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ORIGINAL RESEARCH

Impact of GnRH Agonist Pretreatment on Frozen-Thawed Embryo Transfer Outcomes of Overweight/Obese Women Undergoing Hormone Replacement Therapy

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Background: Overweight and obesity are link to impaired endometrial receptivity and decreased pregnancy success in frozen-thawed embryo transfer (FET) cycles. Depot gonadotropin-releasing hormone agonist (GnRH-a) pretreatment before hormone replacement therapy (HRT) has been shown to improve endometrial function through multiple mechanisms. However, its efficacy in overweight and obese women remains unknown.

Methods: This retrospective cohort study analyzed 1968 FET cycles from a large fertility center in Jiangxi Province between January 2016 and December 2021. Overweight and obese women were defined as those with body mass index ≥24.0 kg/m^2 according to the Chinese criteria and categorized into HRT (n=946) and GnRH-a+HRT (n=1022) groups. The primary outcome measure was the live birth rate. Potential confounders were controlled by 1:1 propensity score matching (PSM) and multivariable logistic regression. Subgroup analysis was performed based on the status of dyslipidemia.

Results: After PSM, 539 women remained in each group with balanced baseline characteristics. The GnRH-a+HRT group demonstrated a significantly higher live birth rate compared to the HRT group (55.84% vs 49.35%, P=0.033). Similarly, women with GnRH-a pretreatment had higher rates of positive hCG test (77.18% vs 68.65%, P=0.002), clinical pregnancy (68.09% vs 60.48%, P=0.009), and implantation (52.41% vs 47.47%, P=0.039), whereas the miscarriage rate was no statistical difference between groups (17.71% vs 16.87%, P=0.771). In the dyslipidemia subgroup, the increased likelihood of live birth remained for the GnRH-a+HRT protocol (adjusted odds ratio [OR]: 1.75, 95% confidence interval [CI]: 1.08–2.85), but was not evident in the normolipidemia subgroup (aOR: 1.18, 95% CI: 0.87–1.58).

Conclusion: In summary, our study provides novel clinical evidence suggesting that GnRH-a pretreatment improves FET pregnancy outcomes in overweight and obese women compared to HRT alone, especially among those with dyslipidemia. The findings support a tailored approach for endometrial preparation in this population; however, further multicenter randomized controlled trials are needed for confirmation.

Keywords: dyslipidemia, frozen-thawed embryo transfer, gonadotropin-releasing hormone agonist, obesity, pregnancy outcomes

Introduction

Overweight and obesity have emerged as significant public health issues worldwide, with their prevalence rising steadily over the past few decades. According to the Global Burden of Disease Study 2021, an estimated 2.11 billion adults aged

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25 years and older are classified as overweight or obese, accounting for 45.1% of the total adult population.[1] In China, the prevalence of overweight/obesity among women of reproductive age (18–49 years) reached 27.1% in 2019.[2]

The negative reproductive effects of overweight and obesity are thoroughly documented.[3] For example, excess adiposity can disrupt the hypothalamic-pituitary-ovarian axis, leading to menstrual irregularity, ovulatory dysfunction, and reduced fecundity.[4] In the context of assisted reproductive technology, overweight and obesity have also been associated with a range of negative outcomes, including reduced ovarian response to stimulation, lower fertilization rate, decreased embryo quality, and diminished clinical pregnancy and live birth rates.[5–7] Importantly, even when transferring morphologically and chromosomally normal embryos, obese women still exhibit lower implantation success and higher miscarriage risk,[8–10] suggesting that impaired endometrial receptivity is a critical limiting factor for this population.

In frozen-thawed embryo transfer (FET) cycles, endometrial preparation is the key step to creating a receptive environment by timely regulating endometrium's growth and differentiation. A mainstream protocol is hormone replacement therapy (HRT) with sequential use of exogenous estrogen and progesterone.[11] This regimen is widely used due to its simplicity, flexibility, and broad applicability for women with or without ovulatory cycles. However, unplanned spontaneous follicular growth and ovulation can still occur at an incidence ranging from 1.9% to 7.4%.[12,13] To address this issue, depot gonadotropin-releasing hormone agonist (GnRH-a) pretreatment is used before HRT for pituitary suppression, thus minimizing endogenous hormonal fluctuations and theoretically facilitating endometrial-embryonic synchronization. While this approach has been shown to have comparable pregnancy outcomes with HRT alone in good-prognosis patients,[14,15] emerging evidence suggests that it may benefit those with reduced endometrial receptivity, such as intrauterine adhesion,[16] thin endometrium,[17,18] recurrent implantation failure,[19,20] and polycystic ovarian syndrome.[14] However, its effectiveness in overweight/obese women has not been systematically studied.

