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ASSISTED REPRODUCTION TECHNOLOGIES

Premature progesterone elevation during the early and mid-follicular phases in fresh in vitro fertilization (IVF) cycles is associated with lower live birth, clinical pregnancy, and implantation rates

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Abstract

Purpose Evaluate follicular phase progesterone elevation (≥ 1.5 ng/mL) prior to trigger during IVF stimulation and its effects on live birth rate (LBR), clinical pregnancy rate (CPR), and implantation rate (IR) in fresh IVF cycles.

Methods This was a retrospective cohort study within an academic clinic. A total of 6961 fresh IVF and IVF/ICSI cycles from October 1, 2015 to June 30, 2021 were included and grouped by progesterone (PR) prior to trigger: PR < 1.5 ng/mL (low PR group) and PR ≥ 1.5 ng/mL (high PR group). Main outcome measures included LBR, CPR, and IR.

Results Among all cycle starts, 1568 (22.5%) were in the high PR group and 5393 (77.5%) were in the low PR group. Of the cycles which proceeded to an embryo transfer, 416 (11.1%) were in the high PR group and 3341 (88.9%) were in the low PR group. The high PR group had significantly lower IR (RR 0.75; 95% CI 0.64–0.88), CPR (aRR 0.74; 95% CI 0.64–0.87), and LBR (aRR 0.71; 95% CI 0.59–0.85) compared to the low PR group. When stratified by progesterone on the day of trigger (TPR), there was a clinically notable decrease in IR (16.8% vs 23.3%), CPR (28.1% vs 36.0%), and LBR (22.8% vs 28.9%) in the high PR group compared to the low PR group even when TPR < 1.5 ng/mL.

Conclusions In fresh IVF cycles in which TPR < 1.5 ng/mL, progesterone elevation ≥ 1.5 ng/mL at any point in time prior to trigger negatively impacts IR, CPR, and LBR. This data supports testing of serum progesterone in the follicular phase prior to trigger, as these patients may benefit from a freeze-all approach.

Keywords Premature progesterone elevation · Follicular phase · Ovarian stimulation · IVF · Pregnancy outcomes

Introduction

Despite attempts at suppressing endogenous gonadotropins with gonadotropin-releasing hormone (GnRH) agonists and antagonists, progesterone elevation (PE) at the time of trigger is common during controlled ovarian stimulation. The incidence of PE on the day of trigger has been demonstrated to be as high as 13–46% in GnRH agonist cycles [1] and 23% in GnRH antagonist cycles [2]. These subtle increases in serum progesterone are concerning, as PE on the day of trigger has been associated with decreased implantation [3], clinical pregnancy [4, 5], and live birth rates [6] following fresh embryo transfer when compared to cycles which proceeded to fresh embryo transfer following low progesterone levels on the day of trigger.

The mechanism by which PE exerts these deleterious effects is unclear; previous studies have attributed these adverse pregnancy outcomes to asynchrony between the endometrium and the embryo [6–8] or impairments in oocyte quality [9, 10]. In natural menstrual cycles, the presence of late follicular phase progesterone is essential for follicular development, ovulation, and endometrial receptivity [6]. In contrast, the hyperstimulated endocrine milieu which results from controlled ovarian stimulation may cause premature PE, thereby maturing the endometrium beyond the optimal window of implantation at the time of embryo transfer.

Previous studies have demonstrated a decline in IVF outcomes and live birth rates when serum progesterone is elevated ≥ 1.5 ng/mL at the time of trigger [2, 11]. Although these data have prompted several IVF clinics to adopt a

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freeze-all approach if serum progesterone is elevated on the day of trigger, there is a paucity of data on the impact of progesterone elevation in the early and mid-follicular phases.

Due to previous research linking elevated serum progesterone levels at the beginning of ovarian stimulation with inferior ART outcomes [12], we believed that a single assessment of serum progesterone at the time of trigger may be an insufficient proxy of the endometrium's exposure to progesterone. Consequently, our center began measuring serum progesterone levels from stimulation start in 2015. Taking advantage of this fact, the objective of this study is to characterize early and mid-follicular phase PE (defined as serum progesterone ≥ 1.5 ng/mL) during IVF stimulation and its effects on implantation, clinical pregnancy, and live birth rates in fresh IVF cycles. We hypothesize that PE ≥ 1.5 ng/mL at any point during stimulation prior to trigger will be associated with decreased implantation, clinical pregnancy, and live birth rates.

