



# Thicker endometrium on hCG trigger day improves the live birth rate of fresh cleavage embryo transfer in GnRH-agonist regimen of normogonadotrophic women

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**Background:** Luteinizing hormone (LH) and progesterone (PROG) on human chorionic gonadotropin (hCG) trigger day are significantly correlated with assisted reproductive technology (ART) outcome. Moreover, LH and PROG are also involved in the functional preparation of the endometrium during the implantation window; however, whether they are related to endometrial thickness (EMT) is still unknown. The aim of the present study was to assess whether EMT has a positive correlation on the live birth rate following fresh embryo transfer (ET), and whether LH and PROG have an impact on EMT.

**Methods:** A total of 2,260 normogonadotrophic women were treated with a GnRH agonist for in vitro fertilization (IVF)/intracytoplasmic sperm injection. Patients with advanced age and poor ovarian reserve were excluded. The levels of LH, PROG, and EMT on the hCG trigger day were divided into binary variables, respectively, by the cutoff values, and which were obtained based on receiver operating characteristic curve analysis of live birth among LH, PROG and EMT levels on the hCG trigger day, respectively. Multivariate binary logistic regression was used to confirm the role of LH, PROG, and EMT on the live birth, and stratified analysis was used to determine whether LH and PROG have an impact on EMT.

**Results:** EMT and LH were protective factors for live births, with odds ratios (OR) of 1.11 [95% confidence interval (CI): 1.066–1.157] and 1.696 (95% CI: 1.345–2.139), respectively. However, PROG was a risk factor for live birth, with an OR of 0.635 (95% CI: 0.526–0.766). The hierarchical cross-table analysis indicated that EMT had no significant difference for live birth in the combination of low LH and high PROG group. In the other subgroups, thick EMT was associated with a higher live birth rate ( $P < 0.05$ ).

**Conclusions:** On hCG trigger day, EMT, LH, and PROG all were independent factors that affected the live birth of fresh ETs. Thick EMT can significantly increase the live birth rate. However, multivariate logistic regression analysis showed that EMT does not affect the live birth rate in combination of low LH and high PROG environment.

**Keywords:** Live birth rate; luteinizing hormone (LH); endometrial thickness (EMT); progesterone (PROG); in vitro fertilization (IVF)

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## Introduction

In the process of human assisted reproductive technology (ART), there are many factors that affect the final live birth outcome, including ovarian reserve, ovarian responsiveness to exogenous gonadotropin (Gn), quality of the embryos, and maternal-fetal cross-talk during the implantation window (1-5). In the early stage of follicular development, endogenous reproductive hormone changes according to the addition of exogenous Gn, and these changes have a significant impact on live birth outcomes (6).

In the existed studies, luteinizing hormone (LH) and progesterone (PROG) on human chorionic gonadotropin (hCG) trigger day are significantly correlated with the outcome of ART in multiples studies, and are independent factors affecting the live birth (7,8). Moreover, it has been confirmed that endogenous LH and PROG are also involved in the functional preparation of the endometrium during the implantation window period (9,10). Although the specific mechanism is not clear, it is reasonable to speculate that LH and PROG on hCG trigger day may interact with the endometrium, thereby affecting the outcome. However, whether they are related to endometrial thickness (EMT) is still unknown, and whether EMT has a positive correlation on the live birth of fresh embryo transfers (ETs) is still unknown (11).

In the GnRH-agonist regimen, we analyzed the relationship between the live births of fresh ETs and indicators on the day of hCG trigger, such as LH, PROG, and EMT. Through subgroup cross-analysis, we clarified the clinical impact of LH and PROG on EMT. The findings provide new information for the preparation of the endometrium in future ART treatment process. We present the following article in accordance with the STROBE reporting checklist (available at <http://dx.doi.org/10.21037/atm-21-1922>).

