Comparison of immediate versus delayed frozen embryo transfer on reproductive outcome

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The aim of this study was to compare impact of immediate versus delayed frozen frozen embryo transfer on reproductive outcome in patients undergoing IVF treatment. A total of 1478 infertile women with frozen embryos, aged between 18--42 years, were included the study. Patients were divided into two groups according to the time of embryo transfer. All transfers done in the first cycle after egg retrieval were deemed "immediate frozen ET" and a transfer done in any subsequent cycle was deemed "delayed frozen ET". The effects of immediate versus delayed FET on beta-hCG positivity, clinical pregnancy rate (CPR), ongoing pregnancy rate (OPR), live birth rate (LBR) and miscarriage rate were compared. Multiple logistic regression analysis was performed to exclude possible factors affecting reproductive parameters. Beta-hCG positivity, the number of patients with gestational sac and clinical pregnancy rates were found to be similar in both groups. The miscarriage rates in the Delayed FET group were found to be higher than the immediate FET group. Therefore, OPR was higher in the immeadiate FET group. When compared to the Delayed FET group, LBR was recorded as 1.3 times higher in the immediate FET group. When the cases with embryo transfer on the fifth or sixth day were compared with the cases with embryo transfer on the 3rd or 4th day, a 2.1 fold increase in LBR was found in the immediate FET group compared to the delayed FET group. Immediate FET done in the first cycle after egg retrieval increases the live birth rates while decreasing the abortion rates.

Keywords

Transfer time; Frozen embryo transfer; Reproductive outcome

1. Introduction

Embryo freezing is a new and reliable method that has found widespread use in the practice of assisted reproductive techniques. Sometimes high progesterone levels, sometimes too many follicles development and sometimes fluid accumulation in the cavity require the embryos to be frozen until the underlying pathology passes. On the other hand, longer-term freezing of the embryos may be required in order to prevent the development of ovarian hyperstimulation syndromes during controlled ovarian stimulation or to create a pool by collecting eggs every month in patients with poor responses. The biggest problem we encounter after the egg freezing process is the question of when the transfer will be done [1, 2].

The good reproductive outcome after frozen ET is similar to fresh cycles, causing this method to be preferred in many patients. The most important advantage of FET cycles is the minimization of the negative effects of estrogen and progesterone hormones, which reach supra-physological levels depending on the drugs used, on the endometrium [3]. Even though such advantages are well-known, information on the optimal timing of frozen embryo transfer is still limited. The transfer can be performed immediately; that is, in the first cycle following the stimulated IVF cycle, or by skipping and delaying at least one cycle. Delayed embryo transfer may cause anxiety and stress in women and could negatively affect the process and success of IVF treatment. Studies conducted to date and comparing immediate versus delayed frozen ET results differ in terms of their results [4–6].

Today, a limited number of embryo transfers can be performed due to regulations imposed by the Ministry of Health that came into force in 2010 (06 March 2010, No. 2713). If pregnancy does not occur after the frozen embryo transfer, conflict between the patient and the physician about the transfer time arise. Therefore, it is apparent that there is a need for objective evidence-based guidelines to determine transfer timing. For all these reasons clarifying the ideal timing of transfer following embryo freezing is very important to increase success and manage expectations. The aim of this study is to compare the impact of immediate (a transfer done in the first cycle after egg retrieval) versus delayed (a transfer done in any subsequent cycle) frozen ET on reproductive outcomes in patients scheduled for frozen-thawed embryo transfer.

