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Impact of Infertility Etiology on Clinical Pregnancy, Cumulative Live Birth Rate, and Time to Live Birth after IVF/ICSI: A Retrospective Cohort Study

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Abstract

Purpose: This study aimed to evaluate the association between infertility etiology and first transfer clinical pregnancy, cumulative live birth rate (CLBR), and time to live birth (TTLB) in couples undergoing their first assisted reproductive technology (ART) cycle.

Methods: A total of 2,444 infertile couples undergoing their first IVF/ICSI treatment were included in this single-center retrospective cohort study. Participants were categorized into nine etiological groups. Baseline characteristics, pregnancy outcomes, and cumulative live birth outcomes were compared across groups. Kaplan–Meier analysis was used to evaluate TTLB, and intergroup differences were assessed using appropriate statistical tests.

Results: Tubal factor infertility was the most common etiology (39.57%). Significant differences were observed among etiological groups in first-cycle clinical pregnancy rate ($P < 0.001$), cumulative live birth rate (CLBR) ($P < 0.001$), and time to live birth (TTLB) (log-rank $P < 0.001$). Patients with ovulatory dysfunction had the highest CLBR (76.8%) and shortest median TTLB (11 months), whereas those with diminished ovarian reserve had the lowest CLBR (37.6%) and prolonged TTLB. First-cycle clinical pregnancy rates ranged from 32.9% in diminished ovarian reserve to 63.7% in ovulatory dysfunction.

Conclusion: Infertility etiology was significantly associated with ART outcomes, including first-transfer clinical pregnancy, cumulative live birth, and time to live birth. These findings support individualized etiology-based counseling and treatment planning to improve reproductive efficiency.

Key words: Infertility Etiology; Assisted Reproductive Technology; Time to Live Birth; Cumulative Live Birth Rate; Retrospective Cohort Study.

Introduction

Globally, infertility rates have been rising annually due to factors such as delayed childbearing, increased societal pressures, and environmental pollution [1, 2]. The recent epidemiological data indicates that approximately 186 million couples worldwide are currently affected by infertility. Infertility imposes substantial physical, psychological, social, and economic burdens on affected individuals and families [3, 4]. Assisted reproductive technology (ART) is one of the

most effective treatments for infertility and plays an important role in helping individuals achieve pregnancy [5].

However, in this era of fast-paced living, the ART community's demand for reproductive efficiency continues to rise. In addition to achieving singleton full-term live births, increasing attention has been directed toward treatment efficiency, including time to live birth (TTLB), duration of care, and economic burden [6, 7]. TTLB serves as a crucial parameter for evaluating the efficiency of ART-assisted conception, comprehensively reflecting the overall efficiency from treatment initiation to successful live birth. It provides important clinical guidance for adjusting clinical treatment strategies [8, 9]. Existing research indicates that ART clinical characteristics and success rates vary among different etiological groups of assisted reproduction (such as tubal factors, diminished ovarian reserve, male factors, etc.)[10, 11]. However, systematic studies on the differences in their TTLB and the underlying mechanisms remain scarce. Some studies focus solely on a single etiology or rely on small sample sizes, making it difficult to comprehensively reflect the differences in assisted reproduction efficiency among various infertility groups with different causes.[12]

Although previous studies have demonstrated that ART outcomes vary across different infertility etiologies, most have focused on specific subgroups or short-term outcomes. Comprehensive evaluations incorporating cumulative live birth rate and time to live birth across multiple etiologies remain limited. Therefore, this study aims to systematically assess the impact of infertility etiology on clinical pregnancy, cumulative live birth rate, and TTLB in a large retrospective cohort, with the goal of informing individualized treatment strategies.

Materials and Methods

Study design

This study is a single-center retrospective cohort study approved by the Institutional Review Board of the First Affiliated Hospital of Army Medical University (Ethics Approval: BKY2025196). Clinical data were retrospectively collected from participants undergoing their first in vitro fertilization/Intracytoplasmic Sperm Injection/preimplantation genetic testing(IVF/ICSI/PGT) fertility treatment at the Reproductive Medicine Center of the First Affiliated Hospital of Army Medical University between January 2021 and December 2022. The data included: general demographic information (female age, female BMI, etc.), etiology, type, and duration of infertility, female anti-Müllerian hormone (AMH) levels, antral follicle count (AFC), gonadotropin (Gn) dosage and duration, trigger day estrogen (E2) and progesterone (P) levels, number of oocytes retrieved, laboratory embryo culture data (cleavage rate, etc.), and pregnancy follow-up outcomes.

Follow-up protocol: Blood HCG levels were measured 10–15 days post-transfer to assess pregnancy positivity. HCG-positive patients underwent ultrasound examination at 28–35 days post-transfer to assess clinical pregnancy. Clinical pregnancy was defined as the presence of a gestational sac detected by ultrasound, either intrauterine or ectopic,

absence of sac indicates biochemical pregnancy. Clinical pregnancies are followed at 60–70 days post-transfer to monitor embryonic development (excluding embryonic arrest, miscarriage, ectopic pregnancy, etc.). Successful pregnancies are followed post-delivery for live birth outcomes. Follow-up concluded upon successful live birth. Non-live births underwent repeated follow-up based on subsequent egg retrieval and transfer cycles, with follow-up ending on October 31, 2024. TTLB was defined as the time interval from the date of first oocyte retrieval to the date of live birth or the end of follow-up. Live birth (LB) was defined as the delivery of at least one infant with vital signs after 22 weeks of gestation.

