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Impact of Frame-By-Frame Monitoring of Embryos on Obstetric And Perinaaaaatal Outcomes In Singleton Pregnancies In Assisted Reproductive Technology Programs

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Abstract

The embryological stage of the implementation of ART programs can be considered one of the most important, since the assessment of the competencies or "quality" of oocytes, their fertilization and in vitro cultivation to the stage of preimplantation embryos largely determine its success. . An efficient method of embryo selection is currently in high demand in this field, since it is a method of selecting embryos that have the highest potential for implantation. Almost all publications on time-lapse microscopy have focused on timing specific embryonic division events and then using this information to create algorithms to help select an embryo for transfer, but there are insufficient data on obstetric and perinatal outcomes.

Keywords: *Assisted Reproductive Technologies, Infertility, Elective Blastocyst Transfer, Time-Lapse Microscopy.*

1. Introduction

The process of morphological study of embryos is one of the most important selection methods, the results of which evaluate a whole group of indicators, such as the number of blastomeres, the proportion of fragmentation, the severity of compaction, size and shape, as well as their correspondence to the stage of development, the formation of the blastocyst, the size of its cavity, the state of the internal cell mass with trophoblast. An efficient method of embryo selection is currently in high demand in this field, since it is a method of selecting embryos that have the highest potential for implantation. The method of continuous video surveillance allows the specialist to obtain a long and detailed chronicle of the development process of each individual embryo. In the process of development, the embryo goes through several stages of development, and the duration of each stage also serves as a significant indicator of quality and potential, which is characterized as development kinetics. In this regard, the introduction of time-lapse technology made it possible for embryologists to arm themselves with an effective tool for selecting promising embryos.

The purpose of the study: isreassess the safety of non-invasive monitoring by evaluating obstetric and perinatal outcomes of pregnancies derived from embryos conceived in a time-lapse incubator compared to standard incubators.

2. Materials And Methods

The study included 760 patients, which served as the platform for the present study. Obstetric and perinatal data on newborns conceived with TDM (study group) or without TDM (control group) were collected in a randomized controlled trial conducted byon the basis of IDK Medical Company JSC (Samara, Russia) in the period from 2016 to 2021.

In the present study, data related to childbirth and obstetrical perinatal aspects were obtained from medical records and reports sent by referral centers, as well as from patient interviews by telephone or emails sent to them. The first and main source of information was the patient. In case the patient mentioned any abnormalities during pregnancy, childbirth or in relation to the newborn, we increased the frequency of interaction in order to obtain accurate information and request copies of medical reports.