## Methods

### *Study population*

The present study was a retrospective study of patients who initiated their first ART cycle with the GnRH-agonist regimen at the Reproductive Medicine Center of the First People's Hospital of Yunnan Province between January 1, 2017 and December 31, 2018. The present study was approved by the Medical Ethics Committee of the First People's Hospital of Yunnan Province (No.: KHLL2020-KY013), and the patients provided signed

informed consent. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). All patients received conventional and standard in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) treatment without any additional intervention, and all treatments were conducted according to relevant guidelines and regulations.

Based on previous research, the premature elevation of PROG on the day of hCG trigger compromises ART outcome; therefore, for patients with PROG  $\geq 2.5$  ng/mL on the day of hCG trigger, fresh ET was cancelled, and frozen ET (FET) was used in a subsequent cycle. A total of 2,260 IVF/ICSI fresh ET cycles were ultimately included in our study.

### *Inclusion criteria*

Patients who met the following criteria were included: controlled ovarian stimulation (COS) for the first time, GnRH-agonist regimen, age <40 years, number of oocytes retrieved >3, antral follicular count (AFC)  $\geq 5$ , and anti-Müllerian hormone (AMH)  $\geq 0.5$  ng/mL. There were available embryos on the third day of oocyte retrieval, and a fresh ET was completed. To exclude endogenous factors that may affect embryo quality or the endometrium, patients with poor ovarian response was excluded according to the Bologna consensus. Patients in whom the cause of infertility was limited to the fallopian tubes or male factors, and those with genetically related causes of infertility were also excluded.

### *Ovarian stimulation and IVF/ICSI-ET*

The GnRH agonist was used to suppress the pituitary gland before stimulating the ovaries exogenously with recombinant follicle-stimulating hormone (FSH). During the mid-luteal phase of the menstrual cycle, 1.25–1.875 mg of triptorelin acetate (3.75 mg, Diphereline; Ipsen, Signes, France) was injected. After almost 14 days, transvaginal ultrasonography was performed, and serum estradiol (E2) concentrations were measured to confirm whether pituitary downregulation was complete. If there were no cysts >2 cm in diameter and circulating E2 concentrations of <50 pg/mL, 150–300 IU of rFSH (75 IU, Gonal-F; Merck-Serono, Aubonne, Switzerland) or/and human menopausal gonadotropin (HMG) (75 IU, Lebaode; Livzon, Zhuhai, China) were administered to initiate ovarian stimulation. The rFSH/HMG dose was adjusted according to the ovarian

response throughout COS. When the average diameter of the 2 leading dominant follicles reached 18 mm, EMT was evaluated by ultrasonographic examination and serum E2, LH, and PROG concentrations were tested, 250 µg of recombinant hCG (250 µg, Ovidrel; Merck-Serono, Modugno, Italy) was injected, and vaginal ultrasound-guided oocyte retrieval was performed 34–36 h later.

According to the condition of the spermatozoa, conventional IVF or ICSI was chosen. The number and morphology of blastomeres, and cellular debris within blastomeres were evaluated daily after fertilization. Fresh cleavage embryos were transferred on day 3 after oocyte retrieval, and the remaining high-quality embryos were cryopreserved for subsequent FET cycles. If there were more than 5 available embryos, blastocyst culture was recommended. To avoid complications caused by multiple pregnancies, and according to Chinese national regulations, as well as the patient's situation, the number of transferred embryos was not greater than 2. Luteal support was provided starting on the day of oocyte retrieval, using PROG sustained-release vaginal gel (90 mg, Crinone; Merck-Serono, Hertfordshire, United Kingdom), PROG soft capsules (0.1 g, Utrogestan; Cyndea, Olvega, Spain), or dydrogesterone tablets (10 mg, Duphaston; Abbott, Olst, Netherlands), based on the patient's condition and according to the manufacturer's instructions. Serum β-hCG concentrations were tested on the 14th day, and if the pregnancy was positive, luteal support was continued for at least 8 weeks.