Methods

This study was approved by the institutional review board at Mass General Brigham (Protocol # 2016P001715). Approval and waiver of written informed consent to retrieve and analyze data were obtained from the institutional review board at Mass General Brigham.

Inclusion criteria

This retrospective cohort study included patients undergoing fresh IVF and IVF/ICSI cycles at the Brigham and Women's Hospital from October 1, 2015 to June 30, 2021. Data were collected from a prospectively maintained departmental database. Cycles had estradiol and serum progesterone (PR) levels measured with each follicular monitoring ultrasound visit beginning on day 7 of stimulation until the day of trigger. Cycles proceeded to fresh transfer of day 3 or day 5 embryos if TPR < 2.0 ng/mL. Cycles utilizing letrozole, donor egg, gestational carriers, and PGT tested embryos were excluded.

Ovarian stimulation

Ovarian stimulation protocols included GnRH antagonists, GnRH agonists for downregulation, estradiol priming, low-dose GnRH agonist flare protocols, or minimal stimulation with clomiphene citrate [12, 13]. Cycles had serum estradiol and PR levels measured with each follicular monitoring ultrasound visit beginning on day 7 of stimulation until the day of trigger. When two or more follicles were ≥ 18 mm in diameter, 5000 IU hCG, 10,000 IU hCG, or dual trigger of 40 mg leuprolide with 1500 IU hCG was utilized for final oocyte maturation. Oocyte retrieval was performed 36 h after the trigger injection. Fertilization was achieved with either conventional IVF or intracytoplasmic sperm injection (ICSI) as clinically indicated. Patients triggered with hCG started Crinone 8% intravaginal gel daily 48 h after retrieval. Cycles with a dual trigger started oral Estrace 3 mg BID and Crinone 8% intravaginal gel 48 h after oocyte retrieval for luteal phase support.

Laboratory protocols and embryo grading

Gametes and embryos were cultured in a humidified incubator maintained at 37 °C under an atmosphere of 5–6% CO_2, 5% O_2, and the balance of N_2. IVF or ICSI was performed 4–6 h or 3–5 h after egg retrieval. The fertilization check was performed 16–18 h after insemination. Zygotes with 2 pronuclei (2PN) were cultured in 25 uL microdrops of a single-step medium (Global Total, IVF OnLine, Guelph, Ontario, Canada) under mineral oil.

Embryos were evaluated on day 3 between 66- and 69-h post-insemination. Morphological grading was based on the number of blastomeres, the extent of fragmentation, and the degree of asymmetry, as previously described [14]. Blastocyst morphology was evaluated on day 5 and scored according to the stage of development and to the quality of the inner cell mass (ICM) and trophectoderm (TE) [15]. Each embryo was scored from 1 to 9 to indicate its development at the time of grading: 1 denoted an arrested embryo, 2 an embryo with < 50% compaction, 3 a full morula, 4 an early blastocyst, 5 an embryo in which > 50% of the volume is occupied by the blastocyst, 6 to 8 with increasing blastocoel formation and expansion, and 9 a fully hatched blastocyst. A grade of A–D and a–d (best to worst) indicated the quality of the ICM and TE, respectively.

Ultrasound-guided embryo transfer was performed on day 3 or 5 depending on the number and quality of embryos available. Serum hCG levels were assessed 14 days after embryo transfer, followed by ultrasound confirmation of an intrauterine pregnancy in all pregnant patients. Patients with a confirmed intrauterine pregnancy continued progesterone supplementation until 10 weeks of gestation.

Progesterone assay

Serum progesterone levels were measured with a solid-phase competitive chemiluminescent enzyme immunoassay. The lower limit of detection for the assay was 0.05 ng/mL, and the analytical sensitivity of the assay was 0.03 ng/mL. Intra-assay and inter-assay coefficients of variation were 6.5 and 6.9%, respectively.

