimates: 1990–2021.

2. Hassabelnabi EAF, Badreldin MA, Behery MA, Rageh KA, Ali EA. Flexible antagonist versus agonist flare protocol in women above 40 undergoing IVF, a retrospective cohort study. J Bras Reprod Assist 2023; 27:381–385.

3. Gu F, Ruan S, Luo C, Huang Y, Luo L, Xu Y, Zhou C. Can repeat IVF/ ICSI cycles compensate for the natural decline in fertility with age? an estimate of cumulative live birth rates over multiple IVF/ ICSI cycles in Chinese advanced-aged population. Aging 2021; 13:14385–14398.

4. Han QS, Zhou Y, Xu Y, Ai KL, Song JY, Sun ZG. Optimal timing of GnRH antagonist initiation in IVF-ET: a retrospective cohort study on advanced maternal age women. Front Endocrinol (Lausanne) 2024; 15:1340230.

5. Furuhashi K, Saeki Y, Enatsu N, Iwasaki T, Ito K, Mizusawa Y, Matsumoto Y, Kokeguchi S, Shiotani M. Piezo-assisted ICSI improves fertilization and blastocyst development rates compared with conventional ICSI in women aged more than 35 years. Reprod Med Biol 2019; 18:357–361.

6. Gennarelli G, Carosso A, Canosa S, Filippini C, Cesarano S, Scarafia C, Brunod N, Revelli A, Benedetto C. ICSI versus conventional IVF in women aged 40 years or more and unexplained infertility: a retrospective evaluation of 685 cycles with propensity score model. J Clin Med 2019; 8:1694.

7. Fancsovits P, Lehner A, Kaszas Z, Nemes A, Dudas B, Joo K, Murber A, Berkes-Bara E, Fekecs G, Urbancsek J. Intracytoplasmic sperm injection does not improve the outcome of IVF treatments in patients with advanced maternal age or low oocyte number: a randomized controlled trial. J Gynecol Obstet Hum Reprod 2023; 52:102625.

8. Duan X, Li Z, Li M, Ma X. Analysis of controlled ovarian hyperstimulation protocols in women over 35 years old with poor ovarian response: a real-world study. BMC Pregnancy Childbirth 2023; 23:813.

9. de Marco MP, Montanari G, Ruscito I, Giallonardo A, Ubaldi FM, Rienzi L, Costanzi F, Caserta D, Schimberni M, Schimberni M. Natural cycle results in lower implantation failure than ovarian stimulation in advanced-age poor responders undergoing IVF: fertility outcomes from 585 patients. Reprod Sci 2021;28: 1967–1973.

10. Conforti A, Esteves SC, Humaidan P, Longobardi S, D'Hooghe T, Orvieto R, Vaiarelli A, Cimadomo D, Rienzi L, Ubaldi FM et al. Recombinant human luteinizing hormone co-treatment in ovarian stimulation for assisted reproductive technology in women of advanced reproductive age: a systematic review and meta- analysis of randomized controlled trials. Reprod Biol Endocrinol 2021a;19:91.

11. Cimadomo D, Fabozzi G, Vaiarelli A, Ubaldi N, Ubaldi FM, Rienzi L. Impact of maternal age on oocyte and embryo competence. Front Endocrinol (Lausanne) 2018;9:327.

12. Bielfeld AP, Schwarze J-E, Verpillat P, Lispi M, Fischer R, Hayward B, Chuderland D, D'Hooghe T, Krussel J-S. Effectiveness of recombinant human FSH: recombinant human LH combination treatment versus recombinant human FSH alone for assisted reproductive technology in women aged 35–40 years. Reprod Biomed Online 2024;48:103725.

13. Cai H, Mol B, Gordts S, Wang H, Shi J. Elective single versus double blastocyst-stage embryo transfer in women aged 36 years or older: a retrospective cohort study. Hum Fertil (Camb) 2023;26: 1185–1194.

