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ORIGINAL RESEARCH

Association of GnRH Agonist Pretreatment with Reproductive Outcomes in Women ≥35 years with Diminished Ovarian Reserve Undergoing Frozen Embryo Transfer: A Large Retrospective Cohort Study

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Purpose: This study aimed to assess whether different endometrial preparation regimens—natural cycle (NC), hormone replacement therapy (HRT), and gonadotropin-releasing hormone agonist pretreatment followed by HRT (GnRH-a + HRT)—are associated with differences in reproductive and perinatal outcomes among women with diminished ovarian reserve undergoing frozen embryo transfer (FET), and to evaluate whether age (<35 vs ≥35 years) modifies these associations.

Patients and Methods: A total of 4629 women with DOR, defined as anti-Müllerian hormone (AMH) <1.2 ng/mL and/or antral follicle count (AFC) <5, undergoing their first autologous FET between 2016 and 2024. Endometrial preparation protocols included natural cycle (NC), hormone replacement therapy (HRT), or gonadotropin-releasing hormone agonist (GnRH-a) pretreatment followed by HRT. Propensity score matching (PSM) and inverse probability of treatment weighting (IPTW) were applied to adjust for baseline differences.

Results: GnRH-a pretreatment before HRT was associated with improved live birth and clinical pregnancy compared with HRT alone, particularly among older women. No significant differences were observed between natural cycle and HRT. Perinatal outcomes among singleton live births were generally comparable across protocols.

Conclusion: GnRH-a pretreatment before HRT may be beneficial for women with diminished ovarian reserve undergoing FET, particularly in those of advanced maternal age.

Keywords: diminished ovarian reserve, frozen embryo transfer, endometrial preparation, GnRH agonist, pregnancy outcomes

Introduction

Diminished ovarian reserve (DOR) is characterized by a reduction in both the quantity and quality of ovarian follicles, most often diagnosed by low anti-Müllerian hormone (AMH) levels and/or a decreased antral follicle count (AFC).[1,2] Women with DOR exhibit impaired ovarian response to stimulation, reduced embryo competence, and ultimately lower live birth rates compared with age-matched counterparts with normal ovarian reserve.[3–5] As maternal age at childbearing continues to rise globally, the prevalence of DOR among patients seeking assisted reproductive technology (ART) has increased, posing a major challenge to reproductive medicine.[6–8] Despite advances in cryopreservation and the widespread use of frozen embryo transfer (FET), reproductive outcomes in this population remain unsatisfactory.[9–11]

Beyond its established impact on oocyte yield and embryo competence, DOR has also been associated with reduced live birth rates and adverse obstetric outcomes in assisted reproduction.[4,12,13] While these outcomes are often attributed to compromised oocyte quality, endometrial factors may also play a contributory role. Prior studies have demonstrated that variations in endometrial preparation protocols, as well as peri-transfer progesterone levels, significantly affect

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implantation and pregnancy and obstetric outcomes.[10,14,15] Overall, these observations raise the possibility that DOR may compromise reproductive outcomes through altered endometrial function.

Despite this, evidence guiding the choice of endometrial preparation regimen for FET in women with DOR remains scarce. In clinical practice, three main approaches are commonly used: natural cycle (NC), hormone replacement therapy (HRT), and gonadotropin-releasing hormone agonist (GnRH-a) pretreatment followed by HRT.[16] While NC preserves corpus luteum function and a physiologic endocrine environment, it requires close monitoring and is unsuitable for women with irregular ovulation.[17] HRT allows for greater flexibility in scheduling but lacks a corpus luteum, which may influence pregnancy outcomes.[18] GnRH-a pretreatment provides profound pituitary suppression to reduce premature ovulation and hormonal fluctuations, potentially improving embryo–endometrium synchronization.[19] However, whether these regimens exert differential effects in women with DOR remains uncertain.

Recent work suggests that, beyond oocyte quantity/quality, the choice of endometrial preparation may also shape outcomes in women with DOR; however, DOR-specific head-to-head evidence remains sparse. In a cohort of young DOR patients undergoing FET, pregnancy rates were lower than in women with normal reserve and exploratory data implicated endometrial aging; while NC, OI, HRT and GnRH-a+ HRT were used, no direct comparison across regimens was performed.[20] In the broader FET population, a large RCT reported higher live-birth and lower miscarriage/antepartum hemorrhage with NC versus HRT,[14] yet multicenter cohorts have yielded mixed findings for GnRH-a+ HRT versus HRT, with some suggesting benefit in selected contexts and others showing no advantage; moreover, several studies linked artificial cycles to higher obstetric risks in specific subgroups.[21–23] Taken together, current literature provides uncertain and partly contradictory signals and is rarely tailored to DOR—especially lacking age-stratified analyses covering both reproductive and perinatal outcomes across NC, HRT, and GnRH-a + HRT. Our study is designed to address this gap by directly comparing these regimens in women with DOR and by testing age as a potential effect modifier.

This study aimed to assess whether, among women with diminished ovarian reserve undergoing frozen-thawed embryo transfer, the endometrial preparation regimen—natural cycle (NC), hormone-replacement therapy (HRT), or gonadotropin-releasing hormone agonist pretreatment plus HRT (GnRH-a + HRT)—is associated with reproductive and perinatal outcomes, and whether age (≥35 vs <35 years) modifies these associations. It addresses the lack of DOR-specific, age-stratified head-to-head comparisons across these regimens that jointly evaluate reproductive and perinatal endpoints.