Table 1 Demographic characteristics of patients in the low and high PR groups

	PR prior to trigger	
	Low PR group (PR < 1.5 ng/mL) *N* = 5393	High PR group (PR ≥ 1.5 ng/mL) *N* = 1568
Age	36.55 (4.50)	35.91 (4.70)
BMI	26.58 (6.85)	24.73 (5.28)
AMH	2.82 (3.28)	3.05 (2.97)
Day 3 FSH	8.64 (10.17)	8.15 (4.66)
E2 on day of trigger or day prior (ng/mL)	1954.04 (1018.73)	2315.50 (1426.26)
Infertility diagnosis		
Diminished ovarian reserve	729 (13.52)	120 (7.65)
Male factor	567 (10.51)	165 (10.52)
Tubal factor	148 (2.74)	48 (3.06)
Endometriosis/uterine factor	156 (2.89)	46 (2.93)
Ovulatory dysfunction	282 (5.23)	71 (4.53)
Unknown	1020 (18.91)	276 (17.60)
Other	709 (13.15)	367 (23.41)
Mixed	1782 (33.04)	475 (30.29)
Stimulation protocol		
Antagonist (antagonist/patch)	4131 (76.60)	1266 (80.74)
Downregulation	332 (6.16)	83 (5.29)
Microflare	747 (13.85)	199 (12.69)
Minimal stimulation	183 (3.39)	20 (1.28)
ICSI		
No	2201 (40.81)	607 (38.71)
Yes	3192 (59.19)	961 (61.29)
Trigger type		
HCG	3265 (60.54)	709 (45.22)
Dual trigger (HCG + leuprolide)	1173 (21.75)	286 (18.24)
Leuprolide	955 (17.71)	573 (36.54)
HMG		
No	1185 (21.97)	471 (30.04)
Yes	4208 (78.03)	1097 (69.96)

Age, BMI, AMH, Day 3 FSH, and E2 on day of or day prior to trigger are expressed as mean (SD)
Infertility diagnosis, stimulation protocol, ICSI, trigger type, and HMG are expressed as *n* (%)

Primary and secondary outcomes

The primary outcome was live birth, defined as a live-born infant after 22 weeks of gestation. Secondary outcomes included implantation rate and clinical pregnancy. Implantation rate was defined as the number of gestational sacs visualized on ultrasound divided by the number of embryos transferred. Clinical pregnancy was defined as the presence of fetal cardiac activity visualized on ultrasound.

Statistical analysis

Patients were categorized into two exposure groups based on PR levels at any point during stimulation prior to the day of trigger: PR < 1.5 ng/mL (low PR group) and PR ≥ 1.5 ng/mL (high PR group). Means and proportions were generated for continuous variables; frequencies and proportions were generated for categorical variables. Relative risks (RR) and 95% confidence intervals (CI) were produced using Poisson regression for counts, Poisson regression with an offset for rates, and log binomial regression for dichotomous outcomes. Regression models for cycle outcomes were adjusted for age, AMH, day 3 FSH, BMI, infertility diagnosis, stimulation protocol, and serum estradiol on the day of trigger. Regression models for transfer outcomes were adjusted for all previously stated covariates in addition to trigger type (hCG versus dual trigger), number of oocytes retrieved, embryo quality, and day of transfer. Generalized estimating equations were used to account for multiple cycles from the same patient. An alpha of 0.05 was considered statistically

significant. All statistical analyses were performed with SAS® version 9.4 (Cary, NC, USA).

Results

A total of 6961 cycles met inclusion criteria: 5393 (77.4%) in the low PR group (PR < 1.5 ng/mL) and 1568 (22.6%) in the high PR group (PR ≥ 1.5 ng/mL). The two groups were similar with respect to age at cycle start, BMI, infertility diagnosis, use of HMG, and day 3 FSH (Table 1). The stimulation protocols employed in both groups were comparable: antagonist protocols comprised 76.6 and 80.74% of cycles in the low PR and high PR groups, respectively.