Participants

Couples diagnosed with infertility undergoing their first IVF/ICSI/PGT treatment at this institution were included in the study, excluding those who discontinued cycle's midway, declined embryo transfer, or were lost to follow-up after embryo transfer. Participants were classified into nine infertility etiology groups according to the primary clinical diagnosis established before treatment initiation as tubal factor, ovulatory dysfunction, endometriosis, diminished ovarian reserve, female multifactorial, male factor (oligoasthenozoospermia and obstructive azoospermia), female-male multifactorial, chromosomal abnormalities, and unexplained infertility. The superovulation protocols and fertilization methods (IVF/ICSI) for each patient are tailored by a team of senior specialists based on individual circumstances.

Statistical methods

Statistical analyses were performed using SPSS version 22.0 and R version 3.6. Continuous variables were assessed for normality using the Kolmogorov–Smirnov test. Normally distributed quantitative data are presented as mean ± standard deviation (SD) and comparisons among multiple groups were performed using one-way analysis of variance (ANOVA). Non-normally distributed quantitative data were expressed as median (interquartile range, IQR) and comparisons were performed using the Kruskal-Wallis test. Categorical variables are presented as frequencies and percentages. Comparisons among multiple groups were conducted using the chi-square (χ^2) test. Kaplan–Meier survival analysis was used to estimate cumulative live birth rates and TTLB, with differences assessed using the log-rank test. $P < 0.05$ was considered statistically significant.

Results

Baseline clinical characteristics of patients

This study screened a total of 2,452 patients. Among them, 8 patients with intrauterine factors were excluded from analysis due to insufficient sample size. Ultimately, 2,444 infertility patients undergoing IVF/ICSI/PGT treatment were included in the statistical analysis. Among the 2,444 included participants, 1,529 (62.6%) achieved a live birth, 878

(35.9%) experienced no pregnancy or pregnancy loss, and 37 (1.5%) remained ongoing pregnancies at the end of follow-up. Tubal factor infertility was the most common etiology in 967 cases (39.57%), followed by multifactorial factors in both partners: (13.95%); male factors: (10.56%); unexplained infertility: (7.53%); ovulatory dysfunction: (6.87%); diminished ovarian reserve: (6.10%); multifactorial female factors: (7.00%); endometriosis: (4.09%); and chromosomal abnormalities: (4.34%) as shown in (Figure 1 & 2). Distribution of infertility types: primary infertility: 1226 cases (50.2%); secondary infertility: 1118 cases (49.8%). There were statistically significant differences in infertility type across etiological groups (χ^2=122.84, P<0.001), Primary infertility was more prevalent among participants with ovulatory dysfunction (70.2%), male factors (69.4%), and unexplained infertility (59.2%). Tubal factors, diminished ovarian reserve, multifactorial female factors, and chromosomal disorders predominantly involved secondary infertility (55.2%, 62.4%, 63.7%, and 68.9%, respectively); Endometriosis patients showed similar proportions of primary and secondary infertility (53.0% vs. 47.0%) (Table 1).

Table 1 Distribution of infertility types among patients with different etiologies

Causes of infertility	Primary infertility(n, %）	Secondary infertility(n, %）
Tubal factor	433(44.8%)	534(55.2%)
Endometriosis	53(53.0%)	47(47.0%)
Ovulatory dysfunction	118(70.2%)	50(29.8%)
Diminished ovarian reserve	56(37.6%)	93(62.4%)
Male factors	179(69.4%)	79(30.6%)
Unknown causes	109(59.2%)	75(40.8%)
Female multi-factor	62(36.3%)	109(63.7%)
Female and male multi-factor	183(53.7%)	158(46.3%)
Chromosomal disease	33(31.1%)	73(68.9%)
Overall	1226(50.2%)	1218(49.8%)
χ^2	122.48	
P value	<0.001	

Analysis of clinical data characteristics

The female age, duration of infertility, female BMI, and basal antral follicle count (AFC) in 2444 patients did not conform to normal distribution as determined by the Kolmogorov-Smirnov test (P<0.05). The median values (P_{25}-P_{75}) were 32 (29-35) years, 3(2-4) years, 21.9(20–24.1) kg/m², and12 (8–18) follicles, respectively. Female age was highest in the diminished ovarian reserve group (mean 35.4 years), followed by the multifactorial group (34.0 years), both significantly higher than other groups (P < 0.001). In contrast, women with ovulatory dysfunction had the lowest mean age at 30.4 years, with statistically significant differences (P<0.001).

The duration of infertility varied significantly among etiological groups (P < 0.001), with the longest duration observed in the multifactorial female infertility group (4 years, IQR: 2–6), followed by the female–male multifactorial group (3.5 years, IQR: 2–6), whereas the shortest duration was observed in patients with chromosomal abnormalities (1 year, IQR: 1–3).

BMI differed significantly across etiological groups (P < 0.001), with the lowest values observed in patients with endometriosis (20.75 kg/m², IQR: 19.6–22.5), while higher BMI values were noted in the ovulatory dysfunction group (22.9 kg/m², IQR: 20.8–25.4), with other groups, including the multifactorial female infertility group (22.2 kg/m², IQR: 20.2–24.7), showing intermediate values.

Significant differences were observed in ovarian reserve markers across etiological groups (P < 0.001). AMH and AFC were highest in the ovulatory dysfunction group (5.9 ng/mL, IQR: 3.4–10.1; 23 follicles, IQR: 18.5–29), whereas markedly lower values were observed in both the diminished ovarian reserve group (0.6 ng/mL, IQR: 0.4–0.9; 5 follicles, IQR: 4–7) and the multifactorial female infertility group (0.8 ng/mL, IQR: 0.5–1.6; 6 follicles, IQR: 4–10). (Table 2).