2. Materials and methods

This observational study was conducted between 01 January 2017 and 31 December 2018 by retrospectively reviewing the files of 35670 patients who applied to Memorial Kayseri IVF-Center or Istanbul IVF-Center with complaints of infertility. Among the examined files, the file of 1478 cases in which embryo freezing was performed was separated. A total
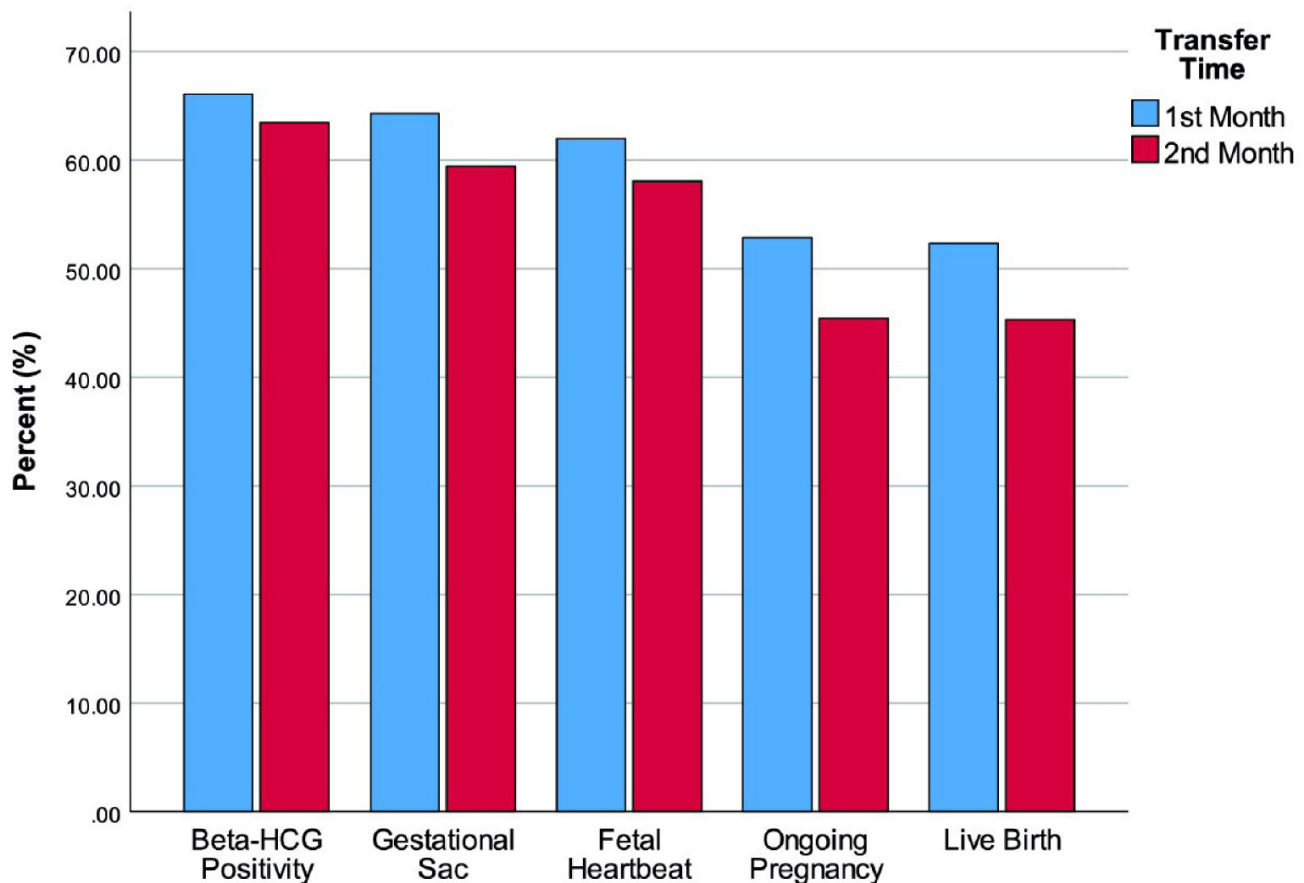
Fig. 1. Pregnancy and live birth rates with regard to transfer time.

of 1478 infertile patients whose ages ranged between 18–42 and who underwent embryo freezing were included in the study.

Standard antagonist protocol was applied for controlled ovarian stimulation. Treatment was started on the 2nd or 3rd day of the cycle with recombinant FSH, which was dosed individually. Gonadotrophin-releasing hormone antagonist was started on the 5th or 6th day of stimulation. Recombinant hCG (Ovitrelle, Merck-Serono, 250 mg, Modugno, BA, Italy) treatment was initiated when at least three follicles with a diameter of 18–20 mm were detected in ultrasonographic evaluation. 36 hours after hCG application oocyte pick-up was performed with 17-gauge needle (Cook Medical, Bloomington, IN, USA) guided by trans-vaginal ultrasonography. All embryos were vitrified in Cryotops as described by previously. The cases were divided into two according to the embryo transfer times performed after embryo freezing. All transfers done in the first cycle after egg retrieval were deemed "early/immediate frozen ET" (n = 734) and a transfer done in any subsequent cycle was deemed "late/delayed frozen ET" (n = 744). We prefer to wait for a cycle in patients with high prosterone on the day of hCG, those whose endometrium is not thick enough during that cycle, those with moderate to mild OHHS, and those with fluid accumulation in the cavity.