A total of 3757 cycles proceeded to embryo transfer on day 3 or day 5 if TPR < 2.0 ng/mL: 3341 (88.9%) in the low PR group and 416 (11.1%) in the high PR group. The two groups were similar with respect to age at cycle start, BMI, infertility diagnosis, use of HMG, day 3 FSH, and stimulation protocol (Table 2).

When assessing pregnancy outcomes by serum progesterone levels prior to the day of trigger, the high PR group had significantly lower IR (RR 0.75; 95% CI 0.64–0.88), CPR (aRR 0.74; 95% CI 0.64–0.87), and LBR (aRR 0.71; 95% CI 0.59–0.85) when compared to the low PR group (Table 3).

When assessing pregnancy outcomes stratified by serum progesterone on the day of trigger (TPR), 3398 cycles had TPR < 1.5 ng/mL and 359 had TPR ≥ 1.5 ng/L (Table 4). Of

Table 2 Demographic characteristics of patients in the low and high PR groups who underwent a fresh embryo transfer

	PR prior to trigger	
	Low PR group (PR < 1.5 ng/mL) *N* = 3341	High PR group (PR ≥ 1.5 ng/mL) *N* = 416
Age	36.82 (4.23)	36.35 (4.17)
BMI	26.95 (6.98)	24.77 (5.35)
AMH	2.60 (2.91)	2.71 (2.51)
Day 3 FSH	8.73 (12.05)	8.30 (5.34)
E2 on day of trigger or day prior (ng/mL)	1825.66 (779.89)	2149.22 (851.04)
Infertility diagnosis		
Diminished ovarian reserve	528 (15.80)	52 (12.5)
Male factor	438 (13.11)	71 (17.07)
Tubal factor	109 (3.26)	22 (5.29)
Endometriosis/uterine factor	86 (2.57)	11 (2.64)
Ovulatory dysfunction	178 (5.33)	23 (5.53)
Unknown	744 (22.27)	93 (22.36)
Other	131 (3.92)	19 (4.57)
Mixed	1127 (33.73)	125 (30.05)
Stimulation protocol		
Antagonist (antagonist/patch)	2499 (74.80)	319 (76.68)
Downregulation	226 (6.76)	39 (9.38)
Microflare	506 (15.15)	54 (12.98)
Minimal stimulation	110 (3.29)	4 (0.96)
ICSI		
No	1507 (45.11)	203 (48.80)
Yes	1834 (54.89)	213 (51.20)
Trigger type		
HCG	2409 (72.10)	281 (67.55)
Dual trigger (HCG + leuprolide)	929 (27.81)	134 (32.21)
Leuprolide	3 (0.09)	1 (0.24)
HMG		
No	787 (23.56)	151 (36.30)
Yes	2554 (76.44)	265 (63.70)

Age, BMI, AMH, Day 3 FSH, and E2 on day of or day prior to trigger are expressed as mean (SD)
Infertility diagnosis, stimulation protocol, ICSI, trigger type, and HMG are expressed as *n* (%)

the cycles with TPR < 1.5 ng/mL, 3341 (98.3%) were in the low PR group and 57 (1.7%) were in the high PR group. In cycles with TPR < 1.5 ng/mL, the high PR group had clinically lower IR (16.8% vs 23.3%), CPR (28.1% vs 36.0%), and LBR (22.8% vs 28.9%) when compared to the low PR group (Table 4).

Discussion

This study confirms our hypothesis that progesterone elevation ≥ 1.5 ng/mL at any point during stimulation confers a poor prognosis following fresh embryo transfer, as the high PR group experienced significantly lower IR, CPR, and LBR when compared to the low PR group.

Although our center began measuring serum progesterone levels during ovarian stimulation in 2015 as a function of logistical ease, the results of this study indicate that it may be advantageous to check serum progesterone levels for patients intending a fresh embryo transfer, as there was a clinically notable decline in IR, CPR, and LBR in the high PR group even if TPR < 1.5 ng/mL (Table 4). Due to the potential for asynchrony between the embryo and endometrium in cycles with TPR < 1.5 ng/mL but serum progesterone ≥ 1.5 ng/mL prior to trigger, these patients may benefit from a freeze-all approach.