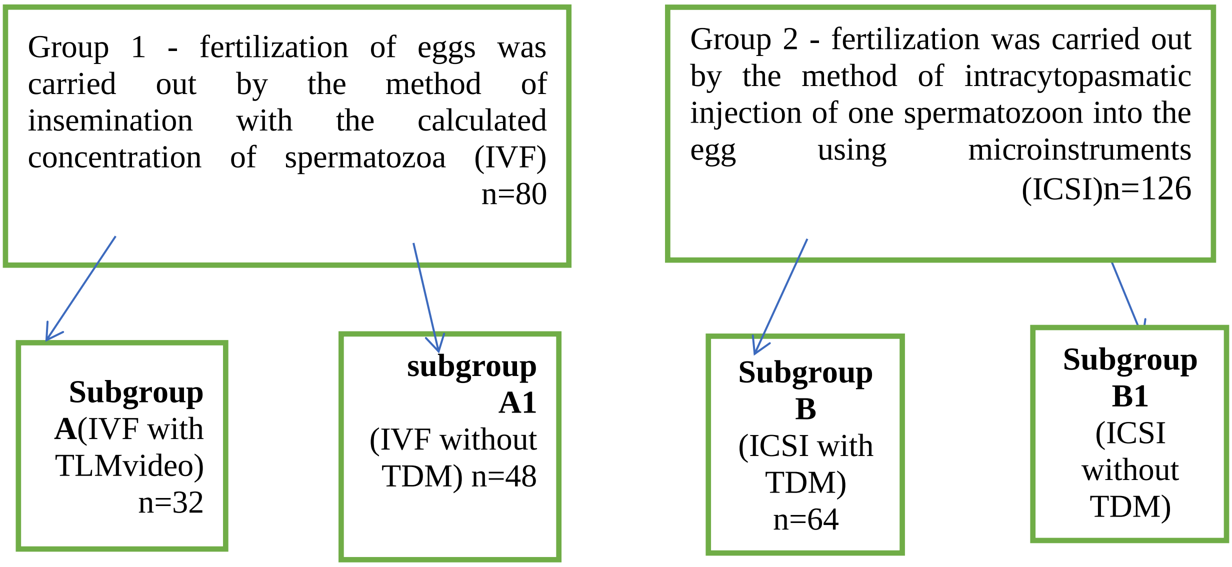

Figure 1 Study Design

2 groups of patients were identified, whose embryos and indicators of their development were analyzed: group 1 - IVF (in which the fertilization of eggs was carried out by the method of insemination with a calculated concentration of spermatozoa) and group 2 - ICSI (fertilization was carried out by the method of intracytopasmatic introduction of one spermatozoon into the egg using microinstruments).

Each of the groups was divided into subgroups, which differed in that the cultivation of embryos for transfer took place either using a standard technique, or a video surveillance system was used (Fig. 1). The parameters characterizing the development of embryos were studied in patients of each studied group. In the work, human embryos were used, the study of which was carried out in compliance with international ethical and legal standards for the treatment of human embryos [Art. 18. Council of Europe Convention for the Protection of Human Rights and Dignity of the Human Being in the Use of Biology and Medicine, 1997]. Permission for the use of embryos in the study was obtained from the Committee on Bioethics at the Samara State Medical University (excerpt from protocol No. 116 dated October 3, 2018).

3. Results and Discussion

The share of the IVF program was: 33.3% (subgroup A) and 43.6% (subgroup A1), the share of the ICSI program was 6.6% (subgroup B) and 56.3% (subgroup B1)respectively ($p > 0.05$).The mean age of women in subgroups A and B and in groups A1 and B1 was 31.70 ± 0.24 and 31.82 ± 0.20 years, respectively ($p > 0.05$). In both groups, the minimum age of the patients was 23 years, the maximum age was 45 years.

In both groups, the majority of women were under the age of 35 - 73.8% of patients in the main group and 70.9% of patients in the control group ($p > 0.05$). In subgroups A, B -c, the use of video monitoring and the proportion of women with primary infertility was 61.8%, in A1, B1 subgroups - 53.3%, secondary infertility was in 38.2% and 44% of women, respectively (p> 0, 05).

