Effect of the Timing of Frozen Embryo Transfer on Pregnancy Outcomes in High Ovarian Response Patients Undergoing Freeze-All Strategy

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Abstract

**Background:** Frozen embryo transfer (FET) can greatly improve the pregnancy outcomes for high ovarian response (HOR) population. However, it is not known whether the impaired endometrial receptivity derived from controlled ovarian hyperstimulation (COH) can be fully recovered in the first menstrual cycle after oocyte retrieval, and whether the timing of FET is a risk factor on pregnancy outcomes in HOR population undergoing freeze-all strategy.

**Methods:** A retrospective cohort study to compare the pregnancy outcomes of the immediate and delayed FET groups in HOR population undergoing freeze-all strategy. Propensity score matching was used to make the potential risk factors of the immediate and delayed FET groups comparable. Multivariable regression analysis was used to study the effect of the timing of FET on pregnancy outcomes in the entire cohort and propensity score-matched cohort, even in different COH protocol cohorts as subgroup analysis.

**Results:** We showed that the immediate FET group were no worse than delayed FET group in the entire cohort [clinical pregnancy rate (CPR), adjusted odd ratio (OR), 0.942, 95% confidence interval (CI), 0.784-1.133; spontaneous abortion rate (SAR), adjusted OR, 1.118, 95% CI (0.771-1.623); live birth rate (LBR), adjusted OR, 1.060, 95% CI (0.886-1.267)]. The same results were obtained by χ² test in the propensity score-matched cohort (CPR, 60.5% versus 63.5%; SAR, 11.6% versus 12.3%; LBR, 48% versus 49.3%) (P > 0.05). Subgroup analysis indicated that pregnancy outcomes of immediate FET were non-inferior to delayed FET in short-acting gonadotropin-releasing hormone agonist (GnRH-a) long protocol (P > 0.05). The SAR of the immediate FET group were lower than that of the delayed FET group in GnRH antagonist protocol (adjusted OR, 0.646, 95% CI, 0.432-0.966) and long-acting GnRH-a long protocol (adjusted OR, 0.375, 95% CI, 0.142-0.990) (P < 0.05), no differences were observed in CPR and LBR (P > 0.05).

**Conclusions:** These findings indicate that immediate FET might not affect pregnancy outcomes in HOR patients undergoing freeze-all strategy. Delaying FET could increase the SAR in GnRH-ant and long-acting GnRH-a long protocols.

**Background**

Controlled ovarian hyperstimulation (COH) is the key step in in vitro fertilization and embryo transfer (IVF-ET). High ovarian response (HOR) refers to the abnormal sensitivity of the ovary to gonadotropin, which leads to simultaneous development of multiple follicles and increases the risk of ovarian hyperstimulation syndrome (OHSS) [1]. Supraphysiological steroid hormones during COH affect endometrial receptivity by changing the endometrial immune environment and gene expression [2–4], resulting in poor pregnancy outcomes [5]. Adopting the freeze-all strategy in HOR patients can greatly reduce the risk of OHSS and avoid the influence of COH on endometrial receptivity [6]. An increasing number of studies have confirmed that frozen embryo transfer (FET) has better pregnancy and perinatal outcomes than fresh embryo transfer [7–9].
However, the best time to perform FET following COH in HOR patients is controversial in clinical work. Postponement of FET would increase the anxiety of patients [10]; in the immediate FET cycle, poor endometrial receptivity or physical condition may not be fully recovered to the pre-stimulation state, which may affect pregnancy outcomes [11]. It is not clear whether the detrimental effects on endometrial receptivity caused by COH could sustain over a long period of time, up to the subsequent menstrual cycle, especially in patients with HOR who are most affected by COH. Moreover, the use of different gonadotropin-releasing hormone (GnRH) analogues in the process of COH disturb the reproductive endocrine physiology by inhibiting pituitary function in different ways and degrees [12], and it is controversial whether the timing of FET affects pregnancy outcomes in different COH protocols [11, 13].

Thus, this study aimed to investigate whether the FET timing affect the pregnancy outcomes in patients with HOR undergoing freeze-all strategy, and whether different COH protocols affect pregnancy outcomes in the subsequent FET cycle, and to provide reference results for the HOR population to choose the optimal time to start FET.

Materials And Methods

Study population and design

We conducted a retrospective cohort study including all patients from January 2015 to March 2019 at our reproductive medicine center and the study was conducted in accordance with ethical standards (2020PS006F), informed consent was obtained from all subjects. The inclusion criteria were as follows: (1) patients on their first IVF or intracytoplasmic sperm injection (ICSI) cycle who were diagnosed with HOR and adopted freeze-all strategy, and had at least one embryo that could be used for FET. The diagnosis criteria of HOR is more than 5000 pg/ml estradiol on human chorionic gonadotropin (HCG) day or more than 15 oocytes retrieved [14, 15]; (2) we only selected three different GnRH analogues stimulation protocols, including short-acting GnRH agonist (GnRH-a) long protocol, long-acting GnRH-a long protocol, and GnRH antagonist (GnRH-ant) protocol; (3) women aged 20–45 years old; and (4) hormone replacement therapy (HRT) for endometrial preparation in FET cycle. The exclusion criteria were as follows: (1) presence of uterine abnormalities; (2) patients with endometriosis and adenomyosis; (3) presence of autoimmune, endocrine and metabolic diseases; (4) previous diagnosis of uterine adhesion; (5) patients with chromosomal abnormalities; (6) patients who underwent blastocyst biopsy for pre-implantation genetic testing; (7) patients using frozen donor semen; (8) patients using long-acting GnRH-a as pretreatment for FET after freeze-all cycle; and (9) patients with ectopic pregnancy as pregnancy outcome.