Materials and Methods

Patients

This study performed a single-center, retrospective cohort study at the Reproductive Medical Center of Tongji Hospital. Ethical approval was obtained from the Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (approval number TJ-IRB202404020). Given the retrospective design and use of de-identified data, the requirement for individual informed consent was waived by the committee. This study was conducted in accordance with the Declaration of Helsinki. Oocyte retrievals occurred between 2015 and 2024; all frozen–thawed embryo transfer (FET) cycles were conducted at our center from 2016 to 2024. Eligible participants were women with diminished ovarian reserve (DOR), defined as AMH < 1.2 ng/mL and/or AFC < 5, undergoing their first autologous FET and prepared with one of three standardized regimens: natural cycle (NC), hormone-replacement therapy (HRT), or gonadotropin-releasing hormone agonist pretreatment plus HRT (GnRH-a + HRT). This initial screening yielded DOR candidates (n=17820). Then we applied prespecified exclusions: uterine anomalies (n=3,881); preimplantation genetic testing or donor/frozen-banked oocytes (n=54; combined to avoid double counting); chromosomal abnormalities in either partner (n=307); endometriosis (n=1330); and missing critical data (n= 7619). After exclusions, the final analytic cohort included eligible cycles (n=4629), distributed across regimens as HRT (n=3547), GnRH-a + HRT (n=613), and NC (n=469).

All variables were retrieved from archival records at the Reproductive Medical Center of Tongji Hospital, including the institutional electronic medical record (EMR) and the assisted reproduction laboratory database. Structured queries using unique patient and cycle identifiers were used to extract demographics; ovarian reserve measures (AMH, AFC); stimulation and embryology records (in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) method, oocyte number, fertilization, embryo stage/quality); endometrial preparation regimen (NC, HRT, or GnRH-a + HRT) and luteal support; cycle-monitoring results; and pregnancy and obstetric outcomes. Records were de-identified prior to analysis. Data quality checks included duplicate detection, unit harmonization (eg, AMH in ng/mL), range and consistency checks, and cross-validation of key fields against the original case records.

Endometrial Preparation Protocols

All cycles were managed at a single center under uniform protocols, with the regimen selected jointly by the clinician and patient according to menstrual regularity and clinical context. In natural-cycle FET, monitoring began on cycle days 10–12 with transvaginal ultrasonography to track endometrial thickness and dominant follicle growth, alongside serum progesterone measurement; ovulation was defined by follicular collapse and/or a progesterone concentration above 5 ng/mL. Intramuscular progesterone for luteal support was started one day after confirmed ovulation, and embryo transfer was scheduled according to progesterone exposure, with cleavage-stage embryos transferred after three days and blastocysts after five days. In hormone-replacement cycles, oral estradiol valerate (Progynova, Bayer Schering Pharma) was initiated on cycle day 1 using a step-up schedule of 2 mg per day for days 1–4, 4 mg per day for days 5–8, and 6 mg per day for days 9–12; from day 13, endometrial thickness and anovulation were confirmed by ultrasound, the estradiol dose was adjusted to achieve an endometrium of at least 8 mm, and intramuscular progesterone 40 mg daily was commenced once this threshold was reached, with transfer timed to three or five days of progesterone exposure for cleavage-stage embryos or blastocysts, respectively. In cycles with gonadotropin-releasing hormone agonist pretreatment, a single depot of triptorelin or leuprorelin 3.75 mg was administered on menstrual day 2, followed approximately 28 days later by the same hormone-replacement regimen and transfer timing as described above. According to the standardized institutional protocol, luteal-phase support (LPS) was progesterone-based and continued through the first serum Human chorionic gonadotropin (hCG) pregnancy test (approximately 12–14 days after transfer); if positive, LPS was extended into early gestation. In hormone-replacement therapy FET cycles, exogenous progesterone was mandatory because no corpus luteum is present; in modified natural-cycle transfers, progesterone-based LPS was routinely provided. For statistical analyses, LPS regimens were categorized as vaginal gel plus oral dydrogesterone, vaginal suppository plus oral dydrogesterone, intramuscular progesterone plus oral dydrogesterone, or other single-route/uncommon combinations.

IVF and Embryology Procedures

Fertilization method (standard IVF, intracytoplasmic sperm injection, or rescue ICSI) was recorded. Embryos were cultured to the cleavage stage or to the blastocyst stage based on routine laboratory criteria. Cleavage-stage quality was assessed by cell number, fragmentation, and symmetry. Blastocysts were graded using the Gardner system. Vitrification and warming followed validated standard operating procedures with continuous quality control. The transfer stage and the number of embryos transferred were documented.[24,25]

Outcomes

In this study, we evaluated both pregnancy outcomes and perinatal outcomes. The primary outcomes were the live birth rate and the clinical pregnancy rate. Live birth was defined as the delivery of at least one live-born infant. Clinical pregnancy was defined as ultrasonographic visualization of an intrauterine gestational sac with fetal cardiac activity. A positive serum hCG test that did not progress to a clinical pregnancy was referred to as a biochemical pregnancy. Miscarriage was defined as spontaneous loss after sonographic confirmation of an intrauterine gestational sac. Ectopic pregnancy was defined as a confirmed extrauterine gestation by ultrasound or surgery. Multiple pregnancy was defined as the presence of two or more gestational sacs at the first viable scan.