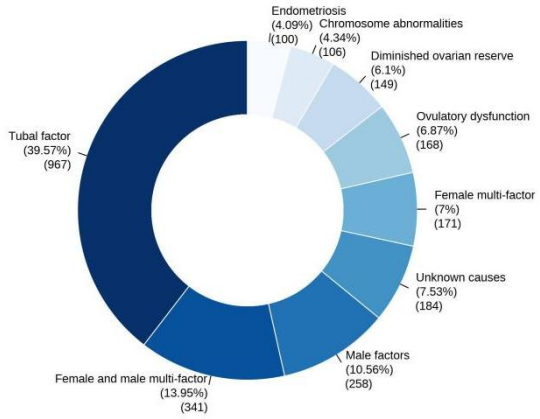


Figure 1

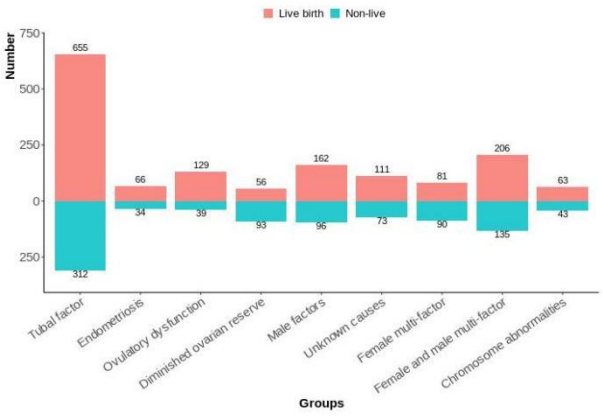


Figure 2

Treatment and laboratory data

Patients with infertility due to diminished ovarian reserve had the highest initial dosage of ovarian stimulation medication, at 225 (188–225) IU, which was significantly higher than that in patients with infertility of other etiologies (P<0.001). This was followed by patients with female multifactorial infertility and those with infertility due to chromosomal disorders, with initial dosages of 200 (150–225) IU and 188 (150–225) IU, respectively, and no statistically significant difference was noted between these two groups (P>0.05). The initial dosages in patients with female multifactorial infertility and chromosomal disorder-related infertility were significantly higher than those in

patients with infertility due to ovulatory dysfunction, unexplained causes, male factors, tubal factors, and endometriosis (P<0.001).

Patients with infertility due to chromosomal disorders had the shortest duration of ovarian stimulation, at 10 (9–12) days; those with infertility of other etiologies had ovarian stimulation duration of 11 to 12 days. A statistically significant difference was observed in the duration of ovarian stimulation among patients with infertility of different etiologies (P<0.001).Patients with diminished ovarian reserve had the highest total dose of follicle-stimulating hormone (FSH), at 2475 (2075–2850) IU, whereas those with ovulatory dysfunction had the lowest, at 1875 (1550–2250) IU. A statistically significant difference was found in the total dosage of ovarian stimulation medication among patients with infertility of different etiologies (P<0.001).

Patients with diminished ovarian reserve had the lowest estrogen (E2) and progesterone (P) levels on HCG trigger day, at 1389 (899-2149) pg/mL and 1.0 (0.7-1.5) ng/mL, respectively. The highest estrogen levels were observed in the ovulatory dysfunction group, while the highest progesterone levels were seen in patients with chromosomal abnormalities at 1.4 (1.0-2.0) ng/mL. Comparisons of E2 and P levels on HCG trigger day among patients with different causes of infertility showed statistically significant differences (P<0.001).

Patients with ovulatory dysfunction retrieved the highest number of retrieved oocytes (15 [10-21]); followed by those with chromosomal abnormalities and male factor infertility (both 12 [8-16]); patients with diminished ovarian reserve retrieved the lowest number (5 [2-7]). Patients with diminished ovarian reserve had significantly fewer retrieved oocytes than those with other causes of infertility, while those with ovulatory dysfunction had significantly more retrieved oocytes than other groups. Intergroup comparisons showed statistically significant differences (P<0.001). There were no statistically significant differences in cleavage rates or high-quality embryo formation rates among patients with different etiologies (P>0.05) Table 2.

Table 2 Clinical, treatment, and laboratory characteristics of patients with different infertility etiologies

Parameters(N)	Tubal factor (967)	Endometriosis (100)	Ovulatory dysfunction (168)	Diminished ovarian reserve (149)	Male factors (258)	Unknown causes (184)	Female multi-factor (171)	Female and male multi-factor (341)	Chromosomal disease (106)	*P* value
Female age	31.6±3.95	31.7±3.55	30.4±3.51	35.4±4.99	31.0±4.10	32.5±3.96	34.0±4.39	32.6±4.26	32.1±4.03	<0.001
Fertility duration(year)	3(2-5)	3(2-5)	3(2-5)	3 (2-6)	3(2-5)	3(2-5)	4(2-6)	3.5(2-6)	1(1 -3)	<0.001
BMI(kg/m²)	22(20-24.2)	20.75(19.6-22.5)	22.9(20.8-25.4)	21.2(19.6 -24.2)	21.6(19.9-23.5)	21.6(20.2-23.6)	22.2(20.2-24.7)	22.2(20.5-24.9)	21.6(19.9 -23.4)	<0.001
AMH(ng/mL)	2.5 (1.5 -4.0)	2.1 (1.5 -3.8)	5.9 (3.4 -10.1)	0.6 (0.4 -0.9)	2.9 (1.6 -4.2)	2.2 (1.5 -3.5)	0.8 (0.5 -1.6)	2.2 (1.0 -3.9)	2.6 (1.4 -3.7)	<0.001
AFC	13(10-18)	11(8-16)	23(18.5-29)	5(4-7)	14(11-18)	12(10-16)	6(4-10)	12(7-17)	13(10-18)	<0.001
Gn starting dosage	150(150-188)	150(150-188)	150(150-188)	225(188-225)	150(150-200)	156(150-200)	200(150-225)	175(150-225)	188 (150-225)	<0.001