This study aims to evaluate the differences in pregnancy outcomes between HRT and GnRHa+HRT protocols in overweight/obese women undergoing FET cycles.

Methods

Study Design and Participants

This retrospective cohort study was conducted at the Center for Reproductive Medicine, Jiangxi Maternal and Child Health Hospital affiliated to Nanchang Medical College, in line with the Declaration of Helsinki. Ethical approval was obtained from the Ethics Committee of Jiangxi Maternal and Child Health Hospital (No. 2024–03-040). The requirement for individual written informed consent was waived by the committee, as the study involved only secondary analysis of de-identified data, and no direct patient contact or intervention occurred. All patient data were anonymized to ensure confidentiality.

Overall, 17192 HRT-FET cycles were screened from January 2016 to December 2021. All included women were aged between 20 and 40 years, were infertile due to fallopian tube and/or male factors, and had a body mass index (BMI) $\geq$24.0 kg/m^2 according to the Chinese criteria for overweight/obesity.[21] Exclusion criteria were: (1) congenital uterine anomalies including unicornuate, bicornuate, septate, or duplex uterus; (2) acquired uterine/endometrial diseases including endometriosis, adenomyosis, submucosal fibroid, intrauterine adhesion, or thin endometrium (<7 mm); (3) polycystic ovary syndrome or pathologic obesity caused by endocrine diseases (eg, Cushing's syndrome); (4) a history of recurrent miscarriage or recurrent embryo implantation failure; (5) use of donated gametes or presence of chromosomal abnormalities in either partner; (6) cycles with preimplantation genetic testing (PGT); and (7) lost to follow-up or core data missing. Cycles were also excluded in cases of spontaneous follicular growth during HRT. For patients with multiple FETs in the study period, only the first ones were included for analysis.

Endometrial Preparation Protocols

For the HRT protocol, endometrial preparation was initiated on the second or third day of the menstrual cycle. Patients received oral estradiol valerate (Progynova, Bayer, Germany) at a dose of 6 mg per day. Transvaginal ultrasound alongside serum progesterone measurements were performed weekly to monitor endometrial development and exclude unplanned folliculogenesis. Once the endometrium reached a minimum thickness of 7 mm and serum progesterone levels

were below 1.5 ng/mL, patients were given 60 mg of intramuscular progesterone (Xianju Pharma, China) for secretory transformation.

For patients undergoing GnRH-a+HRT protocol, 3.75 mg of leuprorelin (Beiyi, Lizhu Pharma, China) was administered via intramuscular injection on menstrual day 2 or 3 preceding the FET cycle. Pituitary desensitization was confirmed 28 days later by transvaginal ultrasound and serum hormone assessment. The criteria included endometrial thickness <5 mm, follicle-stimulating hormone <5 mIU/mL, luteinizing hormone <5 mIU/mL, and estradiol <50 pg/mL. Endometrial preparation was then commenced using the exact dosages and monitoring schedule for estradiol and progesterone as in the standard HRT protocol. The decision to use GnRH-a pretreatment was not based on a medical indication but rather on a mutual agreement between physicians and patients, aiming to improve scheduling flexibility and reduce the risk of cycle cancellation.

Embryo Transfer and Luteal-Phase Support

Embryo vitrification and warming procedures were conducted using standardized commercial kits (Kitazato Biopharma, Japan), following protocols previously described.[22] High-quality embryos were defined as either cleavage-stage embryos graded as I–II with 7 to 10 blastomeres according to the Cummins criteria, or day 5 to 6 blastocysts with a morphological score of ≥4BB based on the Gardner and Schoolcraft grading system.[23,24] Up to two embryos were transferred per cycle. In cases involving cleavage-stage embryos, the transfer occurred on the fourth day after progesterone transformation, while blastocyst transfer occurred on the sixth day. This timing aligns with the theoretical day of oocyte retrieval, with the start of progesterone supplementation (P+0) corresponding to embryonic Day 0, thereby ensuring optimal synchronicity between the endometrial window of implantation and the embryo's developmental stage.[11] All transfers were performed under abdominal ultrasound guidance to ensure accurate embryo placement.

Luteal phase support was started from the day of embryo transfer, consisting of 90 mg daily of vaginal progesterone gel (Crinone, Merck Serono, Germany) and 20 mg daily of oral progesterone (Duphaston, Abbott Biologicals, Netherlands). Upon confirmation of pregnancy, estradiol supplementation was gradually reduced, whereas progesterone support was maintained until the 10th week of gestation.