Since the primary outcome measure of our study was to evaluate clinical pregnancy rate (CPR), ongoing pregnancy rate (OPR), live birth rate (LBR), and miscarriage rate the rate of each parameter per pregnancy was recorded. As a result, the effects of immediate versus delayed FET on beta-hCG positivity, CPR, OPR, LBR, and miscarriage rate were compared. Clinical pregnancy rate defined as evidence of a gestational sac, confirmed by ultrasound examination. Ongoing pregnancy rate defined as evidence of a gestational sac with fetal heart motion at 12 weeks, confirmed with ultrasound examination. Live birth rate defined as delivery of a live fetus after 24 completed weeks of gestational age. Serum beta-hCG levels were measured in all patients on the 12th day of embryo transfer. The the loss of fetus before 20 weeks of gestation was defined as abortus, birth between 20 and 37 weeks of gestation was defined as preterm birth, and birth after 37 weeks of gestation was defined as mature birth. Women older than 42 years of age and those who had undergone fresh cycle transfers were excluded from the study. The necessary permissions for this study were obtained from the Erciyes University Clinical Research Ethics Committee. While conducting the study, the principles in the Good Clinical Practices Guide and the Helsinki Declaration were taken as basis. Informed consent was obtained from all individual participants included in the study.

Table 1. Summary of patients characteristics with regard to transfer time.

| | Transfer Time | | Total | P |
	First month (Immediate FET) (n = 734)	After first month (Delayed FET) (n = 744)		
Age	37 (31–39)	36 (31–39)	37 (31–39)	0.979
Male Factor	145 (19.75%)	146 (19.62%)	291 (19.69%)	0.949
Number of Transfers	3 (2–3)	2 (2–3)	2.5 (2–3)	0.755
P4 (3rd Day)	0.05 (0.04–0.12)	0.05 (0.05–0.12)	0.05 (0.04–0.12)	**0.014**
P4 (Progesterone Day)	0.27 (0.12–0.54)	0.27 (0.08–0.48)	0.27 (0.09–0.54)	0.171
Endometrial Thickness (Progesterone Day)	10.36 ± 1.51	10.18 ± 1.43	10.27 ± 1.47	**0.020**
Endometrial Thickness (Transfer Day)	10.60 ± 1.40	10.51 ± 1.47	10.55 ± 1.44	0.241
Embryo Count				
1	288 (39.24%)	274 (36.83%)	562 (38.02%)	
2	444 (60.49%)	469 (63.04%)	913 (61.77%)	0.522
3	2 (0.27%)	1 (0.13%)	3 (0.20%)	
Embryo Transfer Day				
3rd	209 (28.47%)	220 (29.57%)	429 (29.03%)	
4th	28 (3.81%)	40 (5.38%)	68 (4.60%)	0.474
5th	488 (66.49%)	475 (63.84%)	963 (65.16%)	
6th	9 (1.23%)	9 (1.21%)	18 (1.22%)	
Cycle Day During Transfer	17.26 ± 2.13	17.47 ± 2.37	17.36 ± 2.26	0.066
Beta-hCG Positivity	485 (66.08%)	472 (63.44%)	957 (64.75%)	0.289
Gestational Sac	472 (64.31%)	442 (59.41%)	914 (61.84%)	0.053
Fetal Heartbeat	455 (61.99%)	432 (58.06%)	887 (60.01%)	0.124
Pregnancy Status				
Missed	84 (11.44%)	104 (13.98%)	188 (12.72%)	**0.015**
Ongoing	388 (52.86%)	338 (45.43%)	726 (49.12%)	
Missed Week	8 (7–8)	8 (7–8)	8 (7–8)	0.879
Live Birth	384 (52.32%)	337 (45.30%)	721 (48.78%)	**0.007**
Preterm	68 (9.26%)	79 (10.62%)	147 (9.95%)	
Term	316 (43.05%)	258 (34.68%)	574 (38.84%)	
Preterm week	34 (33–36)	34 (33–36)	34 (33–36)	0.979

Data are given as mean ± standard deviation or median (1st quartile-3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables.