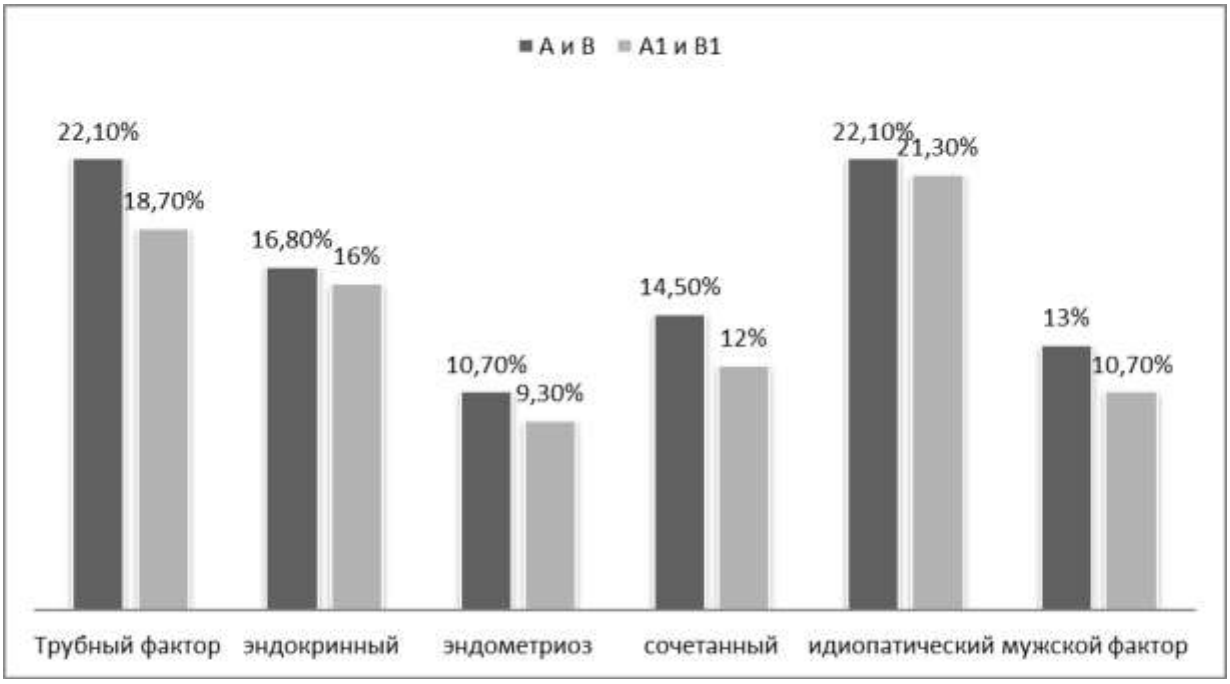

Figure 2. The structure of infertility in the studied groups

The most common cause of infertility in the subgroups with and without TDM was tubal factor (22.10% and 18.7%, respectively) ($p > 0.05$) and idiopathic factor (22.10% and 21.30%, respectively) ($p > 0.05$). There were also no statistically significant differences between subgroups in the duration of infertility (subgroup A-5.56±1.01years and in subgroup A1 -5.43 ± 0.17, in subgroups B and B1-6.66±1.34 years and 6.4±1.38) respectively ($p > 0.05$). Thus, there were no significant differences in the main characteristics of the patients, including both age aspects and the structure of infertility.

The parameters characterizing the development of embryos were studied in patients of each studied group. In group 1 of the patients with the IVF program, the data obtained both on the basis of video monitoring of the development of embryos (subgroup A) and the standard method (subgroup A1) were compared, the results of which are shown in Table 3.2.1. In a comparative analysis of the data, the average values of the following indicators were studied: fertilization (%), crushing (%), growth to the blastocyst (%), freezing (%), average number of embryo transfers, hCG (+) (%), positive ultrasound results (%), CI (%) and the level of multiple pregnancy. As follows from the comparative data in the above tablein the IVF group, the indicators do not have a significant difference. Thus, there were no statistically significant differences between the fertilization rates (%), and they amounted to 74.1±13.9% and 76.7±14.3% in groups A and A1, respectively. Between the crushing indices (%), a minimal difference was revealed: in subgroup A, this parameter was higher - 97.3±3.2%. A similar picture was established when comparing the rate of growth to the blastocyst (%), its average values in the A1 subgroup relative to the subgroup with video surveillance in the A subgroup were higher - 22.3±5.7%. The average values of the freezing index (%) between the studied subgroups also had statistically significant differences: in subgroup A1 they were lower than the results obtained with video control - subgroup Ai amounted to 32.1±5.8%. The average number of embryos per transfer in subgroups A and A1 was 1.03±0.18 and 1.15±0.36, respectively. At the same time, the average number of attempts was 1.72±0.46 and 2.23±0.47, respectively.

It should be noted that the hCG and ultrasound values in subgroup A have a minimal difference, which indicates the high quality of the embryos that are cultured and selected for transfer using video surveillance technology. The multiple pregnancy rate in subgroup A1 is almost 2 times higher than in subgroup A with video surveillance. This also confirms the sufficient level of biological competencies of the developing embryos.

Table 1 Comparative characteristics of the indicators of development of embryos obtained in the IVF program

	And n=32	A1 n=48	IVF Total n=80
Average age of patients	32.6±2.8	33.4±3.4	33.1±3.2
Average attempts	1.72±0.46	2.23±0.47***	2.03±0.53
Average number of years of infertility	5.56±1.01	5.63±1.16	5.6±1.1

Average dose of FGS per stimulation	1457.1±269.7	1573.8±328.4	1527.1±309.8
Average number of received MII oocytes	6.5±1.48	5.69±1.19**	6.01±1.36
% fertilization	74.1±13.9	76.7±14.3	75.6±14.1
% crushing	95.7±2.9	97.3±3.2**	96.7±3.2
% growth to blastocyst	18.4±4.2	22.3±5.7***	20.7±5.4
Freeze %	35±6.9	32.1±5.8*	33.3±6.4
cf. Embr. transfer	1.03±0.18	1.15±0.36*	1.1±0.3
HCG (+),%	36.7±6	42.5±7.4***	40.2±7.5
Ultrasound, %	34.3±7.1	36±6.7	35.4±6.9
CI, %	36.9±8.9	39.3±7.3	38.3±8
Multiple pregnancy rate	4.77±0.86***	8.22±1.72	6.15±2.12

*Note: *-p<0.05, **-p<0.01, ***-p<0.001 statistical significance in relation to IVF group with video.*

When comparing the data in the studied subgroups ICSI-B, B1, we see that the indicators do not have a significant difference. There were no statistically significant differences between the fertilization rates (%), and they amounted to 71.5 ± 16.5% and 74.4 ± 13.8% in subgroups B and B1, respectively. Between the crushing indicators (%), a minimal difference was revealed and in the B1 subgroup, the indicator was higher - 98.2 ± 6.5%. A similar picture was established when comparing the rate of growth to the blastocyst (%), the average values of subgroup B1 were higher - 24.3 ± 4.9% (Table 2.).