Outcome Measures

The live birth rate per transfer cycle was designated as the primary outcome. Secondary outcomes included the positive hCG rate, clinical pregnancy rate, implantation rate, and miscarriage rate. A live birth was defined as the delivery of a viable infant at 28 weeks of gestation or later. A positive hCG test was defined as a serum β-hCG concentration of ≥5 IU/L measured 14 days after embryo transfer. Clinical pregnancy was confirmed by the ultrasound presence of a gestational sac regardless of fetal cardiac activity one-month post-transfer. The implantation rate was calculated as the ratio of observed gestational sacs to the total number of transferred embryos. A miscarriage was characterized as the spontaneous loss of a clinical pregnancy before reaching 24 weeks of gestation.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation (SD), and their normality was assessed using the Shapiro–Wilk test. Depending on the distribution, between-group comparisons were performed using either Student's *t*-test for normally distributed data or the Mann–Whitney *U*-test for non-normally distributed data. Categorical variables were presented as counts and percentages, and comparisons were made using the chi-squared test or Fisher's exact test, as appropriate.

To minimize potential selection bias and balance baseline characteristics between the HRT and GnRH-a+HRT groups, one-to-one propensity score matching (PSM) was conducted. Matching was performed using the nearest-neighbor algorithm without replacement, with a caliper width of 0.1 SD of the logit of the propensity score. The following variables were included in the PSM model as potential confounders: maternal age, BMI, antral follicle count, infertility duration, type and cause of infertility, controlled ovarian stimulation (COS) protocol, peak endometrial thickness during the COS cycle, number of oocytes retrieved, fertilization method, number of prior embryo transfer failures, duration of estradiol administration, number and stage of embryos transferred, transfer of high-quality embryos, and embryo

vitrification duration. Covariate balance before and after matching was visually assessed using histograms of the propensity score.

To further explore potential effect modification, subgroup analyses were conducted according to BMI category, with overweight (24.0–27.9 kg/m^2) and obesity (≥28.0 kg/m^2) defined based on Chinese criteria.[21] Given the significant impact of lipid metabolism on reproductive outcomes,[25–28] subgroup analyses were also performed among overweight and obese patients stratified by dyslipidemia status. According to the Chinese guideline,[29] dyslipidemia was defined as meeting one or more of the following criteria: serum triglycerides ≥1.70 mmol/L, total cholesterol ≥5.20 mmol/L, low-density lipoprotein cholesterol (LDL-C) ≥3.40 mmol/L, or high-density lipoprotein cholesterol (HDL-C) <1.00 mmol/L. Additionally, multivariate logistic regression analysis was used to estimate adjusted odds ratios (aORs) and 95% confidence intervals (CIs) for pregnancy outcomes in the GnRH-a+HRT versus HRT group, controlling for the same set of covariates used in the PSM procedure.

All data analyses were conducted using SAS version 9.4 (SAS Institute Inc., USA). A two-sided P-value of <0.05 was considered statistically significant.

Results

Baseline Characteristics

Table 1 presents the baseline characteristics of study participants grouped by endometrial preparation regimen. Before PSM, 1,968 women met the inclusion criteria, comprising 946 in the HRT group and 1,022 in the GnRH-a+HRT group. Patients in the GnRH-a+HRT group had an order age, a lower antral follicle count, a higher proportion of secondary infertility, and more prior times of embryo transfer failure. In the COS cycle, they were less likely to use a GnRH-a based protocol, with a decreased number of oocytes retrieved and thinner peak endometrial thickness. In the FET cycle, single and blastocyst-stage embryo transfers were more common in the GnRH-a+HRT group, and the embryos had a longer cryopreservation duration. After PSM, each group consisted of 539 women, and all characteristics were well-balanced with no significant differences (Table 1 and Figure 1).