In cycles with TPR < 1.5 ng/mL, the high PR group had clinically lower IR (16.8% vs 23.3%), CPR (28.1% vs 36.0%), and LBR (22.8% vs 28.9%) when compared to the low PR group (Table 4). Although we believe that these results are clinically notable and have the potential to impact medical practice, statistical significance between the low PR and high PR groups was not attained likely due the low number of transfers in the high PR group. The discrepancy in the number of transfers in the low PR group ($N=3341$) and the high PR group ($N=57$) in cycles with TPR < 1.5 ng/mL is largely due the fact that providers at our center began adopting a freeze-all approach if serum progesterone ≥ 1.5 ng/mL at any point during stimulation due to the observed decrease in live birth rates. It is essential to note that high PR during stimulation with TPR < 1.5 ng/mL was not a rare occurrence at our center, as 66.5% (135/203) of cycles with TPR < 1.5 ng/mL resulted in a freeze-all strategy due to elevated progesterone during stimulation despite intending a fresh transfer at cycle start.

Critics may argue that routine monitoring of serum progesterone levels prior to trigger is costly and, thus, a practice which should be discouraged. A serum progesterone assay at our center costs $30.00 USD [16] and ranges from $27.00 to $45.00 USD at private laboratories [17]. If patients have daily serum progesterone measurements from day 7 to day of trigger, this will cost an additional $210–420, on average, depending on the length of the cycle. Although this may marginally increase the total cost of the cycle, we believe this is negligible when compared to the financial and emotional toll of a failed fresh transfer and costs associated with a subsequent fresh stimulation.

Although many IVF centers have ameliorated the decline in pregnancy rates with a freeze-all approach when TPR ≥ 2 ng/mL [18], the progesterone threshold at which a freeze-all strategy is indicated remains controversial. Our study demonstrated a clinically notable decrease in LBR between the low PR and high PR groups when TPR < 1.5 ng/mL (28.9% vs. 22.8%, Table 4) and a statistically significant decrease in LBR (21.7%, aRR 0.69, 95% CI 0.57–0.85) when

Table 3 Pregnancy outcomes by PR group

	Low PR group (PR < 1.5 ng/mL) $N=3341$ *N* (%)	High PR group (PR ≥ 1.5 ng/mL) $N=416$ *N* (%)	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
Implantation rate	22.33%	17.48%	0.75 (0.64–0.88)	n/a
No. of sacs	1467	140		
No. of embryos transferred	6289	801		
Clinical pregnancy				
No	2139 (64.0)	299 (71.9)	0.78 (0.67–0.92)	0.74 (0.64–0.87)
Yes	1202 (36.0)	117 (28.1)		
Live birth				
No	2367 (71.1)	325 (78.1)	0.76 (0.63–0.92)	0.71 (0.59–0.85)
Yes	964 (28.9)	91 (21.9)		

aRR adjusted for age, AMH, day 3 FSH, BMI, infertility diagnosis, stimulation protocol, number of oocytes, embryo quality, trigger type, E2 on day of trigger, and day of transfer

3 transfers missing live birth outcome

4 transfers with leuprolide triggers were removed from adjusted RR

Low PR group missing 10 live birth outcomes

Table 4 Pregnancy outcomes from fresh embryo transfers stratified by TPR

	TPR < 1.5 ng/mL *N* = 3398				TPR ≥ 1.5 ng/mL *N* = 359		
	Low PR group (PR < 1.5 ng/mL) *n* (%) *N* = 3341	High PR group (PR ≥ 1.5 ng/mL) *n* (%) *N* = 57	Unadjusted RR (95% CI)	Adjusted RR (95% CI)	High PR group (PR ≥ 1.5 ng/mL) *n* (%) *N* = 359	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
Implantation rate	23.3%	16.8%			17.6%		
No. of sacs	1467	20	0.72 (0.48–1.08)	n/a*	120	0.75 (0.64–0.89)	n/a*
No. of embryos transferred	6289	119			682		
Clinical pregnancy							
No	2139 (64.0)	41 (71.9)	0.78 (0.51–1.19)	0.82 (0.56–1.21)	258 (71.9)	0.78 (0.66–0.93)	0.73 (0.62–0.86)
Yes	1202 (36.0)	16 (28.1)			101 (28.1)		
Live birth							
No	2367 (71.1)	44 (77.2)	0.79 (0.49–1.28)	0.82 (0.52–1.28)	281 (78.3)	0.75 (0.61–0.92)	0.69 (0.57–0.85)
Yes	964 (28.9)	13 (22.8)			78 (21.7)		

aRR adjusted for age, AMH, day 3 FSH, BMI, infertility diagnosis, stimulation protocol, number of oocytes, embryo quality, trigger type, E2 on day of trigger, and day of transfer