#### ***Hormone measurements and clinical indicator definitions***

Serum hormone concentrations (i.e., AMH, FSH, PROG, LH, and E2) were measured by a Beckman-Coulter Unicel DxI 800 Access Analyzer (Beckman-Coulter, Brea, CA, USA). For all tests, the inter-assay coefficient of variation was less than 15%, and the intra-assay variation was less than 10%. EMT was detected using the ACUSON NX3 Ultrasound System (Siemens, Munich, Germany).

2PN was defined as the zygote with the presence of 2 pronuclei on the first day after oocyte retrieval; normal fertilization rate was defined as the ratio between the number of 2PN zygotes and the total number of oocytes retrieved; high-quality embryos referred to normal fertilization on day 1, normal morphology and size on day 3, total number of 6–10-blastomere embryos, and a cellular debris ratio ≤20%; live birth referred to whether the fetus was alive after parturition.

#### ***Statistical analysis***

Values were expressed as mean ± standard deviation or median (interquartile range, 25th–75th percentiles) according to the data distribution. Data comparison was performed by independent sample *t*-test or Mann-Whitney U-test according whether data normally distribution. Baseline data were all included in the multivariate logistic regression, and a forward stepwise likelihood ratio model was used. The receiver-operating characteristic (ROC) curve was used calculating for cutoff values. According to the cutoff value, the variable of LH, PROG, and EMT on the day of hCG trigger were divided into binary groups, respectively. An EMT greater than cutoff value constituted the thick EMT group, otherwise constituted the thin EMT group; LH or PROG greater than cutoff value was the high group, and below was the low group. Through the combination of LH and PROG groupings, stratified analysis was carried out to determine the role of EMT in each subgroup. All statistical analysis were performed by SPSS version 26 (IBM, Armonk, NY, USA). A 2-tailed P value of less than 0.05 was considered to be statistically significant.

## **Results**

#### ***Baseline analysis of live births***

A total of 2,260 fresh ET cycles were included in the present study, of which 844 were live births. The baseline data comparison of the live births found that the fertilization method and E2 on the day of hCG trigger had no significant impact on final outcome (*Table 1*). The EMT, LH, and PROG on the day of hCG trigger were found to have significant differences in the live birth group (*Figure 1*).

#### ***Multivariate regression for live births of fresh ETs***

After the baseline analysis of live births, all variables were included in the multivariate logistic regression model. *Table 2* summarizes the main independent factors affecting live births following fresh ETs. Of these, EMT, LH, and PROG on the day of hCG trigger were all independent factors affecting live births. EMT and LH were protective factors for live births, and their adjusted odds ratios (OR) were 1.11 [95% confidence interval (CI): 1.066–1.157] and 1.696 (95% CI: 1.345–2.139), respectively. However, PROG as a risk factor for live births, with an adjusted OR of 0.635 (95% CI: 0.526–0.766).

**Table 1** Baseline analysis of live births following fresh embryo transfers

Variables	Live births (n=844)	No live births (n=1,416)	P value
Age (years)	30.30±3.73	31.22±4.00	<0.001
BMI	21.84±2.66	22.23±2.71	0.001
AMH (ng/mL)	3.39 (2.19–5.07)	3.17 (2.11–4.71)	0.019
AFC	11 (10–13)	11 (9–13)	<0.001
Duration of COS (days)	12 (11–13)	12 (11–13)	0.004
Dosage of Gn in COS (IU)	2,825 (2,300–3,425)	3,050 (2,450–3,725)	<0.001
Indicators on the day of hCG trigger			
LH (mIU/mL)	0.70 (0.52–0.94)	0.60 (0.45–0.84)	<0.001
E2 (pg/mL)	2,942 (2,020–3,914)	2,896 (1,949–3,864)	0.240
PROG (ng/mL)	0.95 (0.66–1.31)	1.03 (0.71–1.45)	<0.001
EMT (mm)	12 (10–13)	11 (10–13)	<0.001
Method for fertilization, n (%)			
IVF	682 (80.8)	1,147 (81.0)	
ICSI	162 (19.2)	269 (19.0)	
No. oocytes retrieved	12 (9–15)	11 (8–15)	0.001
Zygote 2PN rate	0.67 (0.50–0.80)	0.62 (0.44–0.76)	<0.001
No. embryos transferred, n (%)			
1	36 (4.3)	171 (12.1)	
2	808 (95.7)	1,245 (87.9)	
No. high-quality embryos transferred, n (%)			
0	61 (7.2)	197 (13.9)	<0.001
1	199 (23.6)	442 (31.2)	
2	584 (69.2)	777 (54.9)	