Parameters(N）	Tubal factor (967)	Endometriosis (100)	Ovulatory dysfunction (168)	Diminished ovarian reserve (149)	Male factors (258)	Unknown causes (184)	Female multi-factor (171)	Female and male multi-factor (341)	Chromosomal disease (106)	*P* value
Total duration of Gn used	12(11-13)	12(10-13)	11(10-12)	11(10-13)	11(10-113)	11(10-13)	12(10-14)	11(10-13)	10(9-12)	<0.001
Total dosage of Gn used	2075(1725-2484)	1950(1700-2475)	1875(1550-2250)	2475(2075-2850)	2000(1700-2450)	2025(1675-2450)	2450(2000-3169)	2225(1800-2638)	2025(1688-2363)	<0.001
HCG trigger day E2(pg/mL）	3266(2019-4649)	3038(2056-4171)	3753 (2321-5732)	1389 (899-2149)	3224(2037-4711)	3024 (1945-4387)	1719 (1106-2907)	2579(1534-4304)	2925(2301-4474)	<0.001
HCG trigger day P(ng/mL）	1.2 (0.9 -1.8)	1.3 (0.9 -1.7)	1.2 (0.8 -1.7)	1.0 (0.7 -1.5)	1.2 (0.9 -1.8)	1.2 (0.8 -1.7)	1.1 (0.8 -1.6)	1.2 (0.8 -1.6)	1.4 (1.0 -2.0)	<0.001
Number of oocytes retrieved	11(8-15)	10(7-15)	15(10-21)	5(2-7)	12(8-16)	11(8-14)	6(4-10)	10(6-14)	12 (8 -16)	<0.001
Cleavage rate	0.83 (0.67-0.94)	0.83 (0.67-1.00)	0.82 (0.71-0.92)	0.86 (0.65-1.00)	0.71 (0.57-0.86)	0.80 (0.67-0.93)	0.83 (0.71-1.00)	0.80 (0.61-0.93)	0.48 (0.27-0.60)	0.146
High-quality embryo rate	0.43 (0.22-0.62)	0.44 (0.16-0.67)	0.46 (0.30-0.59)	0.50 (0.00-0.62)	0.40 (0.20-0.60)	0.40 (0.23-0.59)	0.50 (0.13-0.67)	0.42 (0.20-0.67)	0.6(0.33-0.8)	0.935

Transplantation outcomes

Comparison of first transplantation outcomes

The first-cycle pregnancy outcomes among patients with different etiologies of infertility showed significant differences in chi-square tests (χ^2=51.37, P<0.001). Patients with ovulatory dysfunction had the highest clinical pregnancy rate (63.7%) after the first embryo transfer, followed by those with tubal factors (57.3%), male factors (57.0%), and combined factors (54.0%). Patients with diminished ovarian reserve achieved only a 32.9% clinical pregnancy rate at first transfer, significantly lower than those with ovulatory dysfunction, tubal factors, male factors, or combined factors (P<0.001), and also lower than those with chromosomal abnormalities or endometriosis (P<0.05). Patients with ovulatory dysfunction and tubal factors demonstrated superior first-cycle clinical pregnancy rates compared to those with multifactorial female infertility P<0.05 (Table 3).

Table 3 First-cycle embryo transfer outcomes and cumulative live birth outcomes by infertility etiology

Cause of infertility(N）	Outcomes in the first embryo transfer			cumulative live birth rates	
	Non-pregnancy	Biochemical pregnancy	Clinical pregnancy	Non-live	Live birth
Tubal factor(967)	330(34.13%)	83(8.6%)	554(57.3%)	312(32.3%)	655(67.7%)
Endometriosis(100)	33(33.00%)	14(14.0%)	53(53.0%)	34(34.0%)	66(66.0%)
Ovulatory dysfunction(168)	47(27.98%)	14(8.3%)	107(63.7%)	39(23.2%)	129(76.8%)
Diminished ovarian reserve(149)	88(59.06%)	12(8.1%)	49(32.9%)	93(62.4%)	56(37.6%)
Male factors(258)	85(32.95%)	26(10.1%)	147(57.0%)	96(37.2%)	162(62.8%)

Unknown causes(184)	72(39.13%)	16(8.7%)	96(52.2%)	73(39.7%)	111(60.3%)
Female multi-factor(171)	81(47.37%)	14(8.2%)	76(44.4%)	90(52.6%)	81(47.4%)
Female and male multi-factor(341)	128(37.54%)	27(7.9%)	186(54.5%)	135(39.6%)	206(60.4%)
Chromosomal disease(106)	36(33.96%)	13(12.3%)	57(53.8%)	43(40.6%)	63(59.4%)
Overall	900(36.82%)	219(9.0%)	1325(54.2%)	915(37.4%)	1529(62.6%)
χ^2		51.37		84.12	
P value		<0.001		<0.001	

Comparison of cumulative live birth rates

The distribution of cumulative live birth outcomes differed significantly across etiological groups ($\chi^2 = 84.12$, $P < 0.001$). The highest cumulative live birth rate was observed in patients with ovulatory dysfunction (76.8%), followed by tubal factor infertility (67.7%), endometriosis (66.0%), and male factor infertility (62.8%). In contrast, substantially lower rates were observed in patients with diminished ovarian reserve (37.6%) and chromosomal abnormalities (47.4%).