Table 2 Comparative characteristics of the indicators of development of embryos obtained in the ICSI program

	At n=64	B1 n=62	ICSI Total n=126
Average age of patients	34.6±7^	34.9±7.2	34.8±7.1^
Average attempts	2.2±0.6^^^	2±0.44*^^	2.1±0.53
Average number of years of infertility	6.66±1.34^^^	6.4±1.38^^^	6.53±1.36^^^
Average dose of FGS per stimulation	1503.2±264.7	1645.9±361.9**	1573.4±323.1
Average number of received MII oocytes	6.33±1.16	5.31±0.97***	5.83±1.18
% fertilization	71.5±16.5	74.4±13.8	73±15.2
% crushing	97.3±1.4^	98.2±6.5***^^^	97.8±4.6^^^
% growth of doblastocyst	18.3±3.7	24.3±4.9***^	21.3±5.3
Freeze %	31.5±6.1^^	31.6±6.7	31.6±6.4^
avg.embr.change	1.28±0.45^^	1.37±0.49^^	1.33±0.47^^^
HCG (+),%	30.1±6.6^^^	35±6.6***^^^	32.5±7^^^
Ultrasound, %	24.1±5^^^	25.3±4.9^^^	24.7±5^^^
CI, %	24.1±4.6^^^	32.6±7.2***^^^	28.3±7.4^^^
Multiple pregnancy rate	0±0^^^	20±3.77***^^^	9.84±10.38

Note: **-p<0.05, **-p<0.01, ***-p<0.001 statistical significance in relation to the ICSI group with video. ^-p<0.05, ^^-p<0.01, ^^^-p<0.001 statistical significance in relation to the corresponding indicators of IVF groups.*

The mean values of the freezing index (%) also had statistically significant differences. The average number of embryos per transfer in subgroups B and B1 was 1.28±0.45 and 1.37±0.49, respectively. At the same time, the average number of attempts was 2.2±0.6 and 2±0.44, respectively.

It should be noted that the difference between hCG and ultrasound in subgroup B is less. This indicates a high potential for implantation of embryos that were selected using video surveillance technology. The absence of a difference between CNB and CI indicates that all the embryos that gave birth were implanted.

Moreover, the average number of embryos per transfer in this group is slightly lower than in subgroup B1, i.e. on average, fewer embryos were needed to achieve pregnancy.

Noteworthy is the extremely high rate of multiple pregnancy in subgroup B1 (ICSI without video). This is a risk group, since obstetric risks and the risks of giving birth to premature and low birth weight children in this group are extremely high. Attention should be paid to this group and a more rigorous selection of embryos for transfer should be carried out, while at the same time reducing the number of transferred embryos.

There are a number of works in the scientific literature [3; 4], which found a higher proportion of excellent quality embryo transfers in the video technology group.

In most publications [12; 14] considered the assessment of 10-12 morphodynamic indicators of embryonic division, which allows demonstrating the advantage of time-lapse technology. It can be unequivocally stated that this methodology for assessing embryos does not have a negative impact on their development, since all studies revealed fairly high results in the level of pregnancy development.

Thus, we can conclude that continuous video monitoring of embryos under stable cultivation conditions is more informative in terms of assessing their development in comparison with static observations. This makes it possible to increase the efficiency of identifying embryos with the highest potential for implantation.

The results obtained allow us to conclude that the method of continuous cultivation of embryos with video monitoring of their development reduces the negative impact of external factors and increases the proportion of high-quality embryos. The ability to obtain images of embryos at different stages of their development makes it possible to use additional computer technologies for ranking embryos, which improves the quality of their selection.

Currently, the system for auto-detection of the morphodynamic profile of human embryos in vitro is being tested and additional data is being labeled. Complementing the morphodynamic profiles with the results of pregnancy transfers and outcomes will make it possible to form data sets for training the decision support system. Currently, there is an intensive development of non-invasive time-lapse technology at the intersection of medicine and information technology. The accumulated factual material will make it possible to form algorithms for training artificial intelligence and its application to select the most competent embryo for implantation. This will allow to achieve higher rates of pregnancy and childbirth.

