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ORIGINAL ARTICLE

Endometrial Thickness (Compaction) and Serum Progesterone Level on the Day of Thawed Frozen Embryo Transfer as a Predictor of Early Reproductive Outcomes

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Abstract

Background: **The majority of studies have found that the thin endometrium during *in vitro* fertilization (IVF) therapy has a negative impact on pregnancy outcomes and that levels of serum progesterone may affect pregnancy outcomes. The study's primary aim was to investigate any potential associations between the clinical pregnancy rate and serum progesterone levels on the day of the transfer of frozen embryos. Our study's secondary endpoint involved using transvaginal ultrasonography (TVUS) on the day of the transfer of frozen embryos to determine if endometrial compaction is related to increased rates of pregnancy.**

Aim: **The primary aim of the study was to investigate the possible relationship between level of serum progesterone concentrations on the day of frozen embryo transfer and clinical pregnancy rate, while secondary end-point of our study was to investigate whether endometrial compaction is associated with increased pregnancy rates using Transvaginal ultrasonography on the day of frozen embryo transfer.**

Patients and methods: **Our study included 120 women who underwent frozen-thawed embryo transfer during the period from August 2021 to April 2022. They were selected according to inclusion criteria: age (20−39 years), primary or secondary infertility, and undergoing frozen embryo transfer (FET) regardless of the cause of the freezing of the embryos (supernumerary embryos obtained after transfer of a fresh embryo, elective embryo freezing due to ovarian hyperstimulation syndrome, or other causes).**

Result: **We demonstrated that endometrial compaction is not linked to statistically significant enhancements in biochemical or clinical pregnancy and that serum levels of P4 at or over 10 ng/mL on the day of frozen embryo transfer are not linked to statistically significant enhancements in either.**

Conclusion: **On the day of the frozen embryo transfer, endometrial compaction and levels of serum progesterone did not show any clinically significant improvement in the biochemical or clinical pregnancy rates.**

Keywords: Endometrial thickness, Frozen embryo transfer, Serum progesterone

1. Introduction

Endometrial thickness and clinical pregnancy have been the subject of ongoing controversy for many years.[1,2] The majority of research has found that thin endometrium has a negative impact on pregnancy success during *in vitro* fertilization (IVF) therapy, though the exact mechanism is unknown.[3,4] Endometrial thickness may represent endometrial receptivity, which refers to the endometrium's ability to receive embryos when the window for implanting is open, that is, ~7 days

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following ovulation in the natural monthly cycle. More indicative of endometrial receptivity is the status of the endometrium on the day of transfer than the day of progesterone injection or human chorionic gonadotropin (hCG) trigger, both of which occur for a minimum of 3–5 days prior to the transfer of the embryo.[5] The endometrium's state varies during the natural cycle of menstruation as well as during treatment for IVF. One of the typical changes is that following administration of hCG or progesterone during IVF cycles, the endometrial pattern may change from pattern A (triple-line pattern)/pattern B (intermediate isoechogenic pattern) to pattern C (homogenous, hyper-echogenic pattern). However, little is known about the thickness of the endometrial changes following the administration of hCG or progesterone.[6,7] But neither the ideal duration of progesterone (P4) exposure prior to frozen embryo transfer (FET) nor the serum (P4) levels needed to optimize cycle outcomes have been established. Because of this, it is intriguing to determine whether or not serum P4 levels on the day of FET have an association with the ongoing pregnancy rate (OPR).[8] There is little evidence on this subject, and it relies on retrospective research with contradicting outcomes.[9,10] According to one recent proposal, the mid-luteal phase has an ideal window of P4 levels with the highest pregnancy rate.[11]

The study's primary objective was to investigate any potential associations between the clinical pregnancy rate and serum progesterone levels on the day of the transfer of embryos. Our study's secondary endpoint involved using transvaginal ultrasonography (TVUS) on the day of the transfer of embryos to determine if endometrial compaction is related to increased rates of pregnancy.