3. Endometrial preparation

Artificial hormonal endometrial preparation was performed in all patients. Blood was drawn from the patients in all groups on the second day of the cycle to determine the basal FSH, LH, E2 and progesterone levels. On the same day, transvaginal USG examination was performed to determine the presence of residual follicle or ovarian cyst, as well as endometrial thickness and endometrial pattern. In the evaluation made on the second day, if the endometrial thickness is 4 mm or less and the serum E2 level is below 50 pg/mL, the artifical preparation of endometrium was planned. Endometrial preparation was started with estradiol valerate 2 mg twice daily. Additionally, 100 mg of aspirin and 5 mg of folic acid per day were added to the treatment. On the 12th day of the treatment, the patient was called for transvaginal USG control. If the endometrial thickness reached a minimum of 8 mm or in the presence of a triple-line view intramuscular and vaginal progesterone administration started. Estradiol valerate treatment was continued for another 2–3 days in patients with an endomerile thickness of less than 8 mm. Patients with no increase in endometrial thickness despite the prolongation of treatment were excluded from the study. Immediate or delayed FET was performed on the 17th or 18th days of the menstrual cycle. Artificial endometrial preparation was successfully performed in all participants. On the planned day of transfer, frozen embryos were thawed and embryo qualities were evaluated. The transfer was performed if at least one healthy embryo of good quality was detected as a result of this evaluation. Micronized progesterone was initiated vaginally for luteal support. Estradiol valerate treatment was continued 3 times a day. In the presence of a positive pregnancy test, luteal support was continued and USG was performed at the 4th week of the transfer and the presence of gestational sac and thus clinical pregnancy was confirmed.

3.1 Statistical analysis

Analyses of all data was performed on SPSS v21 (SPSS Inc., Chicago, IL, USA). Q-Q and histogram plots were used to determine whether variables were normally distributed. Data are given as mean ± standard deviation or median (1st

Table 2. Summary of patient characteristics depending on whether she has a live birth or not.

	Live Birth		
	Live birth (-) (n = 757)	Live birth (+) (n = 721)	P
Age	37 (32–39)	37 (30–39)	**0.010**
Male Factor	164 (21.66%)	127 (17.61%)	0.051
Number of Transfers	3 (2–3)	2 (2–3)	**0.010**
P4 (3rd Day)	0.06 (0.05–0.15)	0.05 (0.04–0.08)	**< 0.001**
P4 (Progesterone day)	0.25 (0.05–0.45)	0.31 (0.17–0.54)	**< 0.001**
Endometrial Thickness (Progesterone Day)	10.19 ± 1.50	10.35 ± 1.43	**0.042**
Endometrial Thickness (Transfer Day)	10.50 ± 1.48	10.61 ± 1.38	0.151
Embryo Count			
1	280 (36.99%)	282 (39.11%)	
2	474 (62.62%)	439 (60.89%)	0.176
3	3 (0.40%)	0 (0.00%)	
Embryo Transfer Day			
3rd	270 (35.67%)	159 (22.05%)	
4th	58 (7.66%)	10 (1.39%)	
5th	419 (55.35%)	544 (75.45%)	**< 0.001**
6th	10 (1.32%)	8 (1.11%)	
Cycle Day During Transfer	17.11 ± 2.51	17.63 ± 1.92	**< 0.001**

Data are given as mean ± standard deviation or median (1st quartile-3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables.

quartile-3rd quartile) for continuous variables according to normality of distribution, and as frequency (percentage) for categorical variables. Normally distributed variables were analyzed with the independent samples *t*-test. Non-normally distributed variables were analyzed with the Mann Whitney U test. Categorical variables were analyzed with Chi-square tests. Multiple logistic regression analysis (forward conditional method) was performed to determine significant factors of live birth. Two-tailed *P*-values of less than 0.05 were considered statistically significant.

4. Results

Summary of patients characteristics with regard to transfer time was shown in Table 1 and Fig. 1. Likewise, summary of patient characteristics depending on whether she has a live birth or not was shown in Table 2. As shown in Table 1, when we tested with the help of univariate analysis whether there was a difference in the properties recorded between patients who underwent immediate versus delayed FET the mean ages of the patients in both groups were found to be similar. Likewise, there was no difference between the groups in terms of male factor infertility frequency and previous transfer numbers. The 3rd day progesterone values of the Immediate FET group and the delayed FET group, and the endometrial thickness values measured on the progesterone initiation day were found to be significantly different. There was no difference in the number of embryos transferred and embryo transfer days between the two groups. The cycle days on which the transfer was performed were also similar in both groups. There was no significant difference between the two groups in terms of beta-hCG positivity, gestational sac detection rates and clinical pregnancy rates. However, on-going pregnancy rates and live birth rates were significantly higher in the immediate FET group compared to the delayed FED group. Miscarriage rates were significantly higher in delayed FET group compared to immediate FET group. The increase in miscarriage rates in the delayed FET group may explain the decreased OPR and LBR in these patients.