Perinatal outcomes were evaluated among singleton live births only to minimize bias from vanishing twins and were counted once per woman. Recorded measures included gestational age at delivery (weeks) and birth weight (grams), mode of delivery (vaginal or cesarean), preterm birth (delivery before thirty-seven completed weeks), low birth weight (less than two thousand five hundred grams), and macrosomia (more than four thousand grams). Gestational diabetes mellitus was diagnosed by standard oral glucose tolerance testing, and hypertensive disorders of pregnancy were diagnosed according to the criteria of the International Society for the Study of Hypertension in Pregnancy. Major fetal malformation was recorded if documented before discharge. Outcome information was abstracted from electronic medical records and, when necessary, verified through standardized postpartum telephone follow-up and entered into the study database.

Statistical Analysis

Analyses were performed in R v4.5.1 and IBM SPSS Statistics 26. Descriptive statistics and group comparisons. Normality of continuous variables was assessed with the Shapiro–Wilk. Given non-normal distributions, continuous data are presented as median (IQR) and compared with Kruskal–Wallis tests; categorical data are n (%) and compared with χ^2 or Fisher's exact tests. Two-sided $p<0.05$ was considered statistically significant. To address treatment-selection bias, we conducted two prespecified pairwise matchings: NC vs HRT and GnRH-a + HRT vs HRT. Propensity scores (logistic regression) included age, Body-Mass Index (BMI), AMH, AFC, infertility duration, and infertility type. Nearest-neighbor matching without replacement (1:2 ratio; caliper 0.02 on the logit scale) was used; a sensitivity analysis for GnRH-a + HRT vs HRT applied a 0.01 caliper. Balance was judged by standardized mean differences (SMD<0.10), variance ratios, and empirical CDF metrics. Within matched sets (stratified by subclass ID), associations between regimen and each binary outcome were estimated using conditional logistic regression. We fit a hierarchy of models: (M0) exposure only; (M1) + age, BMI, AMH, AFC, infertility duration/type; (M2) M1 + endometrial thickness at transfer; (M3) M1 + number of embryos transferred; (M4) M1 + both thickness and embryo number. Effects are reported as odds ratios (OR) with 95% CIs and Wald P values; effective sample size and number of strata are provided per model. Multicollinearity was screened in an approximate unconditional model (VIF<5). Analyses used complete-case data per outcome; no imputation was performed.

Results

Baseline Characteristics of the Study Population

A total of 4,629 patients who met the inclusion and exclusion criteria for diminished ovarian reserve and underwent frozen embryo transfer were analyzed, including 469 in the NC group, 3,547 in the HRT group, and 613 in the GnRH-a + HRT group (Figure 1). Before propensity score matching, several baseline characteristics differed significantly among the three groups. As shown in Table 1, groups differed in Body-Mass Index (BMI) and AMH (both $p<0.050$), whereas age, AFC, Follicle-Stimulating Hormone (FSH), and the duration of infertility were comparable ($p>0.050$). The distribution of infertility diagnosis (primary vs secondary) and infertility etiology also differed across groups ($p<0.050$). Significant between-group differences were observed for estradiol on the trigger day, total gonadotropin dose, numbers of retrieved oocytes, MII oocytes, and 2PN zygotes, blastocyst formation rate, endometrial thickness at transfer, ovarian stimulation protocols, luteal phase support, and the distributions of embryos thawed and surviving (all $p<0.050$).

Propensity Score Matching and Covariate Balance

After matching, 458 patients in the NC group were matched to 912 patients in the HRT group, and 599 patients in the GnRH-a + HRT group were matched to 1,189 patients in the HRT group (Tables S1 and S2). Baseline characteristics were well balanced between the matched groups, with all standardized mean differences below 0.1.

Pregnancy Outcomes

In the matched cohort, conditional logistic regression showed that the GnRH-a + HRT group had a higher live birth rate than the HRT group (aOR=1.37, 95% CI 1.09–1.73, $p=0.008$) and a higher clinical pregnancy rate (aOR=1.41, 95% CI 1.14–1.76, $p=0.002$). The proportion of multiple pregnancies was also higher in the GnRH-a + HRT group (aOR=2.25, 95% CI 1.35–3.74, $p=0.002$). The proportions of miscarriage (aOR=1.21, 95% CI 0.86–1.71, $p=0.267$) and biochemical pregnancy (aOR=0.96, 95% CI 0.64–1.42, $p=0.822$) were comparable between the two groups (Table 2).

When comparing the NC and HRT groups, the live birth rate (aOR=0.94, 95% CI 0.71–1.26, $p=0.692$), clinical pregnancy rate (aOR=0.95, 95% CI 0.58–1.44, $p=0.669$), miscarriage rate (aOR=0.92, 95% CI 0.58–1.44, $p=0.701$), biochemical pregnancy rate (aOR=0.91, 95% CI 0.56–1.46, $p=0.684$), and multiple pregnancy rate (aOR=1.24, 95% CI 0.56–2.78, $p=0.601$) were broadly similar (Table 3).