2. Patients and methods

This is an observational, prospective cohort study. It was carried out at the Al-Azhar University-based International Islamic Centre for Population Studies and Research's (IICPSR) assisted reproduction (ART) unit. All methods used in human-participant research have been in compliance with international ethical standards. The IICPSR's Research Ethics Committee provided the necessary ethical approval. Ethics approval and informed consent to participate were obtained from all eligible participants prior to their participation in the study. The eligible women signed written informed consent. We included 120 women who underwent frozen-thawed embryo transfer during the period from August 2021 until April 2022. They were selected according to inclusion criteria: age (20–40 years), primary or secondary infertility, and undergoing FET regardless of the cause of the freezing of the embryos (supernumerary embryos obtained after a transfer of fresh embryos, elective embryo freezing due to ovarian hyper stimulation syndrome, or other causes). Transfer of a single embryo, failure of recurrent implantation, recurrent miscarriage, uterine pathology, transfer of a fresh embryo, and any clinically relevant systemic illness that contraindicates assisted reproduction or pregnancy were the exclusion criteria. Hormonal replacement therapy (HRT) protocol was started on day one of the menstrual cycle for endometrial preparation using oral 2 mg estradiol valerate tablets three times daily (white tablets); (Cycloprogynova; Bayer) three times daily. Trans vaginal ultrasound (TVS) was done on day 9 or 10 of the cycle. If the thickness of the endometrium was less than 8 mm, the estradiol dose was increased to 4 mg for 8 h a day for 2 days. TVS was repeated, if no leading follicle ($\geq$14 mm) was present and the endometrial thickness is $\geq$ 8 mm; intramuscular Prontogest (Merk) 100 mg ampoule was added daily. Thawing and transferring of FET was commenced on 3–5 days later according to the stage of cryopreserved embryos.

Embryo thawing and transfer were carried out according to our ART unit protocol. Before transfer, the surviving embryos had been cultivated to the cleavage stage or the blastocyst stage if their membranes were morphologically normal, their cytoplasm was clear, and there were no breaches of the zona pellucida. Venous Blood sample (3 mL) was collected by the researcher for assessment of serum progesterone on day of FET. Eight samples were rejected because of hemolysis. Serum progesterone in the accepted samples was measured by ELFA technique enzyme linked fluorescent assay by VIDAS apparatus using commercial kits from Biomerieux, France. Abdominal ultrasonography (AUS) with full blader was done by the researcher to measure the endometrial thickness immediately before FET in comparison with the previous measurement on the day of commencement of parenteral progesterone. A quantitative B-HCG test with a value of 25 mIU/mL or more was used to diagnose pregnancy 2 weeks after FET. About 2 weeks following the positive pregnancy test, a gestational sac that had a fetal heartbeat was observed during transvaginal scanning, confirming a clinical pregnancy.

2.1. Statistical methodology

Data collected were reviewed and coded. These numerical codes were entered into the computer,

which then performed statistical analyses employing the Statistic Package for Social Science Version 22 (SPSS 22). Descriptive statistics: 1 Quantitative data: were presented as mean and standard deviation (mean ± SD) 2 Qualitative data: were expressed as numbers and percentages. 2- Chi square-test (χ^2) for comparing qualitative data, Student's *t*-test for comparing quantitative data of two independent samples with normal distribution and homogeneity of variance, Mann–Whitney test for comparing quantitative data of two independent samples with no normally distributed variable, and Pearson correlation for studying the relationship between variables were used in the analysis of statistical data comparing the groups. The coefficient interval was set to 95 %. The following probability (*P*) values were used to calculate the significance level: statistics were deemed significant at $P < 0.05$.

3. Results

A total of 120 female patients underwent frozen thawed embryo transfer were included in the study, the results came out with overall positive clinical pregnancy rate of 58.3% (70 patients) and negative clinical pregnancy rate of 41.7 % (50 patients) which showed no statistical significance in relation to progesterone levels on day of Frozen thawed embryo transfer "Table 1", also "Table 2" showing no statistical significance of the endometrial compaction on day of frozen thawed embryo transfer in relation to either positive or negative clinical pregnancy rate (Figs. 1–3, Tables 3 and 4).

4. Discussion

4.1. Endometrial compaction

There is a lot of heterogeneity in the present literature on endometrial compaction during FET cycles. No statistically significant change in the thickness of the endometrium (compaction) was shown in our study. Endometrial compaction and expansion were not shown to be related to ongoing pregnancy. This is the same finding[12] reported for either comparable or lower pregnancy rates. Our study results of endometrial compaction did not agree with the results of[13,14] studies who reported higher clinical pregnancy rates with endometrial compaction. This contradictory result could be explained due to using AUS for the assessment of EMT in all patients on the day of FET. Obesity interferes with AUS since ultrasonography wave signals have difficulty penetrating fat to image the organs beneath. Patients who have predominantly fat under their skin have inferior ultrasound imaging compared with individuals who have predominantly intraperitoneal fat. In contrast, TVUS bypasses the abdominal pannus and uses a high-frequency transducer for assessing the pelvic organs while producing high-quality images of the structures inside its range.[15] Consequently, it has been found that the EMT on the day of FET was significantly thinner and that the EMT changes by AUS were significantly higher compared with TVUS in the compaction of endometrium and no change groups. When the thickness of the endometrium stays within the range of 8.7–14.5 mm

Table 1. Pregnancy outcome in relation to serum progesterone levels on frozen embryo transfer day.