Patients were divided into immediate FET group and delayed FET group, which were defined as that the FET took place either within the first menstrual cycle following oocyte retrieval or afterwards.
According to age, anti-Müllerian hormone, body mass index (BMI), number of antral follicles in bilateral ovaries, and prior response to stimulation, we can predict the HOR population and determine the initial dose of gonadotropin to prevent the occurrence of OHSS [16, 17]. All patients were treated with the following three COH protocols: the short-acting GnRH-a long protocol involved daily subcutaneous injection of 0.05 mg short-acting GnRH-a triptorelin (Diphereline, 0.1 mg, IPSEN, France) at the middle luteal phase of the menstrual cycle as pituitary down-regulation for 14 days, introducing gonadotropin at the subsequent menstruation; the long-acting GnRH-a long protocol involved injection of a quarter to full dose (0.75–3.75 mg) of long-acting GnRH-a (Diphereline, 3.75 mg, IPSEN, France) intramuscularly in a single dose on the second day of menstruation, gonadotropin was given 20–30 days later when the follicle diameter reached 3–5 mm; the flexible GnRH-ant protocol involved starting gonadotropin on the second day of menstruation, and GnRH antagonist (Cetrotide, Merck Serono, France) was added when the lead follicle reached 13–14 mm in diameter or the estradiol was more than 300 pg/ml. Follicles development were detected by transvaginal ultrasonography, and the dosage of gonadotropin was adjusted according to different ovarian responses.

When the follicles reached more than 17 mm in diameter by mean, trigger was performed for final oocyte maturation. HCG or triptorelin was used alone or in combination in the GnRH-ant protocol. Only HCG was used for trigger in GnRH-a long protocol. Oocyte retrieval was performed 36 hours after triggering by transvaginal ultrasound-guided aspiration.

Hormone replacement therapy (HRT) was used for endometrial preparation, 4–8 mg of estradiol valerate (Progynova, Bayer, Germany) orally for at least ten days from the 3rd to 5th day of menstruation to promote the growth of endometrium. Ultrasonic examination should be completed before medication, when the thickness of endometrium is less than 6 mm, the drug can be used, otherwise the FET in this cycle will be cancelled. The luteal phase was supported by vaginal progesterone gel (Crinone, Fleet Laboratories Ltd., UK) 90 mg per day for vaginal administration, and estradiol was maintained at the original dose. Luteal support continued to use until 11 weeks of gestational age.

**Statistical analysis**

The outcomes of our study were clinical pregnancy rate (CPR), spontaneous abortion rate (SAR), and live birth rate (LBR). Clinical pregnancy was defined as detection of a gestational sac on ultrasound image at 7 weeks of gestational age [18]. In China, spontaneous abortion was defined as loss of pregnancy spontaneously after clinical pregnancy and before 28 weeks of gestational age, and live birth was defined as the survival delivery after 28 weeks of gestational age.

As an observational study, multiple maternal and IVF characteristics were considered as potential risk factors that could moderate pregnancy outcomes, and the potential risk factors between the immediate and delayed FET groups were actual unbalanced distribution (Table 1). Thus, we used propensity score matching to make the potential risk factors between the immediate and delayed FET groups balanced and comparable. We used 1:1 nearest-neighbor matching without replacement to compare the variables and tried the match tolerance value from 1 to 0 until $P$ values of the variable between the two groups
were 1,000. $\chi^2$ test was performed for comparison of the categorical variables and the pregnancy outcomes of the immediate and delayed FET group in propensity score-matched cohort (Table 1).

As the effect of FET timing on different COH protocols were controversial, subgroup analysis were performed. Multivariable logistic regression models were calculated on each COH cohort, with the timing of FET as the main exposure of interest. Potential risk factors entered into the multivariable regression model were those that showed clinical relevance or showed a univariate relationship with pregnancy outcomes. The included variables were carefully selected based on the number of events available to ensure the stability of the regression equation. Adjusted odds ratio (OR) and their 95% confidence interval (CI) were calculated to analyze the independent effect of immediate and delayed FET on the pregnancy outcomes.

$P<0.05$ was considered as statistically significant. All statistical analyses were performed using IBM SPSS 26.0 (IBM Corp., Armonk, NY, USA).

**Results**

**Potential risk factors between immediate and delayed FET groups in the entire and propensity score-matched cohort**

A total of 2128 HOR patients adopting freeze-all strategy underwent their first IVF/ICSI cycle (Fig. 1). There are 1130 patients in the immediate FET group and 998 patients in the delayed FET group. Patients’ and IVF characteristics in the immediate and delayed FET groups, which as potential risk factors, were presented in Table 1. Before matching, the distribution of these risk factors were not absolutely balanced. The distribution of COH protocol, number of embryo transferred, embryo stage and multiple pregnancies were significantly different between the two groups ($P<0.05$). No significant differences were found in maternal age, body mass index (BMI), insemination method, and infertility causes ($P>0.05$). We obtained 1366 patients by propensity score matching, and all potential risk factors and the pregnancy outcome of multiple pregnancies among them are balanced and comparable (Table 1).
Table 1: Baseline characteristics of immediate and delayed FET groups in the entire and propensity score-matched cohorts