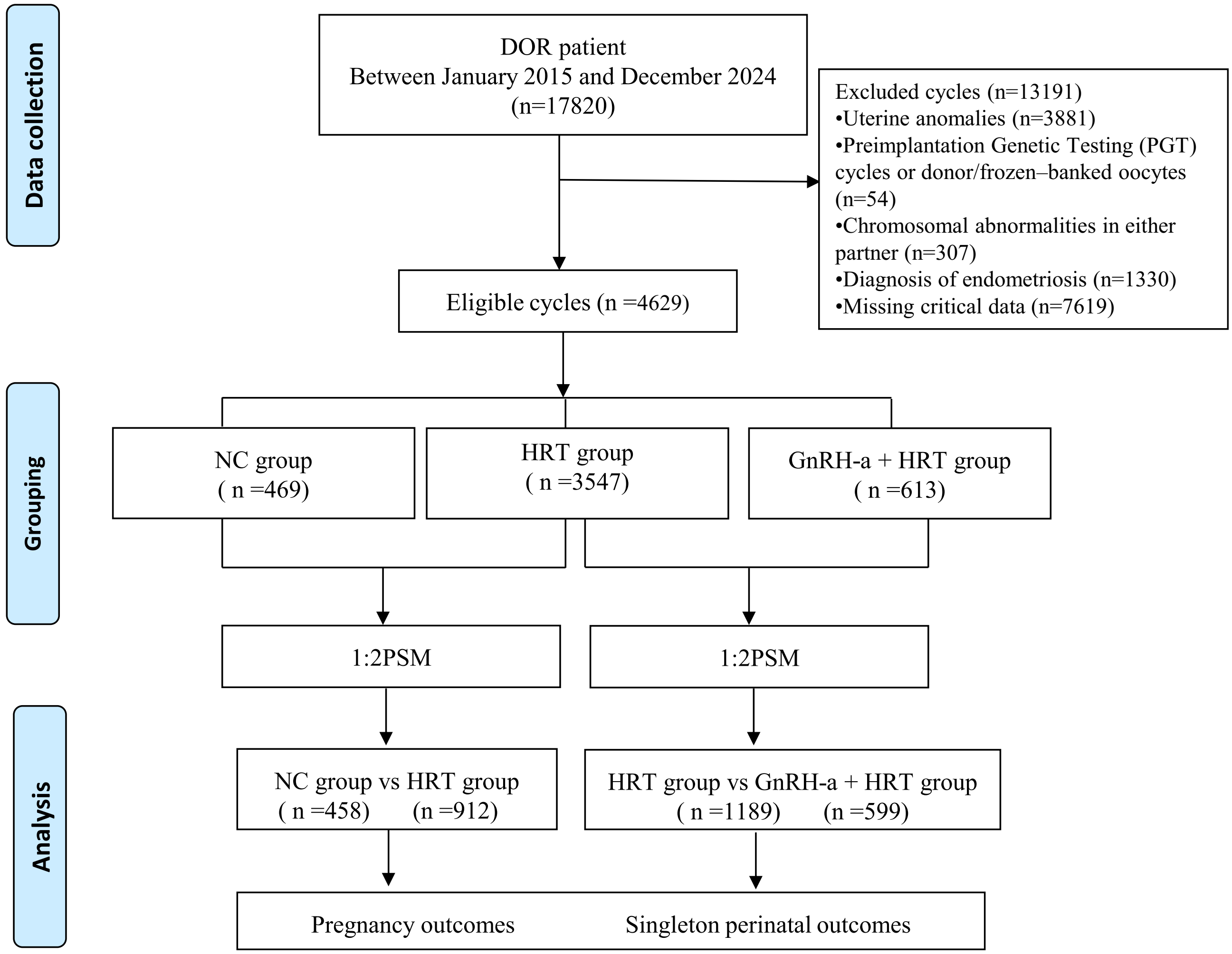

Figure 1 Patient selection, exclusions, and analytic cohorts for frozen–thawed embryo transfer (FET) cycles in women with diminished ovarian reserve (DOR).

Age-Stratified Analysis

In the cohort weighted by stabilized inverse probability of treatment (IPTW) with a protocol-by-age interaction (Table 4), age modified the association for selected outcomes. Among patients aged ≥35 years, GnRH-a + HRT was associated with

Table 1 Baseline Clinical and Cycle Characteristics with Different Endometrial Preparation Protocols

Variable	NC (N=469)	HRT (N=3547)	GnRH-a + HRT (N=613)	*p*
Age, y	36.00 (32.00–40.00)	35.00 (31.00–40.00)	35.00 (32.00–39.00)	0.104
BMI, kg/m2	21.76 (19.92–23.90)	22.03 (20.11–24.22)	21.53 (20.00–23.88)	0.030*
AFC	4.00 (3.00–6.00)	4.00 (3.00–6.00)	4.00 (3.00–6.00)	0.082
AMH level, ng/mL	0.84 (0.56–1.10)	0.86 (0.56–1.14)	0.91 (0.63–1.18)	0.011*
Duration of infertility, y	2.00 (1.00–5.00)	3.00 (1.00–5.00)	3.00 (1.00–5.00)	0.158
Duration of stimulation, d	9.00 (8.00–10.00)	9.00 (8.00–10.00)	9.00 (8.00–11.00)	0.066
FSH, mIU/mL	9.38 (7.45–12.05)	9.18 (7.27–11.87)	9.30 (7.41–11.47)	0.293
E2, pg/mL	1172.00 (777.00–1639.00)	1158.00 (768.00–1699.50)	1323.00 (884.00–1921.00)	<0.0001*
P	0.59 (0.41–0.92)	0.62 (0.40–0.95)	0.62 (0.42–0.95)	0.932
Endometrial thickness, mm	9.40 (8.30–10.70)	9.00 (8.40–9.90)	9.30 (8.50–10.60)	<0.001*
Gonadotropin dose, IU	2850.00 (2400.00–3450.00)	2850.00 (2362.50–3375.00)	3000.00 (2400.00–3600.00)	0.0004*

(*Continued*)

Table 1 (Continued).