	No pregnancy	Pregnant	T	*P*-value	Sig.
	No. = 50	No. = 70			
P4 level on day of FET					
Range	2.16–39.40	2.26–55.30	−1.774•	0.079	NS
Median [IQR]	5.75 [6.23]	8.58 [10.40]			
Mean ± SD	8.464 ± 7.932	11.440 ± 10.130			

Table 2. Pregnancy outcome in relation to endometrial thickness change on day of frozen embryo transfer.

	No pregnancy	Pregnant	T	*P*-value	Sig.
	No. = 50	No. = 70			
Endometrial thickness on day of progesterone start					
Range	9–15	6–15	−0.113	**0.911**	**NS**
Median [IQR]	10.5 [1.5]	10.5[2]			
Mean ± SD	10.781 ± 1.515	10.670 ± 1.636			
Endometrial thickness on day of FET					
Range	7–16	6–14	1.665•	0.069	NS
Median [IQR]	10 [2.88]	9.4 [1.5]			
Mean ± SD	10.068 ± 2.263	9.644 ± 1.872			

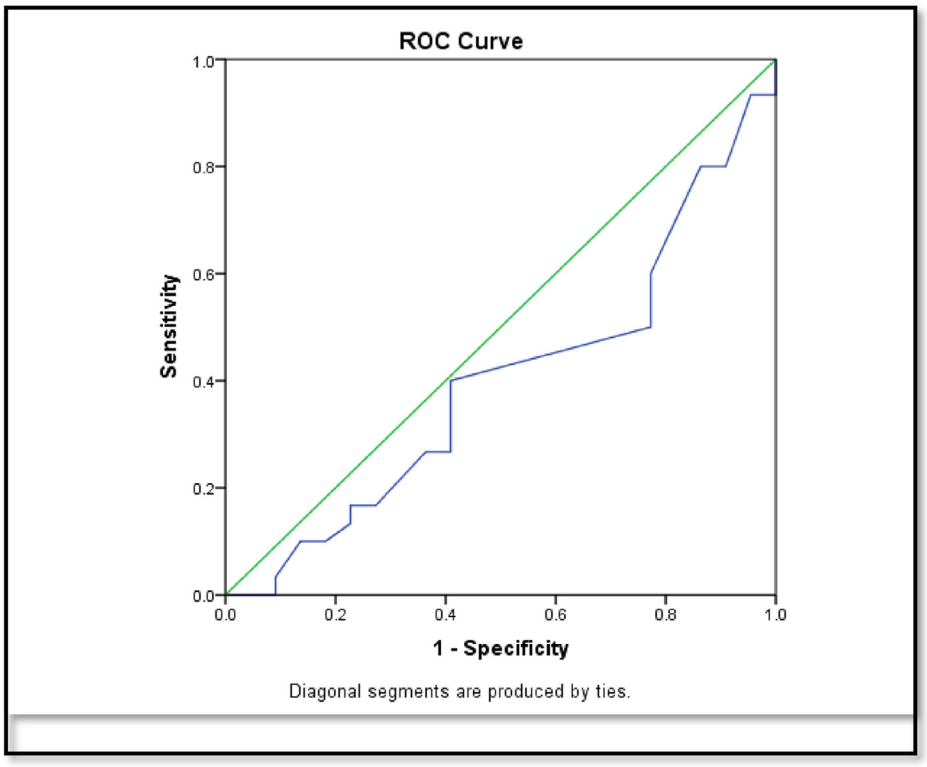

Fig. 1. Receiver operating characteristic curve for endometrial thickness as a pregnancy predictor on the frozen embryo transfer day.