| Potential risk factors | Entire cohort (n = 2128) |  |  | Propensity score-matched cohort* (n = 1366) |  |  |
|------------------------|--------------------------|  |  | Immediate FET\(^a\) | Delayed FET\(^b\) |  |  | Immediate FET\(^a\) | Delayed FET\(^b\) |
|                        | Immediate FET\(^a\) | Delayed FET\(^b\) |  | Immediate FET\(^a\) | Delayed FET\(^b\) |
| Maternal age (years)   | 0.455                   | 1.000                   | 0.455                   | 1.000                   |
| ≤ 34                   | 976 (86.4)              | 851 (85.3)              | 622 (91.1)              | 622 (91.1)              |
| 35–37                  | 114 (10.1)              | 101 (10.1)              | 48 (7.0)                | 48 (7.0)                |
| ≥ 38                   | 40 (3.5)                | 46 (4.6)                | 13 (1.9)                | 13 (1.9)                |
| BMI (kg/m\(^2\))       | 0.431                   | 1.000                   | 0.431                   | 1.000                   |
| <18.5                  | 70 (6.2)                | 58 (5.8)                | 465 (68.1)              | 465 (68.1)              |
| 18.5–24.9              | 750 (66.4)              | 641 (64.2)              | 22 (3.2)                | 22 (3.2)                |
| ≥ 25                   | 310 (27.4)              | 299 (30.0)              | 196 (28.7)              | 196 (28.7)              |
| Insemination method    | 0.056                   | 1.000                   | 0.056                   | 1.000                   |
| IVF                    | 814 (72.0)              | 681 (68.2)              | 490 (71.7)              | 490 (71.7)              |
| ICSI                   | 316 (28.0)              | 317 (31.8)              | 193 (28.3)              | 193 (28.3)              |
| COH protocol           | 0.000                   | 1.000                   | 0.000                   | 1.000                   |
| GnRH-ant protocol      | 485 (42.9)              | 433 (43.4)              | 284 (41.6)              | 284 (41.6)              |
| HCG trigger            | 330 (68.0)              | 306 (70.7)              | 199 (70.1)              | 199 (70.1)              |
| GnRH-a trigger         | 137 (28.2)              | 105 (24.2)              | 79 (27.8)               | 79 (27.8)               |
| Double trigger         | 18 (3.7)                | 22 (5.1)                | 6 (2.1)                 | 6 (2.1)                 |
| Short acting GnRH-a protocol | 566 (50.1) | 434 (43.5) | 335 (49.0) | 335 (49.0) |
| Potential risk factors                        | Entire cohort (n = 2128) | P-value | Propensity score-matched cohort* (n = 1366) | P-value |
|---------------------------------------------|--------------------------|---------|--------------------------------------------|---------|
|                                             | Immediate FET\textsuperscript{a} |       | Immediate FET\textsuperscript{a}           |         |
|                                             | Delayed FET\textsuperscript{b} |       | Delayed FET\textsuperscript{b}             |         |
| Long acting GnRH-a protocol                | 79 (7.0)                 | 131 (13.1) | 64 (9.4)                                   | 64 (9.4) |
| Number of embryo transfer                  |                          | 0.000                             | 1.000                                             |
| 1                                           | 265 (23.5)               | 416 (41.7) | 208 (30.5)                                 | 208 (30.5) |
| 2                                           | 865 (76.5)               | 582 (58.3) | 475 (69.5)                                 | 475 (69.5) |
| Embryo stage                                |                          | 0.000                             | 1.000                                             |
| Cleavage stage                              | 711 (62.9)               | 499 (50.0) | 418 (61.2)                                 | 418 (61.2) |
| Blastocyst stage                            | 419 (37.1)               | 499 (50.0) | 265 (38.8)                                 | 265 (38.8) |
| Cause of infertility                        |                          |                                   |                                                  |
| Tubal factor                                | 720 (63.7)               | 630 (63.1) | 456 (66.8)                                 | 456 (66.8) |
| Ovulatory disorder                          | 304 (26.9)               | 257 (25.8) | 167 (24.5)                                 | 167 (24.5) |
| Male factor                                 | 452 (40.0)               | 420 (42.1) | 273 (40.0)                                 | 273 (40.0) |
| Unexplained factor                          | 48 (4.2)                 | 46 (4.6)    | 16 (2.3)                                   | 16 (2.3) |
| Multiple pregnancies                        | 216 (19.1)               | 137 (13.7) | 106 (15.5)                                 | 112 (16.4) |

**Abbreviations**

BMI, body mass index; COH, controlled ovarian hyperstimulation; FET, frozen embryo transfer; GnRH-a, gonadotrophin-releasing hormone agonist; GnRH-ant, gonadotrophin-releasing hormone antagonist; HRT, hormone replacement therapy; IVF, in vitro fertilization; ICSI, intracytoplasmic sperm injection. Data are presented as number (%).
**Immediate FET and bDelayed FET means FET took place either within the first menstrual cycle following oocyte retrieval or afterwards.**

*The predictors of propensity score matching were maternal age, BMI, insemination method, COH protocol, number of embryo transferred, embryo stage and cause of infertility. The match tolerance was set to 0.000001. Categorical variables were compared with $\chi^2$ test.

# P value of differences of different trigger drugs in GnRH-ant protocol.

**Multivariable logistic regression analysis on FET timing and potential risk factors for pregnancy outcomes in the entire before-matching cohort**

Multivariable logistic regression analysis on the entire before-matching cohort demonstrated no statistically differences on pregnancy outcomes between the immediate and delayed FET groups [CPR, adjusted odd ratio (OR), 0.942, 95% confidence interval (CI), 0.784–1.133; SAR, adjusted OR, 1.118, 95% CI (0.771–1.623); LBR, adjusted OR, 1.060, 95% CI (0.886–1.267)] ($P>0.05$), which were adjusted for maternal age, BMI, COH protocol, insemination method, number of embryo transferred, embryo stage, trigger type, and cause of infertility (Table 2).
Table 2  
Multivariable logistic regression analysis on potential risk factors for pregnancy outcomes in the entire cohort