Relationship between first transplantation outcome and final live birth

The cumulative live birth rate (CLBR) among patients achieving clinical pregnancy after the first embryo transfer was significantly higher than that in the biochemical pregnancy and non-pregnancy groups ($P<0.05$). Comparing cumulative live births between patients who did not achieve pregnancy after the first transfer and those who experienced biochemical pregnancy loss showed no statistically significant difference ($P>0.05$) shown in Table 4.

Table 4 Cumulative live birth outcomes by first embryo transfer result

Outcomes in the first embryo transfer	Live birth (n, %)	Non-live (n, %)
Non-pregnancy	285(18.6%)	615(67.2%)
Biochemical pregnancy	80(5.2%)	139(15.2%)
Clinical pregnancy	1164(76.1%)	161(17.6%)
χ^2	791.8	
P value	<0.001	

Survival analysis of live birth rate and time to live birth (TTLB）

Patients with ovulatory dysfunction maintained the highest CLBR between 12 and 30 months post-retrieval, rising from 56.55% to 75.00%. Patients with tubal factors followed, with a cumulative live birth rate of 49.22% at 12 months post-retrieval, increasing to 66.91% at 30 months. Cumulative live birth rates at 12 months post-retrieval for unexplained, multifactorial, male factor, and endometriosis-related infertility patients were 46.20%, 44.57%, 44.19%, and 44.00%, respectively, increasing to 60.33%, 60.12%, 62.40%, and 66.0% at 30 months. The time required for 50% of couples to achieve live birth varied across etiological groups: 11 and 13 months for ovulatory dysfunction and tubal factor infertility, respectively; 14 months for endometriosis and male factor infertility; 15 months for unexplained and

multifactorial infertility; and 22 months for chromosomal abnormalities. Kaplan-Meier survival analysis revealed significant differences in TTLB among different etiological groups (Log-rank χ^2=82.49, P<0.001) (Table 5, Figures 3&Figures 4).

Table 5 Kaplan-Meier analysis of TTLB in patients with different infertility etiologies

Groups	Cumulative live birth rate				Median-TTLB(95% CI)	*P*
	12-month	18-month	24-month	30-month		
Tubal factor	49.22	61.32	65.15	66.91	13(11.95-14.05)	<0.001
Endometriosis	44.00	64.00	66.00	66.00	14(11.55-16.45)	
Ovulatory dysfunction	56.55	67.86	73.21	75.00	11(10.18-11.82)	
Diminished ovarian reserve	26.85	31.54	36.24	37.58		
Male factors	44.19	57.75	61.63	62.40	14(11.75-16.25)	
Unknown causes	46.20	54.89	59.24	60.33	15(10.57-19.43)	
Female multi-factor	30.99	42.11	45.03	46.78		
Female and male multi-factor	44.57	57.18	59.53	60.12	15(12.49-17.51)	
Chromosomal disease	12.26	42.45	54.72	55.66	22(17.09-26.91)	