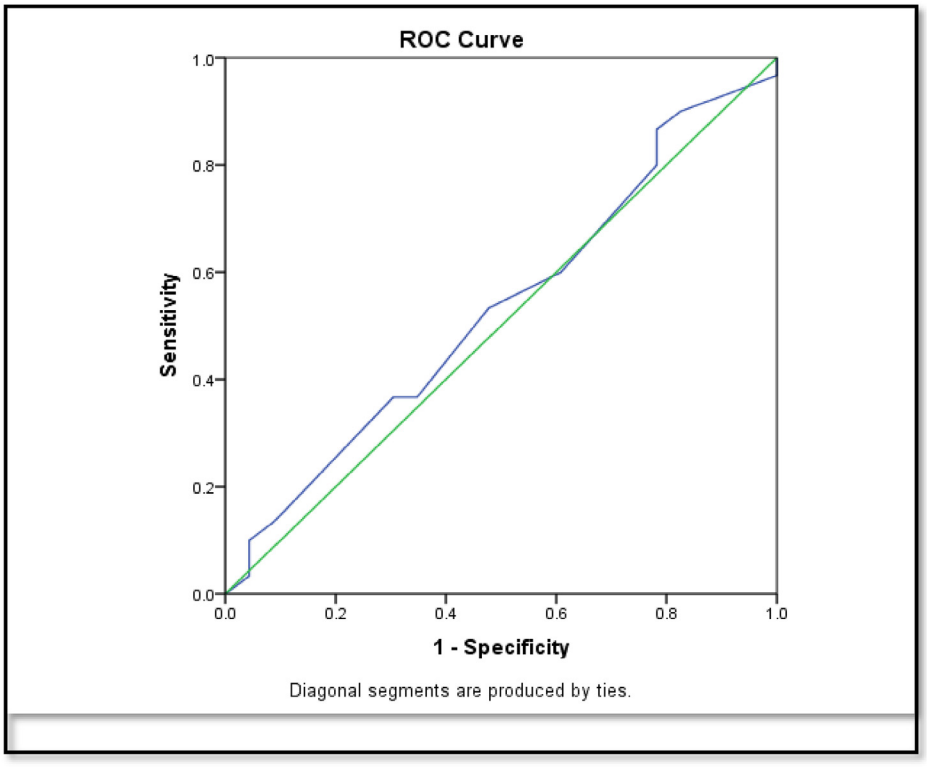

Fig. 2. Endometrial thickness on the day that progesterone was started as a predictor of pregnancy, according to the Receiver operating characteristic curve.

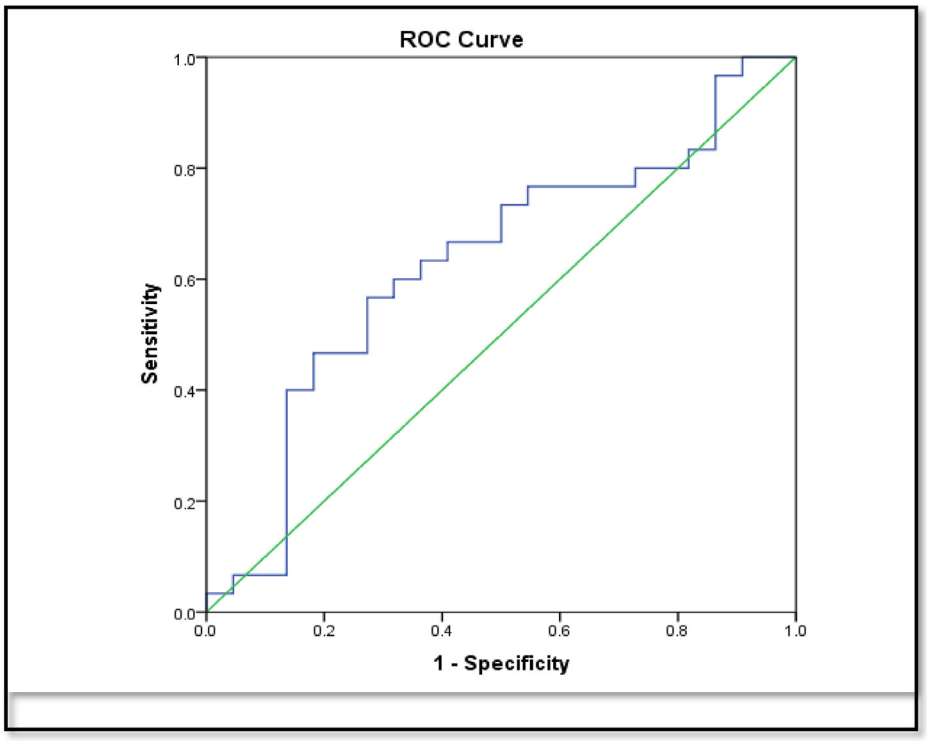

Fig. 3. P4 level's receiver operating characteristic curve as a predictor of pregnancy on the frozen embryo transfer day.