Variable	NC (N=469)	HRT (N=3547)	GnRH-a + HRT (N=613)	p
No. of oocytes retrieved	5.00 (3.00–7.00)	5.00 (3.00–7.00)	6.00 (4.00–9.00)	<0.0001*
No. of MII oocytes	4.00 (3.00–6.00)	4.00 (3.00–6.00)	5.00 (3.00–7.00)	<0.0001*
No. of 2PN	3.00 (2.00–5.00)	3.00 (2.00–5.00)	4.00 (2.00–6.00)	<0.001*
Normal fertilization rate n (%)	75.00 (54.37–100.00)	75.00 (54.55–100.00)	72.73 (55.56–90.00)	0.511
Blastocyst formation rate n (%)	75.00 (50.00–100.00)	66.67 (42.86–100.00)	71.43 (50.00–100.00)	0.037*
Infertility diagnosis n (%)				0.027*
Primary infertility	384 (62.6%)	2017 (56.9%)	273 (58.2%)	
Secondary infertility	229 (37.4%)	1530 (43.1%)	196 (41.8%)	
Infertility etiology, n (%)				0.005*
Female factors	324 (69.1%)	2511 (70.8%)	459 (74.9%)	
Male factor	117 (24.9%)	855 (24.1%)	110 (17.9%)	
Unexplained/Other	28 (6%)	181 (5.1%)	44 (7.2%)	
Ovarian stimulation protocols, n (%)				0.003*
GnRH antagonist	225 (48%)	1497 (42.2%)	301 (49.1%)	
PPOS	178 (38%)	1520 (42.9%)	244 (39.8%)	
Other protocols	66 (14.1%)	530 (14.9%)	68 (11.1%)	
Luteal phase support, n (%)				<0.0001*
Vaginal gel administration and oral administration	159 (33.9%)	1655 (46.7%)	296 (48.3%)	
Vaginal suppository administration and oral administration	179 (38.2%)	1541 (43.4%)	300 (48.9%)	
Intramuscular injection and oral administration	40 (8.5%)	322 (9.1%)	12 (2%)	
Others	91 (19.4%)	29 (0.8%)	5 (0.8%)	
Fertilization, n (%)				0.488
ICSI	137 (29.2%)	1002 (28.2%)	185 (30.2%)	
IVF	322 (68.7%)	2436 (68.7%)	415 (67.7%)	
Rescue ICSI	10 (2.1%)	109 (3.1%)	13 (2.1%)	
No. of embryos thawed				0.003*
1	332 (70.9%)	2329 (66.1%)	402 (65.6%)	
2	131 (28%)	1129 (32%)	210 (34.3%)	
≥3	5 (1.1%)	68 (1.9%)	1 (0.2%)	
No. of surviving embryos				0.011*
1	333 (71.2%)	2342 (66.3%)	406 (66.4%)	
2	130 (27.8%)	1132 (32%)	204 (33.4%)	
≥3	5 (1.1%)	58 (1.6%)	1 (0.2%)	
No. of embryos transferred				0.121
1	338 (72.2%)	2393 (67.7%)	408 (67%)	
2	130 (27.8%)	1140 (32.3%)	201 (33%)	

Notes: Continuous variables are presented as median (first–third quartile) and compared with the Kruskal–Wallis test; categorical variables are n (%) and compared with the χ^2-test. *p* values reflect overall comparisons across the three groups. **p*<0.05.

Abbreviations: NC, natural cycle; HRT, hormone-replacement therapy; GnRH-a, gonadotropin-releasing hormone agonist; BMI, body mass index; AMH, anti-Müllerian hormone; AFC, antral follicle count; FSH, follicle-stimulating hormone; E2, estradiol; P, progesterone; Gn, gonadotropin; PPOS, progestin-primed ovarian stimulation; IVF, in vitro fertilization; ICSI, intracytoplasmic sperm injection; 2PN, two-pronuclear zygote; MII, metaphase-II oocyte.

Table 2 Comparison of Pregnancy Outcomes Between GnRH-a + HRT and HRT Cycles After Propensity Score Matching

Variable	GnRH-a +HRT	HRT	OR (95% CI)	p	aOR (95% CI)	p
Live Birth	190 (31.7%)	300 (25.2%)	1.37(1.11–1.71)	0.004*	1.37(1.09–1.73)	0.008*
Clinical Pregnancy	253 (42.2%)	407 (34.2%)	1.43(1.16–1.76)	< 0.001*	1.41(1.14–1.76)	0.002*
Miscarriage	60 (10.0%)	100 (8.4%)	1.22(0.87–1.70)	0.247	1.21(0.86–1.71)	0.267
Biochemical Pregnancy	43 (7.2%)	89 (7.5%)	0.95(0.65–1.39)	0.772	0.96(0.64–1.42)	0.822
Multiple pregnancy	38 (6.3%)	40 (3.4%)	1.90(1.21–3.00)	0.005*	2.25(1.35–3.74)	0.002*
Ectopic pregnancy	2 (0.3%)	3 (0.3%)				

Notes: ORs are from unadjusted conditional logistic regression in the matched sample (M0; univariate). aORs are from conditional multivariable logistic regression (M1). M1 adjusted for Age, BMI, AMH, AFC, duration of infertility, and infertility type. **p* <0.05.