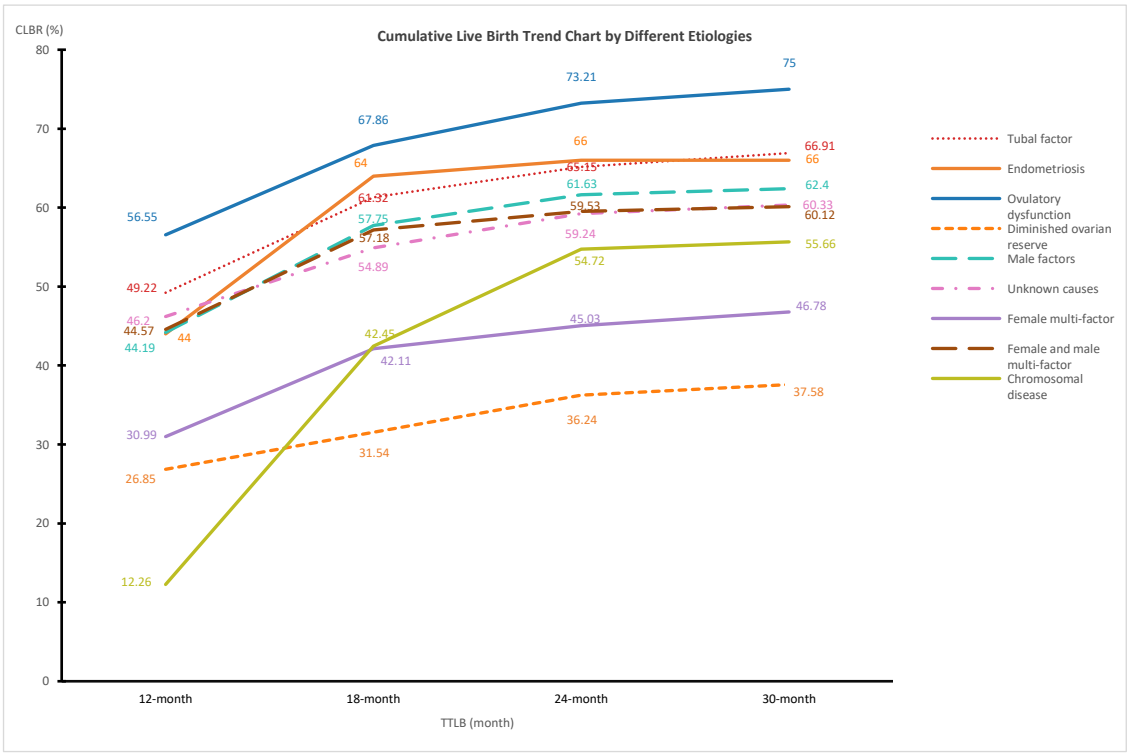


Fig 3

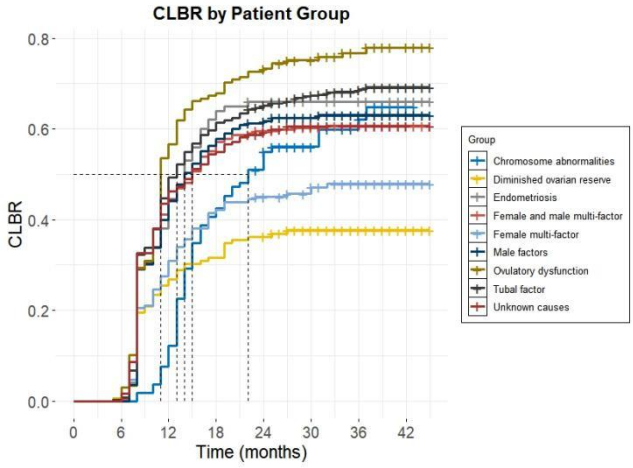


Fig 4(a)

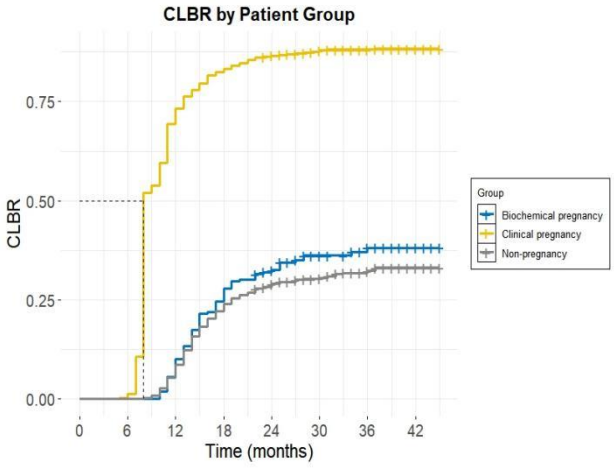


Fig 4(b)

Discussion

The clinical outcomes of ART are influenced by multiple factors, including patient age, duration of infertility, etiology of infertility, embryo quality, hormone profile, and treatment related strategies [10, 13, 14]. Among these variables, infertility etiology is an important contributor to the heterogeneity of ART outcomes [11, 12]. In this study, we systematically evaluated the clinical characteristics, first-cycle pregnancy outcomes, CLBR, and TTLB differences among 9 distinct etiological groups of ART patients based on a large single-center retrospective cohort of 2,444 cases. Our findings provide clinically relevant evidence regarding the influence of infertility etiology on reproductive efficiency and may help guide individualized treatment strategies.

Correlation analysis between baseline characteristics and infertility etiology

Analysis of etiological composition and clinical characteristics

The majority of patients in this study were aged 29–35 years, consistent with the age profile of assisted reproductive populations in China [15, 16] although slightly younger than populations reported in developed countries. This discrepancy may reflect variations in cultural background, fertility policies, and reproductive behavior. Previous studies have confirmed that female age is a key factor influencing ovarian reserve capacity and drug response. Datta et al.[17]demonstrated that among women aged 35-39 undergoing ART, live birth rates gradually decreased with increasing male age, whereas live birth rates in younger and older female groups were independent of male age. Male age was not specifically evaluated in the present study and warrants further investigation in future analyses.The distribution of infertility etiologies varies substantially across countries and regions[18]. This study revealed that among patients treated at the Reproductive Medicine Center of the First Affiliated Hospital of Army Medical University, tubal factors accounted for the highest proportion of infertility cases (39.57%), while male-female combined factors accounted for

13.95% and male-only factors for 10.56%. Pelvic inflammatory disease and tubal inflammatory damage were the predominant contributors to female infertility, consistent with findings by Tian Tian[18] and Guo Huiping [11]from domestic multicenter studies. However, this pattern differs from reports from Western countries, where male factor and unexplained infertility are more prevalent[19], potentially reflecting variations in disease spectrum, diagnostic capabilities, and reproductive attitudes across regions. It should be noted that in this study, couples with male non-obstructive azoospermia who underwent donor insemination and had female-factor infertility were not counted as male-factor infertility.Therefore, the actual proportion of male-factor infertility in clinical practice may be underestimated. Furthermore, the data in this study were collected from patients undergoing their first assisted reproductive treatment between 2021 and 2022. Given the evolving socioeconomic pressures and environmental pollution in recent years, the composition of infertility causes may shift over time, highlighting the need for long-term surveillance of infertility trends. In the study by Guo Huiping[11]secondary infertility was the predominant type of infertility. In contrast, primary and secondary infertility were nearly equally distributed in our study (49.8% vs. 50.2%), which may be attributed to differences in the study region, sample size, and inclusion criteria. Significant variation in infertility etiology was observed according to infertility type: ovulatory disorders, male factors, and unexplained infertility were more commonly associated with primary infertility; the proportions of primary and secondary infertility were similar in patients with endometriosis; tubal factors, diminished ovarian reserve, multiple female factors, and chromosomal disorders were more frequently related to secondary infertility. Patients with multiple contributing factors or diminished ovarian reserve had longer infertility duration, which may be associated with the high complexity of these conditions and irreversible ovarian aging. Patients with chromosomal disorders mostly presented with secondary infertility and had the shortest duration of infertility. This may be due to the limited popularity of chromosomal screening, as most patients are diagnosed with chromosomal abnormalities only after spontaneous abortion. These findings are consistent with those of Zhu et al.[8]and many such patients subsequently proceed directly to preimplantation genetic testing (PGT).