AFC, antral follicular count; AMH, anti-Müllerian hormone; BMI, body mass index; COS, control ovarian stimulation; EMT, endometrial thickness; E2, estradiol; hCG, human chorionic gonadotropin; ICSI, intracytoplasmic sperm injection; IVF, in vitro fertilization; LH, luteinizing hormone, PROG, progesterone, 2PN, 2 pronuclei.

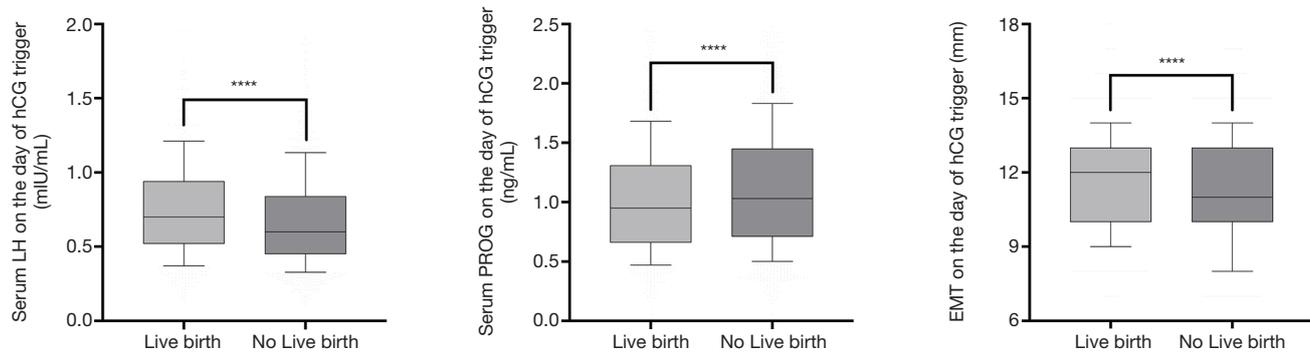
### ROC analysis of EMT, LH, and PROG on live births

In order to analyze whether there was an interaction among the indicators on hCG trigger day, the cutoff values of the 3 independent factors (EMT, LH and PROG) affecting live birth were obtained by ROC curve (Figure 2). EMT and LH were found to be positively correlated with live births, while PROG was inversely. The area under the curve (AUC) (95% CI) and cutoff values were as follows: EMT: 0.571 (95% CI: 0.547–0.595), 10.5 mm; LH: 0.578 (95% CI: 0.554–0.603), 0.665 mIU/mL; and PROG: 0.55 (95% CI: 0.526–0.574), 1.455 ng/mL. The three variables were

divided into binary groups by cutoff values, respectively, and after the combination of LH and PROG groupings, the subgroup Stratified and multivariate analysis of EMT on live birth was performed.