| Potential risk factor variables                  | Adjusted OR* (95% CI) | P-value |
|------------------------------------------------|------------------------|---------|
| **Clinical pregnancy**                          |                        |         |
| FET timing (Immediate FET\textsuperscript{a} versus delayed FET\textsuperscript{b}) | 0.942 (0.784–1.133)   | NS      |
| Age (35–37 versus \leq 34)                      | 0.922 (0.685–1.241)    | NS      |
| Age (\geq 38 versus \leq 34)                    | 0.414 (0.263–0.650)    | \(P<0.001\) |
| BMI (< 18.5 versus 18.5–24.9)                   | 1.078 (0.734–1.585)    | NS      |
| BMI (\geq 25 versus 18.5–24.9)                  | 1.121 (0.911–1.380)    | NS      |
| COH protocol (short-acting GnRH-a versus GnRH-ant) | 1.240 (0.998–1.542)   | NS      |
| COH protocol (long-acting GnRH-a versus GnRH-ant) | 1.376 (0.983–1.928)   | NS      |
| Trigger type (GnRH-a trigger versus HCG trigger) | 1.279 (0.933–1.754)   | NS      |
| Trigger type (Double trigger versus HCG trigger) | 2.714 (1.217–6.053)   | \(P<0.05\) |
| Insemination method (ICSI versus IVF)           | 0.880 (0.691–1.122)    | NS      |
| Number of embryo transferred (2 versus 1)       | 1.534 (1.122–2.099)    | \(P<0.01\) |
| Embryo stage (blastocyst versus cleavage)       | 2.637 (1.968–3.533)    | \(P<0.001\) |
| Tubal factor (yes versus no)                    | 1.114 (0.879–1.410)    | NS      |
| Ovulatory disorder (yes versus no)              | 1.107 (0.874–1.401)    | NS      |
| Male factor (yes versus no)                     | 1.174 (0.926–1.487)    | NS      |
| Unexplained factor (yes versus no)              | 1.475 (0.884–2.460)    | NS      |
| **Spontaneous abortion**                        |                        |         |
| FET timing (Immediate FET\textsuperscript{a} versus delayed FET\textsuperscript{b}) | 1.118 (0.771–1.623)   | NS      |
| Age (35–37 versus \leq 34)                      | 1.083 (0.690–1.699)    | NS      |
| Age (\geq 38 versus \leq 34)                    | 1.980 (0.630–2.276)    | NS      |
| BMI (< 18.5 versus 18.5–24.9)                   | 0.971 (0.507–1.859)    | NS      |
| BMI (\geq 25 versus 18.5–24.9)                  | 1.788 (1.337–2.393)    | \(P<0.001\) |
| COH protocol (short-acting GnRH-a versus GnRH-ant) | 0.826 (0.590–1.157)   | NS      |
| COH protocol (long-acting GnRH-a versus GnRH-ant) | 1.239 (0.760–2.018)   | NS      |
| Trigger type (GnRH-a trigger versus HCG trigger) | 0.875 (0.553–1.385)   | NS      |
| Potential risk factor variables                                              | Adjusted OR* (95% CI) | P-value |
|--------------------------------------------------------------------------|------------------------|---------|
| Trigger type (Double trigger versus HCG trigger)                         | 1.458 (0.640–3.326)    | NS      |
| Insemination method (ICSI versus IVF)                                    | 1.118 (0.771–1.623)    | NS      |
| Number of embryo transferred (2 versus 1)                                | 0.951 (0.618–1.465)    | NS      |
| Embryo stage (blastocyst versus cleavage)                                | 1.188 (0.789–1.788)    | NS      |
| Tubal factor (yes versus no)                                             | 0.730 (0.515–1.034)    | NS      |
| Ovulatory disorder (yes versus no)                                       | 1.332 (0.947–1.873)    | NS      |
| Male factor (yes versus no)                                              | 0.709 (0.491–1.022)    | NS      |
| Unexplained factor (yes versus no)                                       | 0.750 (0.350–1.609)    | NS      |
| Live birth                                                               |                        |         |
| FET timing (Immediate FET\textsuperscript{a} versus delayed FET\textsuperscript{b}) | 1.060 (0.886–1.267)    | NS      |
| Age (35–37 versus ≤ 34)                                                  | 0.928 (0.695–1.240)    | NS      |
| Age (≥ 38 versus ≤ 34)                                                   | 0.357 (0.217–0.587)    | P < 0.001|
| BMI (< 18.5 versus 18.5–24.9)                                            | 1.092 (0.753–1.583)    | NS      |
| BMI (≥ 25 versus 18.5–24.9)                                              | 0.842 (0.689–1.029)    | NS      |
| COH protocol (short-acting GnRH-a versus GnRH-ant)                       | 1.252 (1.012–1.550)    | P < 0.05 |
| COH protocol (long-acting GnRH-a versus GnRH-ant)                        | 1.253 (0.904–1.737)    | NS      |
| Trigger type (GnRH-a trigger versus HCG trigger)                         | 1.331 (0.979–1.809)    | NS      |
| Trigger type (Double trigger versus HCG trigger)                         | 1.943 (0.995–3.794)    | NS      |
| Insemination method (ICSI versus IVF)                                    | 0.897 (0.709–1.136)    | NS      |
| Number of embryo transferred (2 versus 1)                                | 1.420 (1.064–1.895)    | P < 0.05 |
| Embryo stage (blastocyst versus cleavage)                               | 2.246 (1.717–2.937)    | P < 0.001|
| Tubal factor (yes versus no)                                             | 1.302 (1.035–1.639)    | P < 0.05 |
| Ovulatory disorder (yes versus no)                                       | 0.947 (0.754–1.189)    | NS      |
| Male factor (yes versus no)                                              | 1.326 (1.054–1.669)    | P < 0.05 |
| Unexplained factor (yes versus no)                                       | 1.575 (0.970–2.559)    | NS      |

**Abbreviations** BMI, body mass index; FET, frozen embryo transfer; GnRH-a, gonadotrophin-releasing hormone agonist; GnRH-ant, gonadotrophin-releasing hormone antagonist; IVF, in vitro fertilization; ICSI, intracytoplasmic sperm injection; OR, odds ratio; CI, confidence interval; NS, not significant.
Immediate FET and delayed FET means FET took place either within the first menstrual cycle following oocyte retrieval or afterwards.

*Using the multivariable logistic regression and adjusting for maternal age, BMI, insemination method, COH protocol, trigger type, number of embryo transferred, embryo stage and cause of infertility.

