M.V. Medvedev[1], O.S. Kozyra

«Effectiveness of embryo transfer individualization as a method of overcoming repeated negative implantation attempts»

[1] Doctor of Medicine, Professor of the Department of Obstetrics and Gynecology, Dnipropetrovsk Medical Academy of the Ministry of Health of Ukraine;»;
e-mail: medvedev.mv@gmail.com

obstetrician-gynecologist MC "Ivimed" “Rodynne dzherelo»;
e-mail: kozyrochka27@gmail.com

Background

Infertility is one of the most pressing problems of modern medicine and society. Socio-demographic and economic aspects contribute to the development of a negative trend among the population of reproductive age. Among all medical procedures, in vitro fertilization (IVF) is the most widely used method of infertility treatment. However, it does not guarantee pregnancy. According to current statistics about 60 % of couples who sought medical help in specialized institutions must to have the second attempt, and some of them, three or more times. In the structure of reasons of IVF unsuccessful attempts the embryonic factor is only the third. All other is due to implantation problems. Although there are well-characterized morphological and molecular markers of implantation, the full dynamics of the process, as well as the importance of each, are still unclear and need further study. One of the important reasons is the lack of synchronicity between endometrial maturation and embryo development, which leads to a decrease of endometrial receptivity and lack of implantation. The period when the endometrium is receptive to blastocyst nation is called the implantation window. During this period, the plasma membranes of the endometrial epithelium lose microvilli and the apical surfaces of the cells form a dome-shaped protrusion - pinopodium. Pinopodium formation in the middle of the luteal phase (LP) is a major indicator of endometrial readiness for embryo implantation, and an assessment of their condition has been proposed as one of the markers of endometrial receptivity. Normally, pinopodium are formed during LH + 6/7 (receptive endometrium). Day 0 is the peak day of LH before ovulation. Progesterone, day 0 corresponds to LH + 1/2. The formation of pinopodium sooner or later LH + 6/7 leads to the absence of embryo implantation in the in vitro fertilization cycle. The reason for this is a fixed day of embryo transfer, which is incorrect in the case of atypical morphogenesis of pinopodium.

Objective

To determine the influence of the method of embryo transfer personalization in the group of women with repeated implantation failures to the ongoing pregnancy rate.

Materials and methods

There were done the retrospective study of medical histories of 290 women with repeated implantation failures, who were examined and treated at "Medical Center" Intersono" and MC" Ivimed " Rodynne dzherelo" from 2017 to 2020. Statistic was performed with Microsoft Excel (Office Home Business 2KB4Y-6H9DB-BM47K-749PV-PG3KT) and STATISTICA 6.1 software (StatSoftInc., Serial № AGAR909E415822FA).

Characteristics	All examined patients	Group 1	Group 2	p
Number of women, n (%)	291 (100 %)	216 (74,0 %)	75 (26,0 %)	-
Age, Me (25%; 75%)	32,0 (29,0; 37,0)	31,0 (27,0; 38,0)	32,0 (30,0; 37,0)	0,12
BMI, Me (25 %; 75 %)	20,5 (19,5; 22,0)	20,2 (19,3; 22,0)	20,5 (19,8; 21,9)	0,56
Smoking,n (%)	19,5 %	23,4 %	16,0 %	0,189*
Place of residence, (%)				
countryside	19,0 %	20,2 %	17,9 %	0,681*
city	81,0 %	79,8 %	82,1 %	

Image 1 Demographic patients characteristics

Results and discussion

All patients with repeated implantation failures were screened for window of implantation by endometrial scanning electronic microscopy (SEM). The endometrium preparation was carried out in artificial cycle. Endometrial biopsies were performed on days 6, 8, and 10 of progesterone administration. According to the results the group of the study was divided into two subgroups. The first group included patients with pinopodies formation in the period of LH + 6/7 - 75 (26%) - control group. In the second - women with pinopodium formation sooner or later LH + 6/7 -216 (74%) - main group.

The age of the women ranged from 19 to 50 years and was on average 32.0 (29.0; 37.0) years - Me (25%; 75%) without statistically significant differences between groups (p> 0.05). The groups also did not statistically significantly different (p> 0.05) by place of residence, body mass index (BMI), which ranged from 18.0 to 34.0 and smoking.