As shown in Table 2, when we tested the differences between the patients who gave birth and those who did not give birth using univariate analysis, age, number of embryos transferred, progesterone levels on the 3rd day and after, endometial thickness, embryo transfer day and cycle day durign the transfer was significantly different between the two groups. In order to test whether the seven parameters found to be significant in Table 2 have an independent effect on live birth rates we created a model consisting of these parameters. According to this modeling result, we saw that 6 factors had an independent effect on live birth rates. Multiple logistic regression analysis was performed to exclude possible confounding factors affecting LBR (Table 3). When compared to the Delayed FET group, LBR was recorded as 1.3 times higher in the immediate FET group (OR: 1.314, 95% CI: 1.061–1.628, *P* = 0.012). When the cases with embryo transfer on the fifth or sixth day were compared with the cases with embryo transfer on the 3rd or 4th day, a 2.1 fold increase in LBR was found in the immediate FET group compared to the delayed FET group (OR: 2.172, 95% CI: 1.722–2.739, *P* < 0.001). In addition, the number of embryos transferred is low, the transfer on the 5th or 6th day are high, the progesterone level is low on the third day, the P4 levels measured on the progesterone initiation day are high, the cycle day of the transfer is progressing were found significantly associated with higher live birth rate. While it was observed that age

Table 3. Significant factors of the live birth, multiple logistic regression analysis.

	β coefficient	Standard Error	Wald	P	Exp (β)	95.0% Confidence Interval for Exp (β)	
Transfer time (1st month)	0.273	0.109	6.265	0.012	1.314	1.061	1.628
Number of embryo transfer	-0.148	0.045	10.644	0.001	0.862	0.789	0.943
P4 (3rd Day)	-1.843	0.512	12.975	< 0.001	0.158	0.058	0.432
P4 (Progesterone Day)	1.031	0.243	18.028	< 0.001	2.804	1.742	4.512
Embryo Day (5 & 6 days)	0.775	0.118	42.850	< 0.001	2.172	1.722	2.739
Cycle Day During Transfer	0.088	0.025	12.622	< 0.001	1.092	0.137	1.146
Constant	-1.991	0.467	18.197	< 0.001	0.137		

Dependent Variable: Live birth; Nagel kerke R^2 = 0.129.

and endometrial thickness affect live birth in univariate analyses, we found that when it was entered into the model, it was not related to live birth rate alone.

5. Discussion

In a patient for whom IVF/ET is planned sometimes may be necessary to freeze all embryos and postpone embryo transfer due to various conditions thought to negatively affect receptivity and implantation [1]. After freezing, the timing of embryo transfer after oocyte retrieval is occasionally a cause for minor conflict between the patients and physicians. This study compares the effects of immediate and delayed FET cycles on reproductive parameters and the number of cases is high enough to allow us to make strong comments on the subject. In the immediate group, we performed FET in the cycle after freezing. In the delayed FET group, most of the cases were transferred in the second cycle after freezing. In some patients, it was mandatory to transfer time to the 3rd or 4th cycles.

The most significant finding of our study was that the live birth rates in the immediate FET group were 1.3 times higher than in the delayed FET group. Our second important finding is that when we use embryos on the 5th or 6th day in the immediate FET group, the increase in live birth rates is found to be 2.1 times more than cases with embryo transfer on the 3rd or 4th day. Although it is apparent that the increased success with 5th and 6th day embryos is associated with embryo quality, the presence of higher live birth rate with immediate FET is a critical finding of our study. Among the main factors that increase LBR in logistic multivariate analysis modeling, early transfer, use of embryos on the 5th or 6th day, low number of embryos transferred, 3-day low progesterone levels, high progesterone levels measured on the day of progesterone initiation and higher cycle day during transfer are available. We found that maternal age and endometrial thickness, which were seen to affect live birth rates in univariate analysis, disappeared after multivariate analysis. In line with our results, Higgins et al. showed that the frequency of live birth was significantly higher when transfers were performed in the first cycle [7]. Likewise, Huang and colleagues showed that the frequency of pregnancy and live birth were significantly higher in patients who underwent embryo transfer in

the first cycle compared to transfers in later cycles [4]. On the other hand, several studies examining the impact of optimal frozen embryo transfer time on for live birth has been shown that embryo transfer time does not significantly affect reproductive outcome [8–10]. Lattes et al. reported that there was no significant difference in multivariate analyses, even though univariate analysis showed that transfer performed in the first cycle resulted in a significantly higher frequency of live birth compared to embryos transferred in later cycles [5]. When our results and the literature results are evaluated together, it can be concluded that early FET cycles lead to a significant increase in live birth rates compared to delyed FET cycles, considering the scarcity of opposing data.