3 transfers missing live birth outcome

4 transfers with leuprolide triggers were removed from adjusted RR

*aRR not calculated given pooled effect analysis

serum progesterone levels are persistently elevated ≥ 1.5 ng/mL during stimulation and on the day of trigger. The amplified decline in IR, CPR, and LBR seen in cycles with progesterone levels persistently elevated ≥ 1.5 ng/mL during stimulation and on the day of trigger is likely due to the duration of endometrial exposure to elevated progesterone, as has been previously published [5].

A primary strength of this study is the large sample size, allowing us to assess the impact of progesterone elevation in the early and mid-follicular phases on pregnancy outcomes. By conducting the study at a single large academic center utilizing a singular solid-phase competitive chemiluminescent enzyme progesterone immunoassay, we capitalized on low inter-assay and intra-assay variability, allowing for the appropriate comparison between exposure groups. One limitation of this study is its retrospective design; thus, future prospective studies assessing pregnancy outcomes at varying follicular phase progesterone thresholds and durations of progesterone elevation are warranted.

Conclusion

In fresh IVF cycles in which TPR < 1.5 ng/mL, progesterone elevation ≥ 1.5 ng/mL at any point in time prior to trigger negatively impacts IR, CPR, and LBR. These data support routine testing of serum progesterone, as these patients may benefit from a freeze-all approach.

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Author contribution The authors confirm contribution to the paper as follows: study conception and design: KWK and EY; data collection: KWK and AL; analysis and interpretation of results: AL and JSG; drafting and manuscript preparation: JSG. All authors reviewed the results and approved the final version of the manuscript.

Data availability Data were collected from a prospectively maintained departmental database at Brigham and Women's Hospital.

Code availability All statistical analyses were performed with SAS® version 9.4 (Cary, NC, USA).

Declarations

Ethics approval This study was approved by the Mass General Brigham Human Research Committee at the Brigham and Women's Hospital (Protocol # 2016P001715).

Consent to participate The need for informed consent was waived by the Mass General Brigham Human Research Committee as all data was retrieved from routine clinical care medical records.

Conflict of interest The authors declare no competing interests.