Patients from the main group underwent the next attempt of IVF with stimulation protocol modification. The day of embryo transfer was chosen according to the results of SEM. Pregnancy as a result of the treatment cycle occurred in 118 women (61%), 75 (39%) did not become pregnant. While in the control group, stimulation was performed according to a regular protocol and correction of other identified causes of IVF failures. The in vitro fertilization cycle ended with pregnancy in 40 (60%) women, and negative result was fixed in 27 (40%). The study requires the results of live births. In both groups there were patients (8 and 23 respectively) who did not have re-embryo transfer. The main reason was the lack of embryos for transfer.

Group	All examined patients		Patients with confirmed pregnancy		Patients with unsuccessful attempt		Group of patients without embryo Transfer
PINOPODIUM formed on LH 6/7 **(Group 1)**	75	26%	40	60%	27	40%	8
PINOPODIUM formed earlier or later LH+ 6/7 **(Group 2)**	216	74%	118	61%	75	39%	23

Image 3. **Characteristics of patients with repeated implantation failures according to the study groups**

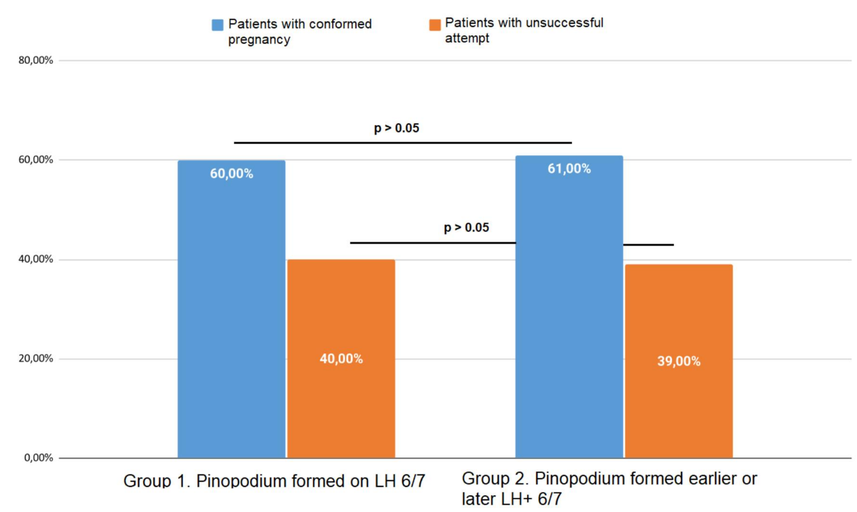

Image 4 **The graphic results**

Conclusion

Infertility is an actual medical and social problem. Implantation disorders take a huge role in structure of vitro fertilization failuer. Displacement of the implant window occurs in 74% of cases according to the study. The level of pregnancy in this group of patients after correction of the endometrial preparation protocol is not statistically different from this indicator in the control group.

Detection and elimination or compensation of the factor which leads to implantation failure increases the clinical pregnancy rate in a group of patients with repeated unsuccessful IVF.

1. Nikas, G. Pinopodes as markers of endometrial receptivity in clinical practice. Hum. Reprod. 1999, 14, 99–106. [CrossRef] [PubMed]
2. Fatemi H. M. The luteal phase after 3 decades of IVF:what do we know? / H. M. Fatemi // Reprod. Biomed.Online.— 2009.— Vol. 19.— P. 4331.
3. Lopata, A.; Bentin-Ley, U.; Enders, A. Pinopodes and implantation. Rev. Endocr. Metab. Disord. 2002, 3, 77–86. [CrossRef] [PubMed]
4. Jin, X.Y.; Zhao, L.J.; Luo, D.H.; Liu, L.; Dai, Y.D.; Hu, X.X.; Wang, Y.Y.; Lin, X.; Hong, F.; Li, T.C.; et al. Pinopode score around the time of implantation is predictive of successful implantation following frozen embryo transfer in hormone replacement cycles. Hum. Reprod. 2017, 32, 2394–2403. [CrossRef] [PubMed]
5. Nikas, G.; Drakakis, P.; Loutradis, D.; Mara-Skoufari, C.; Koumantakis, E.; Michalas, S.; Psychoyos, A. Uterine pinopodes as markers of the ‘nidation window’ in cycling women receiving exogenous oestradiol and progesterone. Hum. Reprod. 1995, 10, 1208–1213. [CrossRef] [PubMed]
16. Quinn, C.E.; Ryan, E.; Claessens, E.A.; Greenblatt, E.; Hawrylyshyn, P.; Cruicshank, B.; Hannam, T.; Dunk, C.; Casper, R.F. The presence of pinopodes in the human endometrium does not delineate the implantation window. Fertil. Steril. 2007, 87, 1015–1021. [CrossRef] [PubMed]