Table 1 Baseline Characteristics Grouped by the Endometrial Preparation Regimen

Characteristics	Before PSM			After PSM		
	HRT (n = 946)	GnRH-a+HRT (n = 1022)	*P*-Value	HRT (n = 539)	GnRH-a+HRT (n = 539)	*P*-Value
Age (years)	31.07±4.41	32.26±4.23	<0.001	32.19±4.17	31.81±4.32	0.167
Body mass index (kg/m^2)	26.13±2.19	26.15±2.10	0.593	26.22±2.24	26.14±2.07	0.717
Antral follicle count	13.40±5.47	12.04±5.73	<0.001	12.8±5.33	12.48±5.84	0.200
Infertility duration (years)	4.79±3.33	4.79±3.17	0.560	4.8±3.45	4.65±3.14	0.938
Infertility type, n (%)			0.028			0.665
Primary	269 (28.44)	246 (24.07)		128 (23.75)	122 (22.63)	
Secondary	677 (71.56)	776 (75.93)		411 (76.25)	417 (77.37)	
Infertility diseases, n (%)			0.679			0.976
Tubal factor	662 (69.98)	710 (69.47)		374 (69.39)	377 (69.94)	
Male factor	106 (11.21)	127 (12.43)		64 (11.87)	62 (11.50)	
Tubal+male factors	178 (18.82)	185 (18.10)		101 (18.74)	100 (18.55)	
COS protocol in the fresh cycle, n (%)			<0.001			0.659
GnRH-a	799 (84.46)	752 (73.58)		419 (77.74)	409 (75.88)	
GnRH-ant	81 (8.56)	153 (14.97)		65 (12.06)	75 (13.91)	
Others	66 (6.98)	117 (11.45)		55 (10.20)	55 (10.20)	
Peak endometrial thickness in the COS cycle (mm)	10.85±2.44	10.55±2.72	0.005	10.57±2.48	10.74±2.72	0.512
No. of oocytes retrieved	15.03±7.58	12.93±7.47	<0.001	13.54±7.01	13.53±7.76	0.306

(*Continued*)

Table 1 (Continued).

Characteristics	Before PSM			After PSM		
	HRT (n = 946)	GnRH-a+HRT (n = 1022)	*P*-Value	HRT (n = 539)	GnRH-a+HRT (n = 539)	*P*-Value
Fertilization method, n (%)			0.243			0.672
IVF	730 (77.17)	765 (74.85)		407 (75.51)	417 (77.37)	
ICSI	179 (18.92)	223 (21.82)		107 (19.85)	102 (18.92)	
IVF+ICSI	37 (3.91)	34 (3.33)		25 (4.64)	20 (3.71)	
No. of prior embryo transfer failure, n (%)			<0.001			0.684
0	577 (60.99)	502 (49.12)		294 (54.55)	285 (52.88)	
1	340 (35.94)	412 (40.31)		218 (40.45)	221 (41.00)	
2	29 (3.07)	108 (10.57)		27 (5.01)	33 (6.12)	
Duration of estradiol use (days)	14.08±2.20	13.87±2.12	0.002	13.91±2.19	13.87±2.04	0.261
No. of embryos transferred, n (%)			0.007			1.000
Single	326 (34.46)	413 (40.41)		208 (38.59)	208 (38.59)	
Double	620 (65.54)	609 (59.59)		331 (61.41)	331 (61.41)	
Embryo stage at transfer, n (%)			<0.001			0.855
Cleavage	549 (58.03)	437 (42.76)		252 (46.75)	255 (47.31)	
Blastocyst	397 (41.97)	585 (57.24)		287 (53.25)	284 (52.69)	
Transfer of high-quality embryo, n (%)	588 (62.16)	611 (59.78)	0.281	311 (57.70)	339 (62.89)	0.081
Embryo cryopreservation duration (days)	30.08±4.49	31.13±4.43	<0.001	31.1±4.38	30.69±4.51	0.146

Notes: Data are presented as mean ± standard deviation or number (percentage).
Abbreviations: HRT, hormone replacement therapy; GnRH-a, gonadotropin-releasing hormone agonist; GnRH-ant, gonadotropin-releasing hormone antagonist; PSM, propensity score matching; IVF, in vitro fertilization; ICSI, intracytoplasmic sperm injection; COS, controlled ovarian stimulation.

Cycle Outcomes

As detailed in Table 2, the FET endometrial thickness was significantly greater in the GnRH-a+HRT group compared to the HRT group (9.82±2.07 mm vs 9.48±1.76 mm, P=0.011). In terms of pregnancy outcomes, the live birth rate was also significantly higher in the GnRH-a+HRT group (55.84% vs 49.35%, P=0.033). Similarly, patients with GnRH-a pretreatment had higher rates of positive hCG test (77.18% vs 68.65%, P=0.002), clinical pregnancy (68.09% vs 60.48%, P=0.009), and implantation (52.41% vs 47.47%, P=0.039), whereas the miscarriage rate did not differ between groups (17.71% vs 16.87%, P=0.771).