**Immediate FET versus delayed FET cycles on pregnancy outcomes in propensity score-matched cohort**

The CPR (60.5% versus 63.5%), SAR (11.6% versus 12.3%), LBR (48.0% versus 49.3%) had no significant differences between the immediate and delayed FET groups in the propensity score-matched cohort ($P > 0.05$), which were detailed in Table 3.

| Pregnancy outcomes         | Immediate FET $^a$ (n = 683) | Delayed FET $^b$ (n = 683) | $P$-value |
|----------------------------|-------------------------------|----------------------------|-----------|
| Clinical pregnancy         | 413 (60.5)                    | 434 (63.5)                 | 0.242     |
| Spontaneous abortion       | 79 (11.6)                     | 84 (12.3)                  | 0.676     |
| Live birth                 | 328 (48.0)                    | 337 (49.3)                 | 0.626     |

**Abbreviations** FET, frozen embryo transfer.

Immediate FET and delayed FET means FET took place either within the first menstrual cycle following oocyte retrieval or afterwards. Data are presented as number (%).

Differences between the groups were evaluated by $\chi^2$ test.

**Subgroup analysis on immediate FET versus delayed FET on pregnancy outcomes in different COH protocol cohorts**

To investigate the effect of FET timing on pregnancy outcomes in different COH protocols, multivariable logistic regression were performed on each COH protocol cohort, including 918 patients in antagonist protocol, 1000 patients in short-acting GnRH-a long protocol, and 210 patients in long-acting GnRH-a long protocol. Multivariable logistic regression analysis demonstrated no statistically differences on pregnancy outcomes between the immediate and delayed FET groups in short acting GnRH-a long protocol (CPR, adjusted OR, 0.998, 95% CI, 0.761–1.308; SAR, adjusted OR, 1.350, 95% CI, 0.854–2.135; LBR, adjusted OR, 0.939, 95% CI, 0.723–1.220) ($P > 0.05$), which were adjusted for maternal age, BMI, insemination method, number of embryo transferred, embryo stage and cause of infertility. However, the SAR of the immediate FET group was lower than that of the delayed FET group in the GnRH-ant protocol (adjusted for maternal age, BMI, trigger type, insemination method, embryo stage, number of embryo transferred, and cause of infertility) and long-acting GnRH-a long protocol (adjusted for maternal age,
BMI) (GnRH-ant protocol, adjusted OR, 0.646, 95% CI, 0.432–0.966; long-acting GnRH-a long protocol, adjusted OR, 0.375, 95% CI, 0.142–0.990) ($P<0.05$). No significant differences were found on CPRs and LBRs in GnRH-ant and long-acting GnRH-a long protocols ($P>0.05$) (Table 4–6).
Table 4
Multivariable logistic regression analysis on potential risk factors for pregnancy outcomes in GnRH-ant protocol

| Potential risk factor variables                        | Adjusted OR* (95% CI)                  | P-value |
|--------------------------------------------------------|----------------------------------------|---------|
| Clinical pregnancy                                      |                                        |         |
| FET timing (Immediate FET\(^a\) versus delayed FET\(^b\)) | 0.957 (0.723–1.267)                    | NS      |
| Age (35–37 versus ≤ 34)                                | 0.799 (0.502–1.270)                    | NS      |
| Age (≥ 38 versus ≤ 34)                                 | 0.387 (0.211–0.708)                    | \(P < 0.01\) |
| BMI (< 18.5 versus 18.5–24.9)                         | 0.781 (0.424–1.439)                    | NS      |
| BMI (≥ 25 versus 18.5–24.9)                           | 0.980 (0.731–1.314)                    | NS      |
| Trigger type (GnRH-a trigger versus HCG trigger)       | 1.228 (0.819–1.693)                    | NS      |
| Trigger type (Double trigger versus HCG trigger)       | 2.562 (1.144–5.740)                    | \(P < 0.05\) |
| Insemination method (ICSI versus IVF)                  | 1.005 (0.696–1.451)                    | NS      |
| Number of embryo transferred (2 versus 1)              | 1.729 (1.043–2.865)                    | NS      |
| Embryo stage (blastocyst versus cleavage)             | 3.069 (1.883–5.003)                    | \(P < 0.001\) |
| Tubal factor (yes versus no)                           | 1.043 (0.745–1.461)                    | NS      |
| Ovulatory disorder (yes versus no)                     | 1.242 (0.909–1.695)                    | NS      |
| Male factor (yes versus no)                            | 1.012 (0.720–1.423)                    | NS      |
| Unexplained factor (yes versus no)                     | 1.267 (0.622–2.581)                    | NS      |
| Spontaneous abortion                                   |                                        |         |
| FET timing (Immediate FET\(^a\) versus delayed FET\(^b\)) | 0.646 (0.432–0.966)                    | \(P < 0.05\) |
| Age (35–37 versus ≤ 34)                                | 1.203 (0.621–2.330)                    | NS      |
| Age (≥ 38 versus ≤ 34)                                 | 1.516 (0.701–3.280)                    | NS      |
| BMI (< 18.5 versus 18.5–24.9)                         | 0.716 (0.245–2.093)                    | NS      |
| BMI (≥ 25 versus 18.5–24.9)                           | 1.399 (0.934–2.093)                    | NS      |
| Trigger type (GnRH-a trigger versus HCG trigger)       | 0.906 (0.569–1.443)                    | NS      |
| Trigger type (Double trigger versus HCG trigger)       | 1.410 (0.615–3.235)                    | NS      |
| Insemination method (ICSI versus IVF)                  | 1.271 (0.756–2.136)                    | NS      |
| Number of embryo transferred (2 versus 1)              | 1.039 (0.556–1.943)                    | NS      |
| Embryo stage (blastocyst versus cleavage)             | 1.543 (0.838–2.840)                    | NS      |
### Potential risk factor variables

| Potential risk factor variables | Adjusted OR* (95% CI) | P-value |
|---------------------------------|-----------------------|---------|
| Tubal factor (yes versus no)    | 0.874 (0.550–1.389)   | NS      |
| Ovulatory disorder (yes versus no) | 1.583 (1.017–2.465) | \( P < 0.05 \) |
| Male factor (yes versus no)     | 0.794 (0.483–1.305)   | NS      |
| Unexplained factor (yes versus no) | 0.977 (0.353–2.707) | NS      |