Table 3 Comparison of Pregnancy Outcomes Between HRT Cycles and Natural Cycles After Propensity Score Matching

Variable	HRT	NC	OR (95% CI)	*p*	aOR (95% CI)	*p*
Live Birth	106 (23.1%)	223 (24.5%)	0.93(0.72–1.21)	0.609	0.94(0.71–1.26)	0.692
Clinical Pregnancy	140 (30.6%)	294 (32.2%)	0.93(0.73–1.18)	0.542	0.95(0.58–1.44)	0.669
Miscarriage	30 (6.6%)	65 (7.1%)	0.91(0.59–1.42)	0.657	0.915(0.58–1.44)	0.701
Biochemical Pregnancy	30 (6.6%)	66 (7.2%)	0.90(0.58–1.41)	0.183	0.91(0.56–1.46)	0.684
Multiple pregnancy	18 (3.9%)	24 (2.6%)	1.53(0.82–2.88)	0.999	1.24(0.56–2.78)	0.601

Notes: ORs are from unadjusted conditional logistic regression in the matched sample (M0; univariate). aORs are from conditional multivariable logistic regression (M1). M1 adjusted for Age, BMI, AMH, AFC, duration of infertility, and infertility type.

Table 4 Age-Stratified Comparisons of Pregnancy Outcomes Between GnRH-a + HRT and HRT Cycles

	<35		≥35	
	aOR (95% CI)	***p***	**aOR (95% CI)**	***p***
Live Birth	1.18(0.90–1.56)	0.228	1.44(1.09–1.95)	0.017*
Clinical Pregnancy	1.04(0.79–1.36)	0.017	1.50(1.15–1.96)	0.003*
Miscarriage	0.60(0.33–1.10)	0.096	1.42(0.98–2.05)	0.062
Multiple Pregnancy	1.23(0.68–2.24)	0.495	2.19(1.18–4.06)	0.013*
Ectopic Pregnancy	1.34(0.25–7.29)	0.737		
Biochemical Pregnancy	0.72(0.43–1.22)	0.228	1.32(0.82–2.11)	0.25

Notes: aORs are from a stabilized inverse probability of treatment–weighted (IPTW) multivariable logistic regression. The model included an interaction between endometrial preparation (GnRH-a + HRT vs HRT) and age group (<35 vs ≥35 years), and age-stratum–specific estimates are reported. Adjusted for BMI, AMH, AFC, infertility duration, infertility type, endometrial thickness, and number of embryos transferred. **p*<0.05.

higher odds of live birth (aOR=1.44, 95% CI 1.09–1.95; *p*=0.017), clinical pregnancy (aOR=1.50, 95% CI 1.15–1.96; *p*=0.003), and multiple pregnancy (aOR=2.19, 95% CI 1.18–4.06; *p*=0.013) compared with HRT. Among patients aged <35 years, no statistically significant differences were observed.

To aid clinical interpretation, IPTW-adjusted predicted rates indicated that in women ≥35 years, live birth was 22.98% with GnRH-a + HRT vs 17.09% with HRT (ARD +5.89 pp; NNT≈17), and clinical pregnancy was 35.58% vs 26.96% (ARD +8.62 pp; NNT ≈12). In women <35 years, absolute rates were numerically higher with GnRH-a + HRT but did not reach statistical significance, consistent with the OR findings (Tables S3 and S4).

Across sensitivity analyses that accounted for repeated cycles using IPTW-weighted GLMMs with a patient-level random intercept, the association of GnRH-a + HRT versus HRT among patients aged ≥35 years remained directionally consistent with the primary analysis—showing higher adjusted odds for live birth and clinical pregnancy—whereas no material differences were observed among patients aged <35 years, supporting the robustness of our findings (Table S5).

Singleton Perinatal Outcomes

For the GnRH-a + HRT vs HRT comparison, 160 and 265 singleton live births were analyzed, respectively. For the HRT vs NC comparison, 201 and 96 singleton live births were included. Gestational age and birth weight were comparable across protocols (Tables 5 and 6). In adjusted analyses of the matched cohort, GnRH-a + HRT and HRT showed similar odds for delivery mode, gestational diabetes, hypertensive disorders of pregnancy, preterm birth, low birth weight, macrosomia, and fetal malformation (all aORs near 1; *p*>0.05; Table 5). Likewise, adjusted comparisons between HRT and NC did not identify significant differences for these outcomes (all *p*>0.05; Table 6).

Overall, after covariate adjustment within the matched set, no between-protocol differences were observed in singleton obstetric or neonatal outcomes.

Table 5 Comparison of Obstetric and Perinatal Outcomes Between GnRH-a + HRT and HRT Cycles After Propensity Score Matching

Variable	GnRH-a + HRT	HRT	OR (95% CI)	p	aOR (95% CI)	p
Delivery mode			0.54 (0.23–1.25)	0.150	0.52 (0.22–1.24)	0.140
Natural labor	28/160 (17.5%)	49/265 (18.5%)				
Cesarean delivery	132/160 (82.5%)	216/265 (81.5%)				
Gender			0.96 (0.50–1.87)	0.910	1.05 (0.53–2.10)	0.890
Male	95/160 (59.4%)	154/265 (58.1%)				
Female	65/160 (40.6%)	111/265 (41.9%)				
Gestational diabetes mellitus	9/160 (5.6%)	12/265 (4.5%)		0.999		0.999
Hypertensive disorders of pregnancy	4/160 (2.5%)	9/265 (3.4%)		0.999		0.999
Low birth weight	9/160 (5.6%)	14/265 (5.3%)	0.50 (0.09–2.73)	0.423		0.997
Macrosomia	6/160 (3.8%)	11/265 (4.2%)		0.999		0.999
Fetal malformation	3/160 (1.9%)	3/265 (1.1%)		0.999		
Preterm birth	12/160 (7.5%)	23/265 (8.7%)	0.30 (0.06–1.47)	0.139	0.17 (0.02–1.49)	0.109
Birth weight, g	3300.00 (3000.00–3550.00)	3300.00 (3000.00–3540.00)		0.556		0.568
Gestational age	39.00 (38.00–39.61)	39.00 (38.14–39.43)		0.357		0.382

Notes: ORs are from unadjusted conditional logistic regression in the matched sample (M0; univariate). aORs are from conditional multivariable logistic regression (M1). M1 adjusted for Age, BMI, AMH, AFC, duration of infertility, and infertility type.