In the present study, the live birth rates of cases with embryo transfer on the 5th or 6th day were found to be significantly higher than the group with embryo transfer on the 3rd or 4th day. In both univariate and multivariate analysis, 5th and 6th day transfers contributed positively and independently to live birth rates. When the literature is examined, it is evident that transfer comparisons are generally performed between the 5th or 6th day embryo. In most of the studies, it was stated that 5th day transfer was more effective on pregnancy rates compared to the 6th day. Sciorio and colleagues reported that the 5th day transfer was superior to the 6th day in terms of achieving clinical pregnancy (43% vs. 33%) [11]. Likewise, Haas et al. observed that 5th embryo day transfers resulted in a statistically higher frequency of pregnancy compared to transfers performed on the 6th embryo day (42% vs. 22%) [12]. Although better results are reported for the 5th day embryo tarnsfer compared to the 6th day in most studies, studies that report no difference also exist [13]. However, the results of our study are important in terms of showing that performing embryo transfer on the 5th or 6th day instead of embryo transfer on the 3rd or 4th day in the immediate FET group increases the live birth rates approximately twice. Therefore, the use of embryos on the 5th or 6th day in transfer besides early transfer will allow a significant increase in reproductive parameters.

One of the most interesting results of our study is the finding that increasing number of embryo transfers have a negative effect on live birth rates. This finding is inconsistent with most studies in the literature. Lattes et al. reported that the

live birth rate of cases with 2–3 transferred embryos increased by 2.2-fold compared to single embryo transfer [5]. In a review examining the relationship between the number of embryos transferred and live birth, Pandian *et al.* reported that, when compared with single fresh embryo transfer, transfer of 2 fresh embryos increased the odds of live birth by 1.94-fold [14]. However, our reslts were thought to be associated with the higher number of embryos transferred in repeated IVF attempts after failed IVF treatment, and due to a possibility of a higher number of cases that had lower probability of IVF success. The increase in the number of such patients in our study group may be due to the fact that a considerable proportion of our patients are referred from other centers after unsuccessful IVF treatment. As a result, even though the number of embryos transferred increased, live births continued to occur at a lower frequency.

In our study, changes in progesterone serum levels measured both on the 3rd day and on the day of initiation of progesterone treatment in the modeling performed as a result of multivariate analysis negatively affected pregnancy rates. A significant decrease in pregnancy rates was observed in cases with high progesteron on the 3rd day or low progesterone measured on the day of initiation of progesterone treatment. Our results are consistent with literature data It has been shown that an increase in progesterone levels on hCG day negatively affects IVF treatment outcome [15–17]. Therefore, it is recommended to postpone embryo transfer to subsequent cycles in patients with elevated progesterone. Ribeiro et al. found that the presence of both low (≤ 0.5 ng/mL) and high (> 1.5 ng/mL) progesterone levels on hCG day reduced the possibility of live birth [18]. Our study is important in terms of showing the positive effect of progesterone values measured on the day of initiation of progesterone treatment during artificial endometrial preparation on pregnancy rates.

The observational nature of this study is an important limitation. Since the data were collected retrospectively, it was not possible to examine all variables that could affect the results. Secondly, since the causes of infertility were not considered (except for male factor), patients with higher or lower probability of pregnancy undergoing FET may have been distributed heterogeneously which may have confused the results. Likewise, since the variables such as the duration of infertility and the number of previous IVF attempts were not evaluated these may have affected the results [19].

6. Conclusions

In conclusion, freeze-thaw embryo transfers result in more frequent live births when performed on the first cycle. Hence, immediate FET should be preferred if there is no other indication for delayed FET. Likewise, embryo transfer on the 5th or 6th days were considerably superior to transfer on the 3rd or 4th days. Othe other hand, this is an expected outcome, since high quality embryos are monitored until the 5th and 6th days, while lower quality embryos are frozen earlier. In addition, the number of embryos transferred, the day of transfer and progesterone levels evaluated at different time-points seem to be valuable for the prediction of the clinical results of FET.

Author contributions

These should be presented as follows: AY, AK, NT and RO designed the research study. NT performed the research. AY analyzed the data. AY, RO, NT and AK wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Erciyes University Clinical Research Ethics Committee (Approval number: 2020/343).

Conflict of interest

The authors declare no conflict of interest.

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