**Live birth**

| Potential risk factor variables | Adjusted OR* (95% CI) | P-value |
|---------------------------------|-----------------------|---------|
| FET timing (Immediate FET\(^a\) versus delayed FET\(^b\)) | 1.216 (0.923–1.601) | NS      |
| Age (35–37 versus \( \leq \) 34) | 0.760 (0.478–1.208) | NS      |
| Age (\( \geq \) 38 versus \( \leq \) 34) | 0.248 (0.121–0.511) | \( P < 0.001 \) |
| BMI (< 18.5 versus 18.5–24.9) | 0.883 (0.484–1.611) | NS      |
| BMI (\( \geq \) 25 versus 18.5–24.9) | 0.799 (0.600–1.064) | NS      |
| Trigger type (GnRH-a trigger versus HCG trigger) | 1.253 (0.918–1.710) | NS      |
| Trigger type (Double trigger versus HCG trigger) | 1.862 (0.949–3.653) | NS      |
| Insemination method (ICSI versus IVF) | 0.942 (0.657–1.350) | NS      |
| Number of embryo transferred (2 versus 1) | 1.629 (1.024–2.593) | \( P < 0.05 \) |
| Embryo stage (blastocyst versus cleavage) | 2.391 (1.528–3.740) | \( P < 0.001 \) |
| Tubal factor (yes versus no)    | 1.145 (0.825–1.588)   | NS      |
| Ovulatory disorder (yes versus no) | 0.993 (0.734–1.345) | NS      |
| Male factor (yes versus no)     | 1.154 (0.826–1.610)   | NS      |
| Unexplained factor (yes versus no) | 1.235 (0.621–2.455) | NS      |

**Abbreviations**

BMI, body mass index; FET, frozen embryo transfer; GnRH-a, gonadotrophin-releasing hormone agonist; GnRH-ant, gonadotrophin-releasing hormone antagonist; IVF, in vitro fertilization; ICSI, intracytoplasmic sperm injection; OR, odds ratio; CI, confidence interval; NS, not significant.

\(^a\)Immediate FET and \(^b\)delayed FET means FET took place either within the first menstrual cycle following oocyte retrieval or afterwards.

*Using the multivariable logistic regression and adjusting for maternal age, BMI, insemination method, trigger type, number of embryo transferred, embryo stage and cause of infertility.
Table 5
Multivariable logistic regression analysis on risk factors for pregnancy outcomes in short-acting GnRH-a long protocol

| Potential risk factor variables | Adjusted OR* (95% CI) | P-value |
|--------------------------------|-----------------------|---------|
| **Clinical pregnancy**         |                       |         |
| FET timing (Immediate FET\(^a\) versus delayed FET\(^b\)) | 0.998 (0.761–1.308) | NS      |
| Age (35–37 versus ≤ 34)        | 0.979 (0.632–1.518)   | NS      |
| Age (≥ 38 versus ≤ 34)         | 0.406 (0.191–0.863)   | \(P<0.05\) |
| BMI (< 18.5 versus 18.5–24.9)  | 1.399 (0.797–2.455)   | NS      |
| BMI (≥ 25 versus 18.5–24.9)    | 1.272 (0.914–1.770)   | NS      |
| Insemination method (ICSI versus IVF) | 0.725 (0.507–1.037) | NS      |
| Number of embryo transferred (2 versus 1) | 1.359 (0.890–2.076) | NS      |
| Embryo stage (blastocyst versus cleavage) | 2.304 (1.586–3.347) | \(P<0.001\) |
| Tubal factor (yes versus no)   | 1.111 (0.769–1.605)   | NS      |
| Ovulatory disorder (yes versus no) | 0.929 (0.631–1.367) | NS      |
| Male factor (yes versus no)    | 1.236 (0.854–1.790)   | NS      |
| Unexplained factor (yes versus no) | 2.149 (0.910–5.075) | NS      |
| **Spontaneous abortion**       |                       |         |
| FET timing (Immediate FET\(^a\) versus delayed FET\(^b\)) | 1.350 (0.854–2.135) | NS      |
| Age (35–37 versus ≤ 34)        | 1.190 (0.598–2.368)   | NS      |
| Age (≥ 38 versus ≤ 34)         | 0.987 (0.279–3.490)   | NS      |
| BMI (< 18.5 versus 18.5–24.9)  | 1.267 (0.515–3.114)   | NS      |
| BMI (≥ 25 versus 18.5–24.9)    | 2.656 (1.660–4.250)   | \(P<0.001\) |
| Insemination method (ICSI versus IVF) | 1.059 (0.559–2.004) | NS      |
| Number of embryo transferred (2 versus 1) | 0.799 (0.409–1.562) | NS      |
| Embryo stage (blastocyst versus cleavage) | 0.843 (0.466–1.526) | NS      |
| Tubal factor (yes versus no)   | 0.443 (0.232–0.848)   | \(P<0.05\) |
| Ovulatory disorder (yes versus no) | 0.856 (0.457–1.606) | NS      |
| Male factor (yes versus no)    | 0.358 (0.178–0.723)   | \(P<0.01\) |
| Unexplained factor (yes versus no) | 0.239 (0.049–1.167) | NS      |
| Potential risk factor variables                                      | Adjusted OR* (95% CI) | P-value |
|---------------------------------------------------------------------|-----------------------|---------|
| Live birth                                                          |                       |         |
| FET timing (Immediate FET\(^a\) versus delayed FET\(^b\))           | 0.939 (0.723–1.220)   | NS      |
| Age (35–37 versus ≤ 34)                                             | 0.962 (0.630–1.468)   | NS      |
| Age (≥ 38 versus ≤ 34)                                              | 0.423 (0.192–0.934)   | P < 0.05|
| BMI (<18.5 versus 18.5–24.9)                                       | 1.270 (0.747–2.161)   | NS      |
| BMI (≥ 25 versus 18.5–24.9)                                        | 0.853 (0.623–1.169)   | NS      |
| Insemination method (ICSI versus IVF)                               | 0.794 (0.560–1.126)   | NS      |
| Number of embryo transferred (2 versus 1)                          | 1.324 (0.893–1.961)   | NS      |
| Embryo stage (blastocyst versus cleavage)                          | 2.270 (1.605–3.211)   | P < 0.001|
| Tubal factor (yes versus no)                                       | 1.459 (1.071–2.092)   | P < 0.05|
| Ovulatory disorder (yes versus no)                                 | 0.916 (0.629–1.334)   | NS      |
| Male factor (yes versus no)                                        | 1.588 (1.111–2.272)   | P < 0.05|
| Unexplained factor (yes versus no)                                 | 2.973 (1.336–6.619)   | P < 0.01|