Table 6 Comparison of Obstetric and Perinatal Outcomes Between Natural Cycle and HRT Cycles After Propensity Score Matching

Variable	HRT	NC	OR (95% CI)	p	aOR (95% CI)	p
Delivery mode			0.71 (0.23–2.25)	0.566	0.87 (0.22–3.43)	0.839
Natural labor	35/201 (17.4%)	15/96 (15.6%)				
Cesarean delivery	166/201 (82.6%)	81/96 (84.4%)				
Gender			1.10 (0.47–2.60)	0.826	2.12 (0.62–7.31)	0.233
Male	114/201 (56.7%)	54/96 (56.2%)				
Female	87/201 (43.3%)	42/96 (43.8%)				
Gestational diabetes mellitus	7/201 (3.5%)	1/96 (1.0%)				
Hypertensive disorders of pregnancy	8/201 (4.0%)	5/96 (5.2%)				
Low birth weight	9/201 (4.5%)	4/96 (4.2%)	0.67 (0.11–3.99)	0.657	0.53 (0.07–3.99)	0.537
Macrosomia	7/201 (3.5%)	5/96 (5.2%)	1.00 (0.06–15.99)			0.999
Fetal malformation	2/201 (0.01%)	0/96 (0.0%)				
Preterm birth	12/201 (6.0%)	9/96 (9.4%)	0.30 (0.06–1.51)	0.145	0.44 (0.08–2.53)	0.354
Birth weight, g	3300.00 (3000.00–3500.00)	3300.00 (3000.00–3600.00)		0.979		0.979
Gestational age	39.00 (38.14–39.43)	38.93 (38.11–39.57)		0.160		0.154

Notes: ORs are from unadjusted conditional logistic regression in the matched sample (M0; univariate). aORs are from conditional multivariable logistic regression (M1). M1 adjusted for Age, BMI, AMH, AFC, duration of infertility, and infertility type.

Discussion

In this large, single-center retrospective cohort of DOR patients undergoing their first autologous FET, GnRH-a pretreatment before HRT was associated with significantly higher clinical pregnancy and live birth rates compared with HRT alone, whereas NC and HRT yielded broadly comparable outcomes. These findings suggest that GnRH-a–augmented regimens may offer advantages for selected DOR patients.

Previous clinical studies also support the potential benefit of GnRH-a pretreatment in specific subgroups.[26–29] Xu demonstrated that GnRH-a FET cycles achieved significantly higher clinical pregnancy and live birth rates compared with HRT, with greater benefit among women <40 years, those with primary infertility, PCOS, or irregular menstruation.[30] Our findings extend this evidence by identifying a distinct subgroup—women aged ≥35 years with DOR—who may also benefit from GnRH-a + HRT. Collectively, these results indicate that the effectiveness of GnRH-a pretreatment is context-dependent, varying with patient characteristics, and highlight the need for individualized protocol selection.[16,31]

In our matched analysis, NC and HRT yielded similar live birth and clinical pregnancy rates in women with DOR. This finding aligns with prior reports in broader infertile populations, such as the study by Agha-Hosseini, which showed no significant differences in reproductive outcomes between natural and artificial cycles when timing was well controlled.[32] Importantly, our study extends this evidence by demonstrating, for the first time, that these regimens also exhibit broadly equivalent efficacy in the specific context of diminished ovarian reserve.

Given baseline differences in BMI, the possibility that BMI modifies the response to GnRH-agonist pretreatment merits consideration. Future subgroup analyses and randomized evaluations should explicitly test BMI-by-regimen interactions to determine whether any apparent advantage of GnRH-a is concentrated among obese patients or extends across BMI strata. Because the "NC" protocol incorporated with progesterone-based luteal-phase support, it operationally corresponds to a modified natural cycle (mNC). Previous studies have reported broadly comparable outcomes between mNC and HRT in some cohorts, mixed findings regarding the incremental value of routine luteal support after mNC-FET—including a randomized trial reporting no clear benefit—and potential benefits of GnRH-a pretreatment in selected subpopulations, particularly those with elevated BMI.[33–36] These patterns support BMI-informed, protocol-specific counseling while acknowledging remaining uncertainty.[34] High-quality evidence focused specifically on women with diminished ovarian reserve remains limited; therefore, the present findings may be regarded as practice-informing yet provisional, pending confirmation in dedicated, adequately powered trials.

A plausible explanation for the superior outcomes with GnRH-a + HRT is that GnRH-a provides deeper and sustained pituitary suppression, thereby minimizing spontaneous ovulation ("escape ovulation") and late-follicular progesterone rise, which can result in embryo–endometrium asynchrony. Randomized trials have demonstrated that adding GnRH-a to artificial cycles effectively prevents spontaneous ovulation and improves cycle synchronization.[37] From a physiological perspective, GnRH-a downregulates pituitary LH and FSH secretion, preventing premature LH surges and providing a more stable endocrine environment for endometrial preparation.[16,38]