Further analyses with adjustment of potential confounders are shown in Table 3. Consistently, the likelihoods for a positive hCG test, clinical pregnancy, and live birth remained increased in the GnRH-a+HRT group, with aORs of 1.63 (95% CI: 1.23–2.17), 1.45 (95% CI: 1.12–1.88), and 1.29 (95% CI: 1.01–1.65), respectively. GnRH-a pretreatment before HRT did not substantially affect the risk of miscarriage (aOR: 1.18, 95% CI: 0.78–1.77).

Subgroup Analysis

The outcomes of subgroup analysis according to the status of dyslipidemia are displayed in Tables 4 and 5. Within the dyslipidemia subgroup, the live birth rate was evidently higher in the GnRH-a+HRT group compared to the HRT group (57.47% vs 45.91%; aOR: 1.75, 95% CI: 1.08–2.85). However, this difference did not reach statistical significance in the normolipidemia subgroup (55.07% vs 50.79%; aOR: 1.18, 95% CI: 0.87–1.58). In addition to live birth, the GnRH-a +HRT regimen in the dyslipidemia subgroup also led to higher rates of positive hCG test, clinical pregnancy, and implantation than the HRT protocol, which were not observed in normolipidemic patients except for the positive hCG test.

In subgroup analysis by BMI category, a total of 913 women were overweight (BMI <28 kg/m^2), and 165 women were obese (BMI ≥28 kg/m^2). Among overweight women, GnRH-a+HRT cycles showed consistently higher rates of positive hCG, clinical pregnancy, and live birth compared with HRT alone, whereas no significant differences were observed in the obese subgroup before and after adjustment (Table S1).

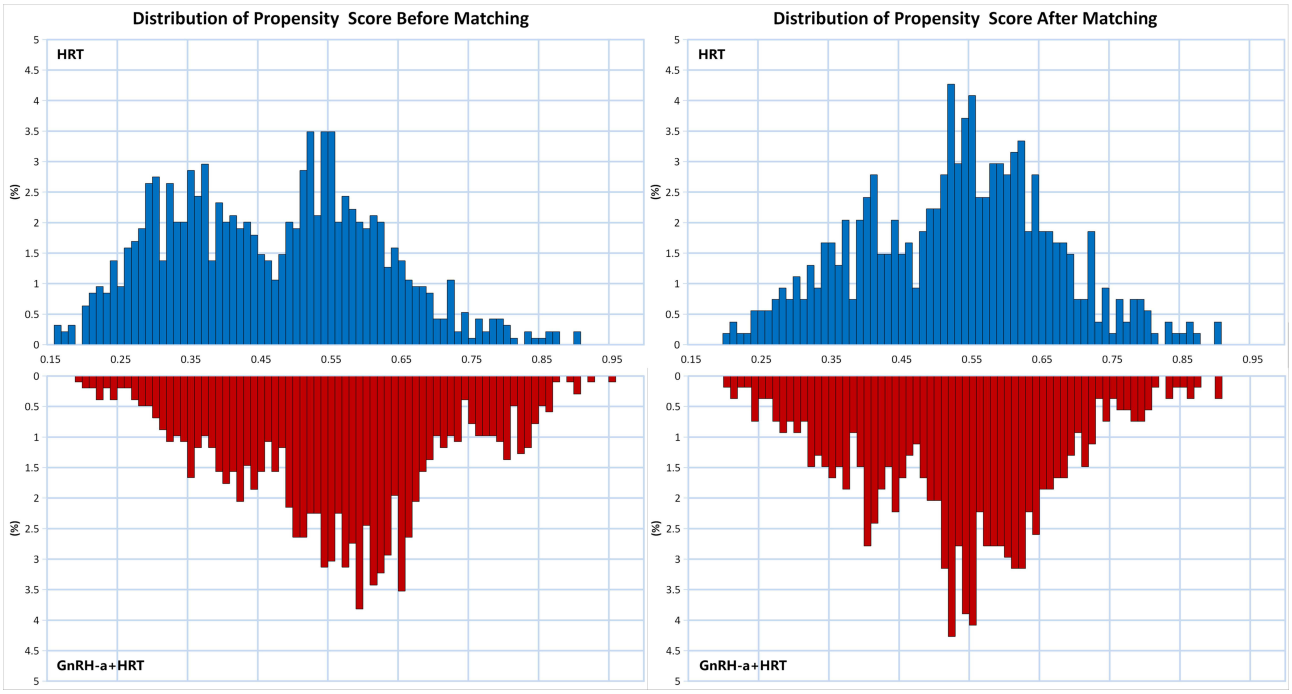

Figure 1 Distribution of propensity scores before and after matching.
Abbreviations: HRT, hormone replacement therapy; GnRH-a, gonadotropin-releasing hormone agonist.