Our study revealed that patients with endometriosis had a significantly lower BMI than those with other etiologies, which may be related to chronic inflammatory burden and altered metabolic status [20]. Low BMI can reduce estrogen synthesis derived from adipose tissue, thereby impairing endometrial receptivity and embryo implantation. Obesity, on the other hand, interferes with endometrial repair [20, 21], which is also detrimental to embryo implantation. In this study, patients with endometriosis showed lower estrogen levels and higher progesterone levels on the day of hCG trigger, which may be associated with the use of non-steroidal aromatase inhibitors (letrozole) during controlled ovarian hyper stimulation[22]. Bonavina [21] suggested that these findings were related to decreased expression of P450 aromatase, a

key enzyme for estrogen synthesis, and abnormal progesterone secretion in granulosa cells of women with endometriosis, which further affect oocyte maturation[23, 24].

In the present study, patients with ovulatory disorders were predominantly diagnosed with polycystic ovary syndrome (PCOS), and had the highest BMI (22.9 kg/m²) and a relatively young mean age. Their AFC, AMH levels, and number of oocytes retrieved were significantly higher than those of other groups, with a lower total Gn dosage and the highest E2 level on the day of hCG trigger, which was consistent with the results of Ni et al[25].The high number of oocytes retrieved and favorable blastocyst formation rate in patients with ovulatory disorders provided more opportunities for subsequent frozen embryo transfer, which may have contributed to the high clinical pregnancy rate pregnancy rate in the first transfer and cumulative live birth rate. The multiple female-factor group included some patients with diminished ovarian function. Therefore, this group showed similar ovarian response and reserve-related indicators (AFC, AMH, number of oocytes retrieved, etc.) to the group with diminished ovarian reserve, both characterized by decreased AFC and AMH, increased initial and total Gn dosage, lower estrogen level on the day of hCG trigger, and lower oocyte retrieval rate. These findings were consistent with the study by Wang et al[12], and the above characteristics were related to reduced ovarian responsiveness associated with declining ovarian reserve. These findings indicate that infertility etiology is closely associated with baseline reproductive characteristics and may partly explain subsequent differences in ART outcomes.

Impact of infertility etiology on first embryo transfer outcomes and cumulative live birth rate

The present study showed that patients with ovulatory disorder-related infertility had the highest first-transfer clinical pregnancy rate (63.7%), and their cumulative live birth rate (76.8%) was also significantly higher than that of patients with other etiologies. This is associated with the higher number of oocytes retrieved and greater availability of high-quality embryos in the ovulatory disorder group, which was predominantly composed of patients with PCOS. These findings are consistent with those reported by Tannus et al.'s[26]study, who reported that after hormonal optimization with ovulation-inducing treatment, patients with PCOS had a higher number of retrieved oocytes, a higher proportion of high-quality embryos, and a higher blastocyst formation rate than patients with other infertility etiologies. Additionally, patients with PCOS had a higher proportion of blastocyst transfer cycles, and both first-transfer clinical pregnancy rate and cumulative live birth rate were significantly higher than those of the control group. In the present study, patients with multiple female factors and diminished ovarian reserve had lower first-transfer clinical pregnancy rates and less favorable live birth outcomes. The cumulative live birth rates in patients with chromosomal disorders and unexplained infertility were 59.4% and 60.3%, respectively, which were higher than those observed in patients with multiple female factors (47.4%) and diminished ovarian reserve (37.6%). The low live birth rates observed in patients

with multiple female factors and diminished ovarian reserve may be associated with advanced maternal age, poor ovarian response, and fewer retrieved oocytes, reduced oocyte quality, and increased embryonic aneuploidy rates [8]. Although the cumulative live birth rate of patients with male factors infertility (62.8%) was lower than in patients with ovulatory disorders and tubal factor infertility, it was still higher than that of patients with chromosomal disorders and diminished ovarian reserve. This may reflect that infertility caused by a single predominant factor is more amenable to correction through ART than infertility involving multiple concurrent factors. The lower live birth rate in the multiple female-factor group may also be associated with concurrent metabolic abnormalities, immune dysfunction, and other conditions that impair embryo implantation, highlighting the potential value of multidisciplinary management [27].

Impact of infertility etiology on TTLB

The present study found that, at 12 months after oocyte retrieval, patients with ovulatory disorders, tubal factor infertility, and unexplained infertility demonstrated relatively favorable cumulative live birth rates of 56.55%, 49.22%, and 46.20%, respectively. At 18 months after oocyte retrieval, the CLBR in patients with endometriosis increased markedly from 44.0% at 12 months to 64.0%, and plateaued at 66.0% after 24 months, which was slightly higher than the 65.15% observed in patients with tubal factors infertility. This may be related to the altered pelvic microenvironment in patients with endometriosis, which may adversely affect early embryo transfer outcomes [12]. Many patients may require targeted interventions (such as medical or surgical treatment) after oocyte retrieval in the fresh cycle, thereby prolonging treatment duration. However, favorable live birth outcomes may subsequently be achieved through frozen embryo transfer following standardized treatment. In addition, a study by Zhu et al.[28] Pointed out that the CLBR of patients with endometriosis is also closely related to factors such as age, duration of infertility, and endometriosis stage, therefore requiring comprehensive individualized evaluation.