### Stratified analysis of EMT on live births by LH and PROG subgroups

The hierarchical cross-table shows that there was no significant difference in the live births for EMT in the combination of low LH and high PROG group (Table 3),

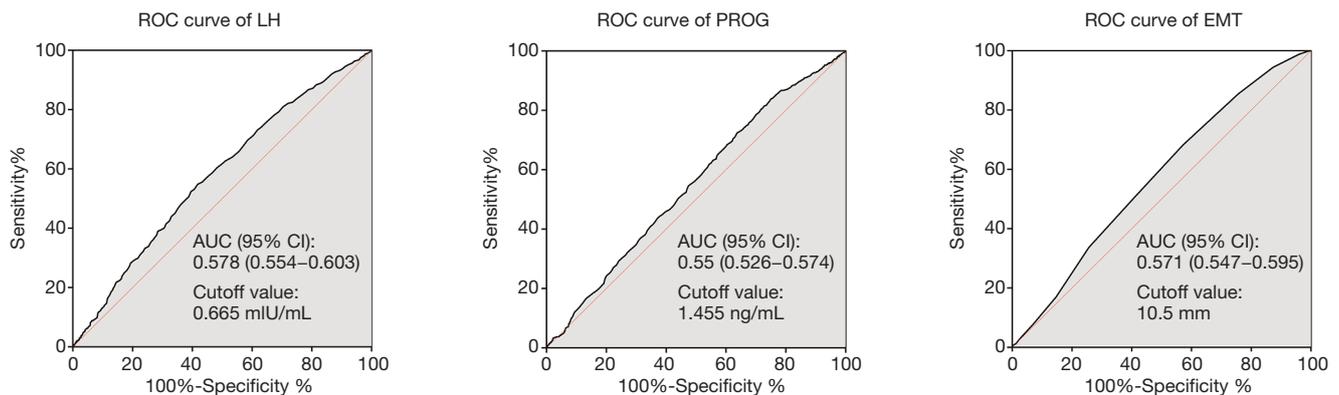


**Figure 1** Box and whisker plot analysis of the luteinizing hormone (LH), progesterone (PROG), and endometrial thickness (EMT) on human chorionic gonadotropin (hCG) trigger day between the groups of live birth and no live birth. Box chart represents the 25th–75th percentiles. Middle line represents the median. whisker represent 10–90 percentile. \*\*\*\*P<0.0001.

**Table 2** Multivariable logistic regression of live births after fresh embryo transfer

Variables	Adjusted OR	95% CI	P value
Age	0.963	0.941–0.985	0.001
BMI	0.958	0.926–0.991	0.013
EMT on hCG day	1.110	1.066–1.157	<0.001
LH on hCG day	1.696	1.345–2.139	<0.001
PROG on hCG day	0.635	0.526–0.766	<0.001
No. oocytes retrieved	1.032	1.009–1.055	0.006
Zygote 2PN rate	1.957	1.28–2.992	0.002
No. embryos transferred	2.014	1.353–2.997	0.001
No. high-quality embryos transferred	1.321	1.139–1.532	<0.001

BMI, body mass index; CI, confidence interval; EMT, endometrial thickness; hCG, human chorionic gonadotropin; LH, luteinizing hormone, OR, odds ratio; PROG, progesterone; 2PN, 2 pronuclei.



**Figure 2** Correlation analysis between luteinizing hormone (LH), progesterone (PROG), or endometrial thickness (EMT) and live birth on the receiver-operating characteristic (ROC) curve. LH and EMT had a positive correlation with live birth, and PROG had a negative correlation. AUC, area under the curve; CI, confidence interval.

**Table 3** Hierarchical cross-table analysis of luteinizing hormone (LH) and progesterone (PROG) on live births in thin and thick endometrial thickness (EMT) groups

Variables	Thin EMT	Thick EMT	P value
High PROG, n (%)			
Low LH (n=261)			0.140
Live births	17 (15.0)	33 (22.3)	
No live births	96 (85.0)	115 (77.7)	
High LH (n=228), n (%)			0.034
Live births	21 (28.0)	65 (42.5)	
No live births	54 (72.0)	88 (57.5)	
Low PROG, n (%)			
Low LH (n=944)			0.003
Live births	119 (29.8)	212 (39.0)	
No live births	281 (70.3)	332 (61.0)	
High LH (n=827), n (%)			0.004
Live births	111 (38.8)	266 (49.2)	
No live births	175 (61.2)	275 (50.8)	