Discussion

FET is increasingly used in assisted reproductive practice to mitigate the adverse effects of COS on endometrial receptivity and to avoid complications such as ovarian hyperstimulation syndrome.[30] Endometrial preparation is crucial in FET cycles as it directly impacts embryo implantation. Our cohort study examined the efficacy of two different protocols, HRT and GnRH-a+HRT, in overweight and obese patients. The results indicate that the depot downregulation protocol significantly improves clinical pregnancy and live birth rates, especially among those with dyslipidemia.

Table 2 Cycle Outcomes Grouped by the Endometrial Preparation Regimen

Outcomes	HRT (n = 539)	GnRH-a+HRT (n = 539)	*P*-Value
Endometrial thickness (mm)	9.48±1.76	9.82±2.07	0.011
Positive hCG rate, n (%)	370 (68.65)	416 (77.18)	0.002
Clinical pregnancy rate, n (%)	326 (60.48)	367 (68.09)	0.009
Implantation rate, n/N (%)	413 (47.47)	456 (52.41)	0.039
Miscarriage rate, n (%)	55 (16.87)	65 (17.71)	0.771
Live birth rate, n (%)	266 (49.35)	301 (55.84)	0.033

Abbreviations: HRT, hormone replacement therapy; GnRH-a, gonadotropin-releasing hormone agonist; hCG, human chorionic gonadotropin.

Table 3 Crude and Adjusted Analyses of Pregnancy Outcomes in the Matched Cohort

	Crude OR (95% CI)	*P*-Value	Adjusted OR (95% CI)	*P*-Value
Positive hCG test	1.55 (1.18–2.03)	0.002	1.63 (1.23–2.17)	0.001
Clinical pregnancy	1.39 (1.09–1.79)	0.009	1.45 (1.12–1.88)	0.005
Miscarriage	1.06 (0.72–1.57)	0.771	1.18 (0.78–1.77)	0.439
Live birth	1.30 (1.02–1.65)	0.033	1.29 (1.01–1.65)	0.043

Abbreviations: OR, odds ratio; CI, confidence interval; hCG, human chorionic gonadotropin.

Table 4 Subgroup Analysis According to the Status of Dyslipidemia

	HRT	GnRH-a+HRT	*P*-Value
Dyslipidemia	n = 159	n = 174	
Lipid profile			
TG (mmol/l)	2.06±1.20	2.03±1.15	0.606
TC (mmol/l)	4.80±0.97	4.85±0.96	0.605
LDL-C (mmol/l)	2.73±1.01	2.82±1.00	0.397
HDL-C (mmol/l)	1.25±0.32	1.32±0.36	0.066
Positive hCG rate, n (%)	104 (65.41)	137 (78.74)	0.007
Clinical pregnancy rate, n (%)	90 (56.60)	120 (68.97)	0.020
Implantation rate, n/N (%)	112 (43.41)	154 (52.20)	0.039
Miscarriage rate, n (%)	16 (17.78)	19 (15.83)	0.708
Live birth rate, n (%)	73 (45.91)	100 (57.47)	0.035
Normolipidemia	n = 380	n = 365	
Lipid profile			
TG (mmol/l)	0.96±0.36	0.94±0.31	0.703
TC (mmol/l)	4.14±0.55	4.11±0.53	0.575
LDL-C (mmol/l)	2.41±0.48	2.43±0.48	0.621
HDL-C (mmol/l)	1.39±0.23	1.43±0.30	0.115
Positive hCG rate, n (%)	266 (70.00)	279 (76.44)	0.047
Clinical pregnancy rate, n (%)	236 (62.11)	247 (67.67)	0.112
Implantation rate, n/N (%)	301 (49.18)	302 (52.52)	0.250
Miscarriage rate, n (%)	39 (16.53)	46 (18.62)	0.545
Live birth rate, n (%)	193 (50.79)	201 (55.07)	0.242

Abbreviations: HRT, hormone replacement therapy; GnRH-a, gonadotropin-releasing hormone agonist; TG, triglycerides; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; hCG, human chorionic gonadotropin.