Data corresponding to outcomes of pregnancy, childbirth and newborns are given intable**3.**Between the two subgroups A:B and A1:B1, no differences were found in the outcomes of pregnancy and childbirth. . There were no significant differences in birth defects, only one minor malformation and 1 perinatal death in the non-TDM group. Data on newborns were not available in two cases (TDM) and four cases (without TDM). When pregnancies were analyzed, no differences were found between the two groups in the incidence of obstetric problems, including bleeding in the second and third trimester 4 (3.6%) TDM vs. 5 (5.3%) in the control group and pregnancy-induced hypertension 6 (5. 4%) in the main group versus 5 (5.3%) in the control group (table 2). Early and late miscarriages were common in the A subgroup (0.9%) versus 3.2% in the A1 subgroup. Delivery at term increases almost 2 times in the A subgroup (39.3% versus 24.5%). More multiple pregnancy in subgroup A1 (8.5% vs. 3.6%)

No statistical difference was found in neonatal outcomes, Apgar score at 5 minutes was 9.5 (95% CI 9.2–9.9) (TLS) vs 9.4 (95% CI 9.2–9.7) (SI). Minor malformations were found in one newborn in group A1 (1.1%), antenatal fetal death in 2 cases in subgroup A.

Table 3 Obstetric and perinatal outcomesin groups with and without video monitoring.

	A and B subgroups n=112	A1 and B1 subgroups n=94	Fisher's exact test
Birth outcome:			
No information	8 (7.1%)	6 (6.4%)	0.214
no pregnancy	50 (44.6%)	51 (54.3%)	0.0436
Miscarriages early and late	1 (0.9%)	4 (4.3%)	0.116
Late miscarriages	1 (0.9%)	3 (3.2%)	0.206
Preterm birth (<37 weeks)	8 (7.1%)	7 (7.4%)	0.2101
Birth at term	44 (39.3%)	23 (24.5%)	0.0093
All births	52 (46.4%)	30 (31.9%)	0.0122
Obstetric complications:			
multiple pregnancy:	4 (3.6%)	8 (8.5%)	0.0786
bleeding in the 2nd and 3rd trimesters	4 (3.6%)	5 (5.3%)	0.2211
Hypertension due to pregnancy	6 (5.4%)	5 (5.3%)	0.2426
C-section	21 (18.8%)	18 (19.1%)	0.141
perinatal outcomes			
Male newborns	32 (28.6%)	13 (13.8%)	0.0051

Newborn females	22 (19.6%)	17 (18.1%)	0.1364
Birth weight over 2800	43 (39.3%)	20 (0%)	0
Low birth weight (<2500 g)	9 (8%)	100%)	0.0036
Apgar score at 5 min	9.5 (9.2–9.9)	9.4 (9.2–9.7)	
Malformations	0 (0%)	1 (1.1%)	0.4563
Antenatal mortality	2 (2.1%)	0 (0%)	0.207
Intrapartum mortality	0 (0%)	0 (0%)	1
Postnatal mortality	1 (0.9%)	0 (0%)	0.5437

To avoid bias and accurately examine the impact of TDM on obstetric and perinatal outcomes, we analyzed two in the subgroups studied and we found no significant differences between the two subgroups.

The incidence of pregnancy-induced hypertension was similar in both groups, and the incidence of other pregnancy disorders was comparable, including bleeding in the second and third trimesters. Gestational age at delivery and preterm birth rates were similar in the TDM and non-TDM groups.

We found no difference in the incidence of congenital malformations between the TDM and non-TDM groups, and the perinatal mortality rate was very low in both groups. Thus, no clinically significant increase in obstetric or perinatal risks was found among pregnancies achieved with TDM, suggesting that this technology does not have any deleterious effect on embryonic development.

Our study, however, has some limitations. Our conclusions are based on retrospective data that were partly obtained through medical questionnaires and phone calls, as this was the only way to collect information on the entire cohort of births resulting from TDM and non-TDM pregnancies that we were notified about. Early pregnancy loss was significantly lower in the TDM group.

Thus, no clinically significant increase in obstetric or perinatal risks was found among pregnancies achieved with TDM, suggesting that this technology does not have any deleterious effect on embryonic development.