**Table 4** Multivariable logistic regression of endometrial thickness on live births in different luteinizing hormone (LH) or progesterone (PROG) groups

Subgroups	Adjusted OR*	95% CI	P value
Low LH (n=1,205)	1.517	1.172–1.962	0.002
High LH (n=1,055)	1.516	1.162–1.980	0.002
Low PROG (n=1,771)	1.527	1.245–1.873	<0.001
High PROG (n=489)	1.874	1.208–2.908	0.005

\*, thick versus thin in EMT. LH, luteinizing hormone; PROG, progesterone; CI, confidence interval; OR, odds ratio; EMT, endometrial thickness.

and the P value is 0.14. In other subgroups, Thick EMT was associated with a higher live birth rate ( $P < 0.05$ ).

#### **Multivariate regression of EMT in the combination of LH and PROG subgroupings**

The multivariate logistic regression analysis in different combination subgroups was performed, and the model was adjusted by age, BMI, number of oocytes retrieved, zygote 2PN rate, number of embryos transferred, number of high-quality embryos transferred. It was found that EMT was still an independent factor affecting the live birth in each subgroup (*Table 4*). However, after combining LH and PROG subgroups, especially, in the combination of low LH

and high PROG group, the adjusted OR was 1.769 (95% CI: 0.896–3.494,  $P = 0.1$ ) (*Table 5*). Moreover, in combination of high PROG and high LH group, the P value was also close to the critical value. *Figure 3* summarizes the adjusted OR value and 95% CI of EMT in the combination subgroups analysis. The results implied that in combination of low LH and high PROG group regardless of the thickness of the endometrium, it cannot promote live birth.

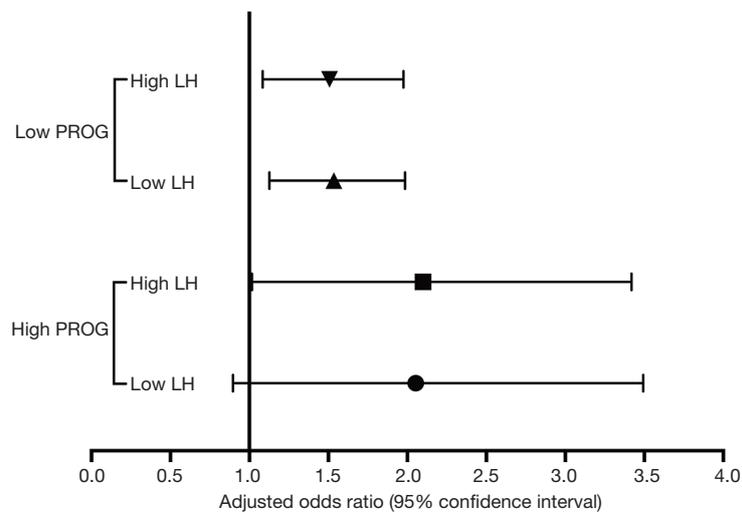
#### **Discussion**

The results of the present study showed that, among the indicators of hCG trigger day, EMT, LH, and PROG were independent factors that affected the live births following

**Table 5** Multivariable logistic regression of endometrial thickness on live births in different luteinizing hormone (LH) and progesterone (PROG) combined subgroups

Subgroups	Adjusted OR*	95% CI	P value
High PROG (n=489)			
Low LH (n=261)	1.769	0.896–3.494	0.100
High LH (n=228)	1.864	1.016–3.420	0.044
Low PROG (n=1,771)			
Low LH (n=944)	1.495	1.126–1.985	0.005
High LH (n=827)	1.464	1.084–1.975	0.013

\*, thick versus thin in EMT. LH, luteinizing hormone; PROG, progesterone; CI, confidence interval; OR, odds ratio; EMT, endometrial thickness.