Table 3. Pregnancy outcome in relation to embryo characteristics (stage and number of frozen embryo transfer).

	Not pregnant	Pregnant	T	*P*-value	Sig.
	No. = 50	No. = 70			
Number of FET					
Range	1–3	2–3	−0.826•	0.411	NS
Median [IQR]	3[1]	3[1]			
Mean ± SD	2.580 ± 0.609	2.667 ± 0.475			
Embryo stage (days)					
Range	3–6	3–6	−0.909•	0.366	NS
Median [IQR]	5[1]	5[2]			
Mean ± SD	4.451 ± 1.006	4.606 ± 0.782			

Table 4. Statistical values of endometrial thickness on day of frozen embryo transfer and P4 level on day frozen embryo transfer that predicts pregnancy.

	Cutoff value	Area under curve	Sensitivity %	Specificity %	Asymptotic 95 % confidence interval	
					Lower bound	Upper bound
Endometrial thickness on day of progesterone start	10.75	0.537	51.9 %	57.1 %	0.371	0.703
Endometrial thickness on day of FET	10.25	0.398	40 %	59.1 %	0.242	0.554
P4 level on day of FET	5.72	0.669	66.7 %	52.4 %	0.451	0.780

during HRT–FET cycles, the best rate of live births is attained. The rate of live births is going to be lowered, whether the endometrium is too thick or too thin.[16]

4.2. Serum progesterone levels

The question of what levels of progesterone in the serum are necessary for optimizing pregnancy

outcomes is brought up by the increase in artificial cycles. There was a strong need for further investigation despite previous investigations in this subject declaring a positive link between P4 levels on the FET day and the outcome of pregnancy.[16] The present research has been designed to evaluate if serum progesterone measured on the FET day with the same endometrial preparation and luteal phase support was related to clinical pregnancy rate or not. P4 enhances the receptivity of the endometrium by regulating cytokines, which results in better trophoblast function at the implantation site as well as suppressing a maternal immunological response against the cells of the trophoblast.[17]

Our unit protocol is to start I.M. progesterone 100 mg daily when the thickness of the endometrium is 8 mm or more[18] explained that IM P4 leads to significantly greater mean serum P4 concentrations compared with vaginal P4, but probably decreased levels of the endometrium. This is thought to be caused by the uterine first-pass effect. The majority of studies were retrospective, which is comparable with our study design; nevertheless, contrary to the present research, previous literature was further constrained by the use of small sample sizes. In our study, we found that serum progesterone levels of 10 ng/mL or more on the FET day didn't show any statistically significant enhancement in the outcome of pregnancy. Serum P4 levels less than 5 ng/mg on the day of FET were linked to reduced rates of live birth, indicating that there's a threshold below which salvaging cycles of FET become challenging. The fact that our group got sufficient P4 replacement treatment to lessen the detrimental effects of reduced P4 concentrations during the luteal phase is another explanation that might be used to clarify these results. Our study result is in accordance with the study of,[19,20] who concluded that P4 concentrations higher than 10 ng/mL on the FET day aren't an important variable for predicting the outcome of pregnancy. In accordance with earlier investigations in this field, which found that a P4 concentration of this magnitude is a good predictor of appropriate corpus luteal function through the luteal phase, a P4 threshold of 10 ng/mL has been established. In his study, which has a similar result to our study,[21] univariate analysis that compared FETs with P4 concentrations that achieved this criterion with those without showed no significant differences in clinical pregnancy, biochemical pregnancy, or the rate of live births among the two groups. They found no differences in the rates of biochemical pregnancy (39.53 % vs. 40.98 %, $P = 0.52$), rates of clinical pregnancy (20.82 vs. 22.78, $P = 0.30$), or rates of live birth (14.25 vs. 16.21, $P = 0.23$) when they compared FET results about P4 levels less than 10 ng/mL and greater than or equal to 10 ng/mL. Similar to those patients, there was not a statistically significant advancement in the outcome of pregnancy in those whose P4 levels reached the 20 ng/mL threshold. Even though there wasn't a difference in the biochemical or clinical pregnancy rates, there was a statistically significant increase in the rate of live births for women with transfer day P4 levels greater than or equal to 5 ng/mL.