References

1. Wu Z, et al. Effect of HCG-day serum progesterone and estradiol concentrations on pregnancy outcomes in GnRH agonist cycles. Reprod Biomed Online. 2012;24:511–20. https://doi.org/10.1016/j.rbmo.2012.02.003.
2. Papanikolaou EG, Pados G, Grimbizis G, et al. GnRH-agonist versus GnRH-antagonist IVF cycles: is the reproductive outcome affected by the incidence of progesterone elevation on the day of HCG triggering? A randomized prospective study. Hum Reprod. 2012;27(6):1822–8.
3. Ochsenkühn R, Arzberger A, Von Schönfeldt V, Gallwas J, Rogenhofer N, Crispin A, et al. Subtle progesterone rise on the day of human chorionic gonadotropin administration is associated with lower live birth rates in women undergoing assisted reproductive technology: a retrospective study with 2,555 fresh embryo transfers. Fertil Steril. 2012;98(2):347–54.
4. Corti L, Papaleo E, Pagliardini L, Rabellotti E, Molgora M, La Marca A, et al. Fresh blastocyst transfer as a clinical approach to overcome the detrimental effect of progesterone elevation at hCG triggering: a strategy in the context of the Italian law. Eur J Obstet Gynecol Reprod Biol. 2013;171(1):73–7.
5. Huang CC, Lien YR, Chen HF, Chen MJ, Shieh CJ, Yao YL, et al. The duration of pre-ovulatory serum progesterone elevation before hCG administration affects the outcome of IVF/ICSI cycles. Hum Reprod. 2012;27(7):2036–45.
6. Santos-Ribeiro S, Polyzos NP, Haentjens P, Smitz J, Camus M, Tournaye H, et al. Live birth rates after IVF are reduced by both low and high progesterone levels on the day of human chorionic gonadotrophin administration. Hum Reprod. 2014;29(8):1698–705.
7. Bourgain C, Devroey P. The endometrium in stimulated cycles for IVF. Hum Reprod Update. 2003;9(6):515–22.
8. Fanchin R, Ferreira AL, Righini C, De Ziegler D, Olivennes F, Frydman R. Consequences of premature progesterone elevation on the outcome of in vitro fertilization: insights into a controversy. Fertil Steril. 1997;68(5):799–805.
9. Huang B, Ren X, Wu L, Zhu L, Xu B, Li Y, et al. Elevated progesterone levels on the day of oocyte maturation may affect top quality embryo IVF cycles. PLoS One. 2016;11(1):e0145895.
10. Papanikolaou EG, Kolibianakis EM, Pozzobon C, Tank P, Tournaye H, Bourgain C, et al. Progesterone rise on the day of human chorionic gonadotropin administration impairs pregnancy outcome in day 3 single-embryo transfer, while has no effect on day 5 single blastocyst transfer. Fertil Steril. 2009;91(3):949–52.
11. Kong N, Liu J, Jiang Y, Zhu Y, Zhang C, Yan G, Huang C. Adverse impact of elevated progesterone levels on human chorionic gonadotropin trigger day on blastocyst transfer outcomes in gonadotropin-releasing hormone agonist cycles. Europ J Obstet Gynecol Reprod Biol. 2022;276:107–12.
12. Cheung LP, Lam PM, Lok IH, Chiu TTY, Yeung SY, Tjer CC, et al. GnRH antagonist versus long GnRH agonist protocol in poor responders undergoing IVF: a randomized controlled trial. Hum Reprod. 2005;20(3):616–21.
13. Dragisic KG, Davis OK, Fasouliotis SJ, Rosenwaks Z. Use of a luteal estradiol patch and a gonadotropin-releasing hormone antagonist suppression protocol before gonadotropin stimulation for in vitro fertilization in poor responders. FertilSteril. 2005;84(4):1023–6.
14. Racowsky C, Combelles CMH, Nureddin A, Pan Y, Finn A, Miles L, et al. Day 3 and day 5 morphological predictors of embryo viability. Reprod Biomed Online. 2003;6(3):323–31.
15. Bakkensen JB, Brady P, Carusi D, Romanski P, Thomas AM, Racowsky C. Association between blastocyst morphology and pregnancy and perinatal outcomes following fresh and cryopreserved embryo transfer. J Assist Reprod Genet. 2019;36(11):2315–24.
16. Mass General Brigham: Patient Estimates. https://patientgateway.massgeneralbrigham.org/MyChart-PRD/GuestEstimates/GetEstimateDetails?svcArea=WP-24e9uXCVWSzEYXIZBsDAXOsA-3D-3D-24kqE853cHDtZ-2BVmykh5-2BSDDgiEoWyT6eEOm3Ph7WnjIQ-3D&isMultiSA=True&token=CQjm7AI6eBiwytyBR1w0VPsC39krv2X5zJ6drr5baKA%3d&template=WP-24z9mHUnA3Ox-2Bo-2Btoi9zCuCg-3D-3D-24dUAenPTYUEh8alkBfUMubjZM94bRgGdyRNfHM3YJQOo-3D&needsRTETrue&location=. Accessed 1 Mar 2023
17. Serum progesterone blood test costs. https://www.findlabtest.com/lab-test/hormone-testing/progesterone-blood-test-cost-quest-745. Accessed 1 Mar 2023
18. Ozçakir HT, Levi R, Tavmergen E, Göker EN. Premature luteinization defined as progesterone estradiol ratio >1 on hCG administration day seems to adversely affect clinical outcome in long gonadotropin-releasing hormone agonist cycles. J ObstetGynaecol Res. 2004;30(2):100–4.