**Figure 3** Adjusted odds ratio (95% confidence interval) (thick versus thin in EMT) for live births in stratified groups of luteinizing hormones (LH) and progesterone (PROG) on human chorionic gonadotropin (hCG) trigger day.

fresh ETs. Thick EMT can significantly increase the live birth rate. However, multivariate logistic regression analysis showed that EMT does not affect the live birth in the combination of low LH and high PROG environments.

LH is believed to play an important role in follicular development and final maturation (12). High LH during the follicular phase may produce more mature oocytes, and is known to increase the live birth rate of fresh ET (13). In both agonist and antagonist regimens, studies have shown that high LH after COS has a beneficial effect on the ART outcome (7,14,15); however, controversies still exist (16-18). Our results showed that high LH on hCG trigger day after COS was beneficial for live birth. There is a lack of research on the impact of LH on the outcome of fresh ETs, especially agonist regimens, and

more cohort analyses are needed in future studies to explore the effects of LH, other than promoting oocyte maturation during the periovulatory period. PROG is particularly important for late luteal support (19). It is generally believed that premature elevated PROG does not affect the quality of oocytes (9); however, it may lead to early offset of endometrial receptivity (8). Therefore, embryo implantation after transfer will be significantly compromised and can affect the cycle outcome (8,20-25). Regarding the cause of premature PROG increase, some researchers believe that follicles exposed to high doses of FSH during COS will respond with an inappropriately high luteinizing hormone human chorionic gonadotropin receptor (LHCGR) expression. This in turn causes high PROG output in response to the trigger (24). EMT on

the day of hCG trigger indicates the state of endometrial development. The thicker the EMT, the higher the possibility of live birth after fresh ET (26). Conversely, if the EMT is low on hCG trigger day, various complications may occur during pregnancy, which will also reduce the ART live birth rate (27-29).

Our findings indicated that, with low LH or high PROG alone, better EMT can also improve ART outcomes. However, with co-existing low LH and high PROG environment, although there EMT is thicker, the live birth rate following fresh ET will not improve. This implies that there is an interaction between LH, PROG, and that endometrium, that is, under the combined action of low LH and high PROG, the implantation condition of the endometrium was compromised. Despite a thick EMT, a better outcome cannot be achieved.

PROG has been found to directly act on the endometrium and participate in the embryo implantation process (30,31). Moreover, the premature elevation of PROG on hCG trigger day was significantly related to a decrease in endometrial receptivity (32). Studies on the effect of LH on the endometrium are relatively scarce, but existing studies have found that LHCGR exists on the endometrium in animal models (33), and that its role is mainly to stimulate uterine growth, proliferation, and diastolic uterine movement (34). In human studies, a functional LHCGR on the endometrium has also been found (35,36), which is regulated by the menstrual cycle and presents periodic changes. The expression of LHCGR reaches the highest level during the endometrial secretion phase (10), so it is reasonable to speculate that the low LH level following hCG trigger may affect the role of the endometrium during the implantation window. To sum up, it can be inferred that thick EMT cannot improve pregnancy outcomes under combination of low LH and high PROG condition on hCG trigger day.

Due to the inherent limitations of retrospective research, there was data selection bias in our study. Furthermore, some patients cancelled the fresh ET for various reasons, particularly when PROG was >2.5 ng/mL on hCG trigger day, this may increase the data bias. If more accurate conclusions are to be drawn, further prospective studies are needed in the future to analyze the interaction mechanism between LH, PROG, and EMT on hCG trigger day and determine the reason for such results. In this way, we can better understand the role of reproductive hormone in the endometrial implantation window in order to improve the success rate of implantation.

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## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at <http://dx.doi.org/10.21037/atm-21-1922>

*Data Sharing Statement:* Available at <http://dx.doi.org/10.21037/atm-21-1922>

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/atm-21-1922>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All study designs were approved by the Ethics Committee of the First People's Hospital of Yunnan Province (No.: KHLL2020-KY013), and the patients provided signed informed consent. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013).

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