Patients with tubal factor infertility may ultimately achieve relatively high live birth rates through repeated embryo transfer attempts. For patients with simple male factors, multiple female factors, and multiple factors in both partners, the cumulative live birth rate at 18 months increased substantially compared with that at 12 months (all increases >12 percentage points), and the subsequent increase was slow. Outcomes in patients with chromosomal abnormalities were less favorable within the first 18 months after treatment initiation but the cumulative live birth rate increased significantly from 18 to 24 months, which may partly reflect the embryo selection effect of PGT. Although PGT may reduce immediate embryo utilization efficiency and may require additional stimulation cycles in some patients, it may reduce miscarriage risk and the likelihood of transferring affected embryos, thereby potentially improving overall live birth efficiency, which is consistent with the research conclusion of Carson[27]et al.

Many patients with multiple female-factor infertility also present with diminished ovarian reserve, and their clinical data characteristics are highly consistent with those of patients with simple diminished ovarian reserve. These patients often have fewer retrieved oocytes and may require repeated oocyte retrieval cycles to accumulate embryos, thereby prolonging TTLB. For women older than 38 years with diminished ovarian reserve, earlier transition to IVF may be considered an appropriate treatment strategy. Mild stimulation protocols may help shorten treatment intervals and improve overall treatment efficiency in selected patients[27].

The present study found that there was no statistically significant difference observed in CLBR and TTLB between patients with biochemical pregnancy loss after the first transfer and those who did not achieve pregnancy. However, approximately half of the couples with biochemical pregnancy after the first transfer required less time to achieve live birth than those without pregnancy, which is consistent with the research results of Buhler et al[29]. Some studies have pointed out that biochemical pregnancy after the first transfer can reduce the abortion rate of subsequent clinical pregnancies and shorten the TTLB to a certain extent, suggesting that active clinical management may be considered for patients experiencing biochemical pregnancy to optimize subsequent treatment protocols.

ART outcomes are influenced not only by infertility etiology but also by several additional factors such as family income [30], couple's educational level[31], medical institution level, and treatment methods. A study by Toftager et al[32] pointed out that the CLBR after the first oocyte retrieval was comparable between the GnRH antagonist group and the GnRH agonist group, but the pregnancy and live birth time in the GnRH antagonist group was significantly shorter than that in the agonist group. These findings suggest that use of a GnRH antagonist protocol together with individualized gonadotropin dose adjustment may optimize ovarian response while shortening TTLB. Collectively, these findings indicate that infertility etiology influences not only the likelihood of live birth, but also the pace at which successful live birth may be achieved during ART treatment.

Conclusion

Assisted reproductive technology outcomes are closely associated with the underlying etiology of infertility. This study demonstrated significant differences in first-transfer pregnancy outcomes, CLBR, and TTLB among patients with different infertility etiologies undergoing ART treatment. Patients with ovulatory disorders had the most favorable treatment outcomes with the highest CLBR and the shortest TTLB; patients with endometriosis and tubal factor infertility showed intermediate outcomes; although patients with chromosomal abnormalities could achieve live birth, they generally required longer treatment duration and potentially greater financial burden; patients with diminished ovarian reserve had the least favorable prognosis, with the lowest CLBR and the longest TTLB.

These findings may help inform individualized treatment planning and patient counseling: for patients with ovulatory disorders, standard ovarian stimulation protocols may effectively utilize their favorable ovarian response to improve treatment efficiency; For patients with endometriosis, targeted medical or surgical management may optimize the pelvic environment and improve subsequent frozen embryo transfer outcomes; For patients with chromosomal abnormalities, PGT technology may be considered when clinically appropriate, and Adequate counseling and discussion of the potential time and financial demands of treatment are also important; For patients with diminished ovarian reserve or multiple female factors, earlier intervention and individualized stimulation strategies may help shorten treatment intervals and improve efficiency to reduce the treatment interval, while strengthening multidisciplinary management.

In addition, ART treatment may impose substantial financial burden particularly for older patients and those requiring multiple stimulation cycles or repeated embryo transfers, especially for elderly patients, patients with diminished ovarian function, and patients with multiple-factor infertility, who need multiple duration of ovarian stimulation and embryo transfers, resulting in a heavy personal burden. Improving treatment accessibility and financial support mechanisms may help reduce the economic and psychological burden on affected couples to reduce the economic and psychological burden of such infertile couples, such measures may facilitate timely treatment access and improve reproductive outcomes. Further prospective multicenter studies are warranted to validate these findings and refine etiology-specific treatment strategies.

Study Limitations and Future Directions

This study used a single-center retrospective design, which may have introduced selection bias and information bias. Potential confounding factors including embryo quality, ovarian stimulation duration, and embryo transfer timing, were not fully accounted for in the analysis. In addition, the influence of male-related factors such as paternal age and semen quality was not specifically evaluated. Although the overall sample size was relatively large, several etiological subgroups had limited sample sizes (e.g, approximately 100 cases in the endometriosis group), which may have reduced the statistical stability of subgroup analyses.

Future prospective multicenter studies with larger sample sizes are needed to incorporate a broader range of potential confounding variables to validate the findings of the present study and to further investigate the biological mechanisms through which infertility etiology may influence ART outcomes.

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