Beyond pituitary suppression, GnRH-a may also act on the endometrium. Endometrial GnRH receptors have been identified, and GnRH-a has been shown to modulate the expression of implantation-related molecules and local immune-inflammatory pathways, thereby enhancing receptivity.[39] This mechanism may be particularly relevant in older women with DOR. Traditionally, advanced maternal age has been viewed as a cause of reduced fertility mainly due to diminished ovarian reserve and increased embryo aneuploidy.[12] However, emerging evidence suggests that endometrial factors may also contribute. A systematic review in Human Reproduction Update highlighted that endometrial receptivity in women of advanced age is an underrated factor in infertility, with live birth rates significantly reduced in women ≥40 years even when donor oocytes or euploid embryos are used.[40]

Further molecular evidence comes from a recent study in Nature Aging, which demonstrated that endometrial aging is accompanied by H3K27ac and progesterone receptor (PGR) loss, both critical regulators of receptivity. Transcriptomic profiling of mid-secretory endometrium revealed impaired receptivity signatures in women aged ≥35 years, independent of embryo quality.[41] These findings provide mechanistic support that endometrial aging contributes to reproductive decline. Taken together, they suggest that GnRH-a pretreatment may partially counteract age-related endometrial changes, explaining why older DOR patients in our study appeared to derive greater benefit from this regimen.

In our pairwise matched comparisons of singleton live births, obstetric and neonatal outcomes were similar between GnRH-a + HRT and HRT, and likewise between NC and HRT. These findings are consistent with systematic reviews reporting no major differences in perinatal outcomes when endometrial preparation is adequately timed.[42] Nevertheless, emerging data suggest that programmed cycles lacking a corpus luteum may predispose women to hypertensive disorders of pregnancy and large-for-gestational-age infants compared with natural or modified-natural cycles.[43–46] While we did not detect such differences in our DOR cohort-possibly due to limited sample size—these signals underscore the need for continued attention to corpus luteum physiology as a determinant of perinatal health.

Another noteworthy finding was the higher incidence of multiple pregnancies in the GnRH-a + HRT group. This is likely attributable to treatment behavior, such as increased double embryo transfer in older women with perceived lower prognosis, rather than a direct pharmacological effect. Importantly, the higher multiple pregnancy rate observed in our cohort warrants caution in clinical decision-making, where feasible, single-embryo transfer should be prioritized, and patient counseling should explicitly balance potential benefits against the risks of multifetal gestation. Given the higher multiple-pregnancy rate observed with the GnRH-a–pretreated HRT protocol, interpretation of effectiveness should account for potential confounding by the number of embryos transferred. To disentangle biological effects of endometrial preparation from transfer practice, future research is best conducted under strict elective single-embryo transfer (eSET) or within SET-only cohorts. Under such conditions, protocol comparisons can prioritize per-transfer/per-embryo implantation, singleton live birth, and maternal–neonatal safety outcomes, enabling a fairer assessment of regimen-specific efficacy. Nevertheless, given the well-established maternal and neonatal risks associated with multiple gestation, our results emphasize the importance of eSET, consistent with ASRM and ESHRE guidance.[47,48]

The strengths of our study include a large, well-characterized DOR cohort, standardized laboratory conditions, and rigorous confounding control through propensity score matching and sensitivity analyses. Moreover, nearly complete baseline clinical and laboratory information was available for all patients, which allowed us to account for a wide range of potential confounders and thus minimized bias as much as possible.

Limitations must also be acknowledged. The retrospective design cannot completely eliminate residual confounding despite advanced statistical adjustment.[49] Several outcomes, such as ectopic pregnancy, were rare, limiting statistical precision. Furthermore, Regimen allocation was not randomized and was markedly imbalanced (HRT predominated), raising the possibility of treatment-selection bias. Although we used PSM and IPTW with balance diagnostics (SMD ≤ 0.10) and overlap/trimming sensitivity analyses, residual confounding cannot be excluded. Accordingly, we report propensity-adjusted estimates as primary. Moreover, potential mechanistic intermediates such as peri-transfer progesterone concentrations or molecular markers of endometrial receptivity were not systematically assessed.[50–52] Finally, as a single-center study, generalizability may be limited.

In conclusion, our findings suggest that GnRH-a pretreatment before HRT may improve pregnancy outcomes in women aged ≥35 years with DOR, potentially by counteracting age-related declines in endometrial receptivity, while NC and HRT confer comparable efficacy in younger patients. Protocol choice should be tailored to patient age, ovarian reserve, endometrial receptivity, monitoring feasibility, and corpus luteum physiology, with strict adherence to elective single embryo transfer to minimize risks from multiple gestation. Future multicenter prospective trials stratified by age and ovarian reserve are needed to validate these results and refine best-practice recommendations.

Conclusion

In this large retrospective cohort of DOR patients undergoing their first frozen embryo transfer, GnRH-a pretreatment combined with hormone replacement therapy was associated with higher clinical pregnancy and live birth rates, particularly in women aged ≥35 years, while natural and artificial cycles yielded broadly comparable efficacy. Obstetric and neonatal outcomes were similar across regimens. These findings suggest that age-related differences in endometrial receptivity may partly explain the greater benefit in older women. Endometrial preparation strategies should therefore be individualized according to patient age, ovarian reserve, and monitoring feasibility, with strict adherence to elective single embryo transfer. Prospective multicenter trials are needed to validate these age-specific effects and refine clinical practice.

Data Sharing Statement

The raw data underpinning the conclusions of this article will be made accessible by the authors without undue reservation. For further inquiries, please direct them to the corresponding author.

Ethics Approval and Informed Consent

Ethical approval was obtained from the Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (approval number: TJ-IRB202404020) with a waiver of individual informed consent due to the retrospective design and use of de-identified data. This study was conducted in accordance with the Declaration of Helsinki.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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