**Abbreviations**  
BMI, body mass index; FET, frozen embryo transfer; GnRH-a, gonadotrophin-releasing hormone agonist; IVF, in vitro fertilization; ICSI, intracytoplasmic sperm injection; OR, odds ratio; CI, confidence interval; NS, not significant.

\(^a\)Immediate FET and \(^b\)delayed FET means FET took place either within the first menstrual cycle following oocyte retrieval or afterwards.

\(^*\)Using the multivariable logistic regression and adjusting for maternal age, BMI, insemination method, number of embryo transferred, embryo stage and cause of infertility.
| Potential risk factor variables | Adjusted OR* (95% CI) | P-value |
|---------------------------------|-----------------------|---------|
| Clinical pregnancy              |                       |         |
| FET timing (Immediate FET\textsuperscript{a} versus delayed FET\textsuperscript{b}) | 0.702 (0.382–1.292) | NS |
| Age (35–37 versus ≤ 34)         | 1.153 (0.461–2.883)   | NS |
| Age (≥ 38 versus ≤ 34)          | 0.706 (10.106–4.696)  | NS |
| BMI (< 18.5 versus 18.5–24.9)   | 0.907 (0.272–3.020)   | NS |
| BMI (≥ 25 versus 18.5–24.9)     | 1.243 (0.605–2.555)   | NS |
| Insemination method (ICSI versus IVF) | 1.306 (0.544–3.132) | NS |
| Embryo stage (blastocyst versus cleavage) | 1.854 (0.944–3.643) | NS |
| Tubal factor (yes versus no)    | 2.545 (0.988–6.552)   | P< 0.05 |
| Ovulatory disorder (yes versus no) | 0.732 (0.226–2.369) | NS |
| Male factor (yes versus no)     | 2.535 (1.058–6.070)   | NS |
| Unexplained factor (yes versus no) | 1.383 (0.239–7.999) | NS |
| Spontaneous abortion            |                       |         |
| FET timing (Immediate FET\textsuperscript{a} versus delayed FET\textsuperscript{b}) | 0.375 (0.142–0.990) | P< 0.05 |
| Age (35–37 versus ≤ 34)         | 0.409 (0.089–1.887)   | NS |
| Age (≥ 38 versus ≤ 34)          | -                     | NS |
| BMI (< 18.5 versus 18.5–24.9)   | 0.548 (0.066–4.518)   | NS |
| BMI (≥ 25 versus 18.5–24.9)     | 1.959 (0.791–4.849)   | NS |
| Live birth                      |                       |         |
| FET timing (Immediate FET\textsuperscript{a} versus delayed FET\textsuperscript{b}) | 1.124 (0.625–2.023) | NS |
| Age (35–37 versus ≤ 34)         | 1.774 (0.730–4.311)   | NS |
| Age (≥ 38 versus ≤ 34)          | 1.501 (0.221–10.185)  | NS |
| BMI (< 18.5 versus 18.5–24.9)   | 1.134 (0.359–3.582)   | NS |
| BMI (≥ 25 versus 18.5–24.9)     | 0.895 (0.454–1.764)   | NS |
| Insemination method (ICSI versus IVF) | 1.607 (0.712–3.631) | NS |
| Embryo stage (blastocyst versus cleavage) | 1.798 (0.959–3.370) | NS |
### Potential risk factor variables

| Potential risk factor variables                          | Adjusted OR* (95% CI)     | P-value |
|----------------------------------------------------------|---------------------------|---------|
| Tubal factor (yes versus no)                             | 2.156 (0.922–5.042)       | NS      |
| Ovulatory disorder (yes versus no)                       | 0.531 (0.159–1.769)       | NS      |
| Male factor (yes versus no)                              | 1.379 (0.635–2.993)       | NS      |
| Unexplained factor (yes versus no)                       | 0.474 (0.070–3.203)       | NS      |

**Abbreviations**

BMI, body mass index; FET, frozen embryo transfer; GnRH-a, gonadotrophin-releasing hormone agonist; IVF, in vitro fertilization; ICSI, intracytoplasmic sperm injection; OR, odds ratio; CI, confidence interval; NS, not significant.

*Immediate FET and delayed FET means FET took place either within the first menstrual cycle following oocyte retrieval or afterwards.

*Using the multivariable logistic regression and adjusting for maternal age, BMI, insemination method, trigger type, embryo stage and cause of infertility.

#Using the multivariable logistic regression and adjusting for maternal age, BMI.

"-" means that the number of miscarriages in the group over 38 years old is 0.