14. C edrin-Durnerin I, Carton I, Massin N, Chevalier N, Dubourdieu S, Bstandig B, Michelson X, Goro S, Jung C, Guivarc'h-L ev^eque A. Pretreatment with luteal estradiol for programming antagonist cycles compared to no pretreatment in advanced age women stimulated with corifollitropin alfa: a non-inferiority randomized controlled trial. Hum Reprod 2024;39:1979–1986.

15. Chen J, Wang Y, Fang C, Li T. A 3–4 h oocyte retrieval-ICSI interval optimizes clinical outcomes for women over 40 years. Sci Rep 2023;13:15035.

16. Chen Y M, Qi Q R, Xie Q Z, Yang Y F, Xia Y, Zhou X D Effect of progestin-primed ovarian stimulation protocol on outcomes of aged infertile women who failed to get pregnant in the first IVF/ ICSI cycle: a self-controlled study. Curr Med Sci 2018b;38:513–518.

17. . Khalife D, et al. Cumulative live-birth rates by maternal age after one or more IVF cycles. Hum Reprod. 2020.

18. 2Gennarelli G, et al. ICSI versus conventional IVF in women aged 40 years or older. J Assist Reprod Genet. 2019.

19. American Society for Reproductive Medicine. Committee opinion: The use of preimplantation genetic testing for aneuploidy (PGT-A). 2024.

20. Vitagliano A, et al. Does maternal age affect assisted reproduction technology outcomes independent of embryo ploidy? Fertil Steril. 2023.

21. Jiang W, et al. Maternal age-related declines in live birth rate following single euploid embryo transfer. J Ovarian Res. 2025.

22. Palermo G, Joris H, Devroey P, Van Steirteghem AC. Pregnancies after intracytoplasmic injection of single spermatozoon into an oocyte. Lancet. 1992;340(8810):17-18.

23. te Velde ER, Pearson PL. The variability of female reproductive ageing. Hum Reprod Update. 2002;8(2):141–154.

24. Broekmans FJ, Soules MR, Fauser BC. Ovarian aging: mechanisms and clinical consequences. Endocr Rev. 2009;30(5):465–493.

25. Leridon H. Can assisted reproduction technology compensate for the natural decline in fertility with age? Hum Reprod. 2004;19(7):1548–1553.

26. Khan MA, Siddiqui SZ, Malik N, Shaikh A. Role of female age in determining the outcome of ICSI. Pak J Med Sci. 2020;36(2):117–122.

27. Ziebe S, Petersen K, Lindenberg S, Andersen AG, Gabrielsen A, Andersen AN. Embryo morphology or cleavage stage: how to select the best embryos for transfer after in-vitro fertilization. Hum Reprod. 1997;12(7):1545–1549.

28. Abbas MA, Ali MM, Ali RH, et al. The impact of female age on ICSI outcomes using testicular sperm in azoospermic patients. Middle East Fertil Soc J. 2017;22(2):134–140.

29. McLernon DJ, Steyerberg EW, te Velde ER, Lee AJ, Bhattacharya S. Predicting the chances of a live birth after one or more complete cycles of IVF: a population-based study. Hum Reprod. 2021;36(5):1280–1289.

30. Wang Y, Chen X, Chen C, et al. Effect of age on IVF/ICSI outcomes in women with endometrioma after laparoscopic cystectomy. Reprod Biol Endocrinol. 2021;19(1):46.

31. Huang B, Lu X, Li Q, et al. Impact of maternal age on pregnancy outcomes after single euploid embryo transfer. J Ovarian Res. 2025;18(1):15.

32. Elmahdy AM, Gadhoum AM. Maternal age and its effect on clinical pregnancy rate in ICSI cycles: a retrospective study. J Reprod Med Ethics. 2023;11(3):

33. Nofech-Mozes R, Zafran N, Ellenbogen A, et al. The effect of low AMH levels and age on IVF/ICSI outcomes. Middle East Fertil Soc J. 2020;25:14.

34. Majzoub A, Agarwal A, Elbardisi H. Sperm DNA fragmentation and its association with outcomes in ICSI: the moderating role of female age. Reprod. Biomed Online. 2021;42(3):456–462