Table 5 Crude and Adjusted Analyses of Pregnancy Outcomes in the Subgroups

	Dyslipidemia		Normolipidemia	
	Crude OR (95% CI)	**Adjusted OR (95% CI)**	**Crude OR (95% CI)**	**Adjusted OR (95% CI)**
Positive hCG test	1.96 (1.20–3.19)	2.49 (1.41–4.40)	1.39 (1.00–1.93)	1.46 (1.04–2.05)
Clinical pregnancy	1.70 (1.09–2.67)	1.87 (1.14–3.08)	1.28 (0.95–1.73)	1.33 (0.97–1.82)
Miscarriage	0.87 (0.42–1.81)	0.86 (0.38–1.94)	1.16 (0.72–1.85)	1.36 (0.82–2.25)
Live birth	1.59 (1.03–2.46)	1.75 (1.08–2.85)	1.19 (0.89–1.58)	1.18 (0.87–1.58)

Abbreviations: OR, odds ratio; CI, confidence interval; hCG, human chorionic gonadotropin.

Previous studies have extensively explored the application of GnRH-a pretreatment in HRT-FET to identify the most indicated population, as this approach is also associated with increased cost, prolonged time, and side effects. In the general population, a recent systematic review of 14 randomized controlled trials (1244 pretreated vs 1208 control cycles) revealed no significant differences in clinical pregnancy (OR: 1.09, 95% CI: 0.87–1.36), implantation (OR: 1.01, 95% CI: 0.85–1.20), miscarriage (OR: 0.75, 95% CI: 0.31–1.82), and live birth (OR: 1.14, 95% CI: 0.68–1.41), suggesting that the regimen should not be used routinely.[14] However, a beneficial role has been demonstrated in certain patient settings. For example, in a retrospective study focusing on recurrent implantation failure patients, the live birth rate in the GnRH-a+HRT group was evidently higher than that in the HRT and natural cycle groups (36.55%, 22.16% vs 16.92%, $P< 0.001$).[20] In patients with polycystic ovarian syndrome, pooled data also showed that pituitary suppression

with depot GnRH-a significantly improved the live birth odds by 22% accompanied by a 25% lower miscarriage risk.[14] In other studies, the efficacy of GnRH-a pretreatment was further reported to be greater in women <40 years, those with primary infertility, PCOS, or irregular menstruation, as well as those undergoing blastocyst transfer and hysteroscopic multiple polypectomies.[31–33] By contrast, no significant improvement was found in older women with intramural fibroids,[34] highlighting that patient characteristics may determine responsiveness to the protocol. In our study, we provide additional clinical evidence that GnRH-a+HRT cycle benefits overweight and obese women, further expanding the application scope of this regimen. The findings should also offer more precise clinical guidance, optimize treatment strategies, and enhance pregnancy success for this specific population undergoing FET.

The underlying biological rationale for this differential benefit in overweight/obese women may relate to their more severely impaired endometrial receptivity, which is negatively affected by hormonal imbalances, metabolic disturbances, and chronic low-grade inflammation.[35] GnRH-a pretreatment may counteract these adverse conditions through multiple mechanisms. First, it promotes the endometrial expression of key receptivity-related molecules, including leukemia inhibitory factor, integrin β3, homeobox A10, prolactin, and insulin-like growth factor binding protein-1, which are essential for epithelial adhesion and stromal decidualization.[36,37] In a mouse model of adenomyosis, GnRH-a treatment also enhanced the abundance and development of pinopodes to facilitate embryo implantation.[37] Second, GnRH-a could downregulate estrogen receptor expression and mitigate progesterone resistance, thereby restoring balanced steroid hormone responsiveness.[38] Concurrently, it suppresses the production of pro-inflammatory cytokines such as tumor necrosis factor-α and monocyte chemotactic protein-1, contributing to a more favorable inflammatory milieu.[39] Finally, GnRH-a pretreatment modulates the endometrial immune microenvironment by enhancing uterine natural killer (NK) cell function,[40] which is essential for pregnancy establishment and normal placentation by regulating extravillous trophoblast invasion and maternal spiral artery remodeling.[41] It also decreases the ratio of Th17/Treg cells, shifting T-cell populations toward a more tolerogenic profile.[42] These changes collectively promote a receptive endometrial state conducive to successful implantation and pregnancy. Accordingly, our study observed that endometrial thickness, an ultrasound-based surrogate marker of receptivity, was also increased in overweight/obese women undergoing GnRH-a +HRT FET cycles. However, no studies to date have directly investigated the role of GnRH-a pretreatment in overweight/obese animal models. Further investigations in such models would be scientifically valuable to provide mechanistic insights for our clinical observations.