### Discussion

In clinical work, when to start the FET cycle after COH is controversial, especially for patients with HOR, who are most affected by COH. As known, in the COH process, increased levels of supraphysiological steroid hormones and premature progesterone affected the gene expression and immune environment of the endometrium, which altered the embryo-endometrium asynchrony and negatively affected endometrial receptivity, reducing the CPR and LBR [5, 19]. Moreover, the secretory activity factors produced by the residual luteal cysts derived from COH would last longer after oocyte retrieval in HOR patients. However, no study has investigated the specific duration of these adverse effects. To avoid this concern, some clinicians recommended the conservative scheme to start the FET cycle at the second or third withdrawal bleeding after oocyte retrieval, which would undoubtedly prolong the IVF treatment period and increase the anxiety of patients who had experienced infertility for many years, increasing their mental and economic loses and affecting their pregnancy outcomes [10, 20]. In our retrospective study, we only selected the HOR population who adopted HRT as endometrial preparation protocol in the past 5 years, and showed no significant differences on CPR, SAR, and LBR between the immediate and delayed FET groups. We believe that it is not accurate to assume that COH will still affect endometrial receptivity in the first withdrawal bleeding cycle after oocyte retrieval and that the HOR population do not have to wait for several menstrual cycles to FET after freeze-all strategy.

In the process of COH, different GnRH analogues have different degrees and properties of inhibition effects on hypothalamic-pituitary-ovarian axis, it also has different effects on corpus luteum [21], which
might have impact on endometrial receptivity and pregnancy outcomes [22]. A retrospective study have showed that immediate FET had similar CPR to delayed FET in patients with GnRH-ant protocol [13], which is in agreement with our subgroup results. However, our results are contrary to a population-based study on short-acting GnRH-a long protocol, which found that delayed FET was better for pregnancy outcomes, they believed that the initial flare up effect of short acting GnRH-a during the down regulation period caused an early rise of progesterone, which affected the outcomes in immediate FET cycle [11]. An important limitation of that study is the small sample size, 67 patients in immediate FET group and 62 in delayed FET group. In this study, 1000 patients with short acting GnRH-a long protocol were studied (434 in immediate FET group and 566 in delayed FET group), and we found that the timing of FET did not affect pregnancy outcomes in short-acting GnRH-a long protocol. However, in the GnRH-ant and long-acting GnRH-a long protocol, we found that the SAR in delayed FET group was significantly higher than that in immediate FET group. Among all the COH protocols, the GnRH-ant protocol has the shortest treatment period, which oocyte retrieval take place after 8–10 days of ovarian stimulation by mean; the short-acting GnRH-a long protocol needs 14 days of down regulation on that basis; while the long-acting GnRH-a long protocol needs a down regulation for more than 20 days. The immediate FET cycle in GnRH-ant protocol can obtain the shortest treatment period, while the delayed FET cycle in long-acting GnRH-a long protocol has the longest treatment period. We know that psychological factors are important factors leading to infertility and spontaneous abortion, its potential impact on neuroendocrine and immune changes could affect early pregnancy risk [23, 24]. We consider that the longer the treatment period, the more anxious the patients are, which could be the cause of the increase in the SAR. Moreover, long acting GnRH-a can effectively improve endometrial receptivity [22], which may be the other reason for the lower SAR in the immediate FET group in long acting GnRH-a long protocol. It is worth mentioning that one research have shown that residual luteal cysts may increase the expression of relaxin in circulation [25], which is related to the endometrial angiogenesis and prevent recurrent abortion [26]. Therefore, the effects of residual luteal cysts in immediate FET cycles that we had previously worried about may be beneficial to endometrial receptivity and pregnancy outcomes.

The limitation of this study lies in the retrospective nature as well as the possibility of unmeasured confounding factors such as smoking habits and alcohol consumption. Although we have obtained many cases with HOR and made the immediate and delayed FET groups comparable by propensity score matching, we have lost 762 cases without successful matching in this process. However, we do not know whether these cases will affect the actual situation. Notably, the pregnancy outcomes we have studied were not the only endpoint, other obstetric outcomes and neonatal outcomes should also be noticed.

In summary, this study implied that immediate FET may not affect the pregnancy outcomes in HOR population undergoing freeze-all strategy although their pelvic environment were not fully recovered. Intended to delay FET in HOR population may increase anxiety of infertility couples and increase the SAR. Clinicians and patients with HOR do not have to worry about FET on the immediate cycle, and they can arrange the start time of FET cycle on their own convenience and desire, making the IVF treatment process more relax and efficient. However, more studies are needed to further investigate the effect of FET timing on other obstetric and neonatal outcomes in the HOR population.
Conclusion

Immediate FET may not have adverse effect on pregnancy outcomes in HOR population undergoing freeze-all strategy. Delaying FET could increase the SAR in GnRH-ant and long-acting GnRH-a long protocols. Intentionally delayed FET by clinicians or HOR patients is not beneficial to pregnancy outcomes.

List Of Abbreviations

BMI: Body mass index; COH: Controlled ovarian hyperstimulation; CI: Confidence interval; CPR: Clinical pregnancy rate; FET: Frozen embryo transfer; GnRH-a: Gonadotropin-releasing hormone agonist; GnRH-ant: Gonadotropin-releasing hormone antagonist; HCG: human chorionic gonadotropin; HOR: High ovarian response; HRT: Hormone replacement therapy; ICSI: Intracytoplasmic sperm injection; IVF-ET: In vitro fertilization and embryo transfer; LBR: Live birth rate; OR: Odd ratio; OHSS: Ovarian hyperstimulation syndrome; SAR: Spontaneous abortion rate.

Declarations

Ethics approval and consent to participate

All the data used in this study were retrospective clinical data, which were approved by the Institutional Review Board at China Medical University (reference number 2020PS006F).

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and analysed during the current study were used under license for the current study, and so are not publicly available.

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

D.L. and X.X.W. conceived and designed the study. N.Z., N.N.Z., Y.Z.G. performed the data collection and analysis. D.L., X.X.W., N.Z. and Y.Z.G. wrote the paper. All authors read and approved the final manuscript.

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