P4 replacement is required in artificial cycles to imitate physiological hormonal function and increase the receptivity of the endometrium; nevertheless, there's currently no agreement on the best route of administration of P4 or if serum P4 is a reliable indicator.[22] This result contradicts a few pieces of literature that are presently accessible. Although cycles under the threshold yielded equal rates of biochemical and clinical pregnancy, a further investigation of the P4 threshold of 5 ng/mL on the FET day revealed that there had been a greater rate of live birth reported in cycles beginning with levels of serum P4 greater than 5 ng/ml. P4 concentrations on the day of the transfer of the embryo have a positive link with the result of pregnancy, according to earlier studies in this field. But after reviewing the results of their studies, it became clear that there was still demand for more studies due to several inherent constraints. Most publications were retrospective, which is comparable with our study's conclusion, but unlike the present research, earlier literature has also been constrained by the small size of the sample.[9–23] In our study, due to the fact that only a few patients had a minimum threshold of progesterone (<10 ng/mL), with most patients having good P4 levels, the results from this study cannot conclude the effect of progesterone levels at the minimum threshold.

Numerous research publications used a threshold of P4 of 10 ng/mL[8–23] in accordance with the value selected here, and one prospective study used a threshold of 9.2 ng/mL.[9] These studies demonstrated an advantageous impact on FET results when P4 reaches such thresholds. Two investigations used the threshold of 20 ng/mL for analysis; one showed findings consistent with the above-mentioned research,[10] but the other showed decreased rates of continued pregnancy as well as live births linked to P4 concentrations over such a 20 ng/mL threshold.[9] The absence of uniformity in P4 replacement techniques and a poor understanding of the level of association between serum and endometrial P4 levels are further limitations of these contradicting

investigations on our results. When endogenous P4 or exogenous IM is administered, serum and endometrial P4 levels correlate well. The uterine first-pass effect is thought to be the cause of this. Furthermore, peak serum P4 and stromal cells create many growth factors that assist concentrations following/ vaginal dose, revealing significant inter-individual variability, most likely due to changes in vaginal absorption, surface area of the vaginal mucosa, and vaginal microbiome differences. As a result, equating endometrial P4 action to serum P4 concentrations is challenging, especially when vaginal luteal phase assistance is employed. This is one theory that could explain the findings of the present study. Considering the greater than or equal to 5 ng/mL P4 threshold, rates of live birth have a positive correlation with P4 concentrations. When the initial circulating level of P4 is so low that it is below this threshold, further P4 injection is not going to be able to mitigate its impact. This study's acknowledged drawback is the fact that extra replacement was not standardized, and the effectiveness of this replacement wasn't checked with additional serum P4 concentrations. Serial P4 measurements might be useful, even though a single P4 measurement in isolation on the day of transfer might not be effective for predicting the result of pregnancy. Future research on this subject is going to be important.

4.3. Conclusion

We found significant endometrial compaction between the start of progesterone and the day of frozen embryo transfer. However, this compaction did not show any statistical significance in relation to the clinical pregnancy rate; according to the available data, assessing endometrial compaction during HRT-FET does not appear to have any advantages. The moderate size of the sample and the absence of a rate of live birth reporting are two drawbacks of our current investigation. Another drawback is that different expert clinicians conducted all TVUS and FET processes, which raised interobserver differences. We showed that serum P4 concentrations at or above 10 ng/mL on the FET day are not linked to statistically significant increases in biochemical or clinical pregnancy. It is obvious that more study is required in this area to better understand optimum P4 replacement and the function of P4 surveillance during artificial cycles. It is possible that raising P4 replacement after low P4 concentrations on FET day alleviated the detrimental impact of low initial P4 levels. P4 levels under 5 ng/mg, on the other hand, were linked to a decreased pregnancy rate, implying that there is a threshold below which increased P4 replacement following FET can not be predicted to avoid pregnancy loss.

4.4. Recommendations

We may recommend that, despite the fact that P4 might have been insufficient on the transfer day, that be possibly corrected by the administration of additional P4, supporting the idea that intervention may remain feasible beyond the day of transfer and that further prospective studies are required.

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Conflicts of interest

No conflict of interest.

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