In stratified analysis, we found that dyslipidemic patients exhibited more pronounced benefits from the GnRH-a+HRT protocol compared to the normolipidemic subgroup. This observation aligns with emerging clinical evidence indicating that dyslipidemia can adversely affect live birth rates after embryo transfer and is associated with a higher risk of miscarriage.[25,26,28] Mechanistically, Zhang et al[43] reported that women with dyslipidemia had increased proportions of $CD56^{dim}$ NK cells and elevated M1/M2 macrophage ratios in the mid-secretory endometrium, along with aberrant expression of inflammatory cytokines and chemokines. This immune imbalance is linked to a displaced window of implantation and a higher abundance of pathogenic bacteria, ultimately contributing to implantation failure.[43] Furthermore, studies from both animal models and human endometrial samples have demonstrated that dyslipidemia dysregulates the expression of transmembrane proteins such as Claudin-3 and Claudin-4 and impairs epithelial tight junction integrity.[44] These findings suggest that dyslipidemia compromises endometrial receptivity through immune dysregulation and epithelial barrier disruption. The more pronounced benefit of GnRH-a+HRT observed in this subgroup may therefore reflect its ability to partially offset these adverse pathways, consistent with the broader mechanisms of GnRH-a pretreatment described above. Nevertheless, this hypothesis remains exploratory and warrants validation in future studies.

To our knowledge, studies in this area are limited in the literature, and our findings provide supporting clinical evidence for the impact of GnRH-a downregulated HRT protocol on FET outcomes in overweight and obese women. While the results are noteworthy, several limitations should be acknowledged. Firstly, although PSM was used to balance covariates and reduce selection bias, the study's observational design cannot eliminate all potential confounding factors, such as diet and exercise level. In addition, the lack of PGT cycles did not allow us to rule out chromosomal abnormalities as a contributing factor to pregnancy failure. Secondly, relying on data from a single medical center may reduce the generalizability of the findings and potentially limits the statistical power, particularly in subgroup

analyses. Especially, although we stratified women by overweight and obesity, no significant differences were detected in the obese subgroup, likely due to the smaller sample size. Further studies with larger obese cohorts are warranted to confirm whether the benefit of GnRH-a pretreatment differs by BMI category. Thirdly, overweight/obese women could present with other concomitant metabolic disorders (eg, insulin resistance) and the use of pharmacological agents such as metformin may also influence reproductive outcomes. Unfortunately, detailed information was not available in our dataset, and therefore we were unable to adjust for these potential confounders. Future studies incorporating these factors will be essential to better delineate their impact.

Conclusion

In summary, our retrospective cohort study reveals that GnRH-a pretreatment improves FET pregnancy outcomes in overweight and obese women compared to HRT alone, especially among those with dyslipidemia. The findings provide valuable insights for fertility practice and serve as a reference for the design of future multicenter, large-scale, randomized controlled trials for confirmation.

Abbreviations

aOR, adjusted odds ratio; BMI, body mass index; CI, confidence interval; COS, controlled ovarian stimulation; FET, frozen-thawed embryo transfer; GnRH-a, gonadotropin-releasing hormone agonist; hCG, human chorionic gonadotropin; HDL-C, high-density lipoprotein cholesterol; HRT, hormone replacement therapy; LDL-C, low-density lipoprotein cholesterol; NK, natural killer; PGT, preimplantation genetic testing; PSM, propensity score matching; SD, standard deviation.

Data Sharing Statement

The datasets generated during and/or analyzed during the current study are not publicly available but may be made available upon reasonable request to the corresponding author.

Ethics Approval and Consent to Participate

The study was approved by the Ethics Committee of Jiangxi Maternal and Child Health Hospital (No. 2024-03-040), and conducted in accordance with the Declaration of Helsinki. Informed consents were waived due to the retrospective nature of study.

Author Contributions

Conception and design of the work: J.H. and Z.H. Data acquisition: Z.H., Y.L., Q.X., Y.D., L.T., X.W., and H.C. Statistical analysis: Q.X., L.X., and J.H. Manuscript drafting: Z.H. and Y.L. Manuscript revision: Q.X. and J.H. Project supervision: L.X., Y.Z., and J.H. 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; have drafted or written, or substantially revised or critically reviewed the article; have agreed on the journal to which the article will be submitted; reviewed and agreed on all versions of the article before submission, during revision, the final version accepted for publication, and any significant changes introduced at the proofing stage and agree to take responsibility and be accountable for the contents of the article.

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Disclosure

The authors have no conflicts of interest to declare.

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