Our data on higher quality embryo transfer using time-lapse microscopy are consistent with those of other researchers [5, 9]. The absence of differences between the two groups in terms of clinical characteristics (age, infertility factors, duration of infertility) suggests that a large proportion of cycles with excellent quality embryo transfer in the main group may be due to the absence of the influence of environmental factors during cultivation in a time-lapse microscope. TLM technology significantly reduces manual contact with culture dishes and embryos, leaving the embryos in optimal growth conditions [10]. A large number of studies over the past 20 years have established a strong relationship between the quality of transferred embryos and the likelihood of pregnancy. The higher the morphological assessment of the quality of the embryo, the higher the likelihood of clinical pregnancy [16, 17]. According to the internal instructions approved by IDK Medical Company CJSC, the age of the woman, the quality of the embryos and the serial number of the IVF and ICSI program are the criteria for choosing the number of transferred embryos. In patients of late reproductive age, in the absence of pregnancy in previous IVF and ICSI programs and / or when embryos of satisfactory quality are obtained, as a rule, transfer of two embryos is discussed to increase the likelihood of pregnancy. However, our study also included patients with an unfavorable prognosis for pregnancy and childbirth. The high proportion of excellent quality embryo transfers, combined with the higher proportion of embryo cryopreservation cycles, suggests that that there is a positive trend towards improved embryo quality with TLM. In our work, we did not analyze the cumulative rate of clinical pregnancy (pregnancy per one cycle of stimulation - after the transfer of a "fresh" embryo and in the absence of pregnancy, subsequent transfer of a thawed embryo). However, a large proportion of cycles with cryopreservation of embryos in the main group may increase this indicator in the future. A retrospective study that included 1882 cycles compared the cumulative live birth rate in the TLM group and in the standard culture group [16]. The cumulative live birth rate did not differ between the TLM group and the control group (51.7% vs. 51.2%, respectively; OR 1.02, 95% CI: 0.85–1.22). However, the live birth rate with fresh embryo transfer was higher for TLM cycles compared with the standard culture group (36.8% vs. 33.9%, respectively, OR 1.28, 95% CI: 1.05–1.57). The high rate of clinical pregnancy and childbirth in both groups of our study may indicate the absence of a negative effect on embryos cultured in a time-lapse incubator. In current publications, 10 to 12 morphodynamic parameters are assessed, which makes it possible to assess the benefits of cultivation in TLM incubators [6, 13]. Artificial intelligence or machine learning enables an unbiased approach to multivariate analysis. In the context of TLT, attempts are being made to use higher processing power to analyze large sets of image data in order to identify combinations of parameters that could be associated with embryonic viability. In 2019, P. Khosravi et al. used artificial intelligence in time-lapse microscopy [3]. After analyzing over 10,000 embryos, they developed a model that was able to predict blastocyst quality with an AUC (area under the ROC) > 0.98. Using a similar approach, D. Tran et al. developed a learning model for automatic analysis of morphokinetic videos [4]. The authors retrospectively analyzed over 10,000 videos from several ART centers and were able to show that their model was able to identify images of blastocysts, the transfer of which led to a progressive pregnancy with AUC> 0.90. In addition, with a deeper understanding of the kinetics of embryonic development, it may be possible to correlate key division parameters with other aspects of embryonic physiology, such as embryonic chromosomal status [15] and response to cryopreservation [16]. Despite the lack of conclusive evidence of the clinical benefit of TLM, it is clear that, compared with static observations, continuous monitoring of embryos under stable culture conditions will provide more information about the development of the embryos. There is an assumption that time-lapse technology can evolve into a full-fledged embryo selection method, including in combination with artificial intelligence and non-invasive tests. It is now quite difficult to predict the future achievements of time-lapse microscopy.

4. Conclusion

The study did not reveal statistically significant differences in clinical pregnancy rates, delivery rates, and early pregnancy loss rates between the TLM group and the conventional embryo culture group. In the non-elective single embryo transfer group using TLM, the clinical pregnancy rate was 10% higher compared to the control group ($p = 0.03$). The birth rate did not differ between the TLM group and the traditional culture group depending on the type of embryo transfer.

Thus, our studies indicate that the use of time-lapse microscopy can increase the effectiveness of IVF and ICSI programs. Continuous monitoring at short intervals provides more information about the development of the embryos than the standard daily assessment. These advantages will allow the clinician to recommend a single embryo transfer to a couple without significantly reducing the chance of pregnancy and delivery, but eliminating the risk of multiple pregnancies.

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