VIA MEDICA

REVIEW PAPER / OBSTETRICS

Ginekologia Polska
2023, vol. 94, no. 4, 326–329

ISSN 0017–0011, e-ISSN 2543–6767

DOI 10.5603/GP.a2022.0054

Implantation of embryos. The way for the improvement of the cumulative life birth rate (CLBR) in the assisted reproductive technology (ART)

Marian Szamatowicz[1, 2], Jacek Szamatowicz[3]

[1]*Department of Medical Sciences Faculty of Health Sciences, Lomza State University of Applied Sciences, Poland*
[2]*Department of Reproduction Gynaecological Endocrinology, Medical University in Bialystok, Poland*
[3]*Department of Gynaecology and Gynaecological Oncology, Medical University in Bialystok, Poland*

ABSTRACT

Despite the willingness, humans belong to the species with the limited procreation possibilities. Infertility affects about 15 % of population is the very important subject for the reproductive medicine. An assisted reproductive technology (ART) offers the significant chance for the infertile couples, but it does not give the guarantee for the pregnancy and for the birth of a healthy child. The implantation of embryo, despite numerous trials and attempts, remain the last barrier in the assisted reproduction technologies; thus, the endometrial receptivity becomes the subject of permanent interest. In this review we have tried to present various methods of improvement of an endometrial receptivity with the conclusion that we still wait for the valuable prognostic factor in the treatment of infertility by ART which could predict the chance for the birth of a healthy child.

Key words: infertility; assisted reproductive technology; implantation; endometrial receptivity

Ginekologia Polska 2023; 94, 4: 326–329

INTRODUCTION

Infertility presents a significant issue for reproductive medicine. There are many definitions of this phenomenon but the most used definition is the inability to conceive after one year of unprotected intercourses. Infertility is identified as childlessness and the World Health Organisation (WHO) expresses no doubts labelling infertility as a disease, what is more, due to its high prevalence infertility has been named a social disease. Approximately 85% of couples are able to conceive spontaneously within 12 months which also means that about 15% of couples have a problem with reproduction. According to data from literature, more than 50 000 million couples have a problem with reproduction [1] with the dominant male factor for this disease [2]. Infertility shows its own specificity. It is always disease of couple; the only effective treatment of this disease is a delivery of healthy baby. Infertility leading to childlessness has various sociopsychological aspects, moreover "infertility stress" is comparable to the stress of neoplastic diseases and acute myocardial infarction. Only AIDS is considered to have a stronger negative impact on life. Young people are very often shocked and overwhelmed without knowledge what to do. The diagnosis of infertility often causes intense emotional reactions. Couples are worried the about potential of having no children, dreams of the continuation of a family and genetic line. Even some parents of the couple are affected by the problem of infertility, as they are not given the chance of becoming grandparents. Among the couples which have problems with reproduction there are different causes of this disease. According to the data from literature nowadays is as the dominant factor male one [2]. Other causes are ovulation disturbances including polycystic ovary syndrome (PCO) [3], oviduct abnormalities most often caused by inflammatory processes and surgical interventions occurred in the past, endometriosis with different advancement stages, unexplained infertility [4], anatomical abnormalities of the uterus. Before the era of the assisted reproductive technology about 50% of infertile couples have been deprived of the effective therapeutic methods. The birth of the first baby after *in vitro* fertilization, unjustly called "test tube baby", has opened a new era in the management of problems with infertility. The Nobel Prize

Corresponding author:
Jacek Szamatowicz
Department of Gynecology and Gynecological Oncology, 24 A Sklodowskiej St, 15–276 Bialystok, Poland
e-mail: jacek.szamatowicz@umb.edu.pl

Received: 23.03.2022 Accepted: 27.04.2022 Early publication date: 6.06.2022

Committee announced *in vitro* fertilization and embryo transfer, in short IVF/ET is the most significant discovery of the 20th Century, as it gives chances for parenthood to millions of couples previously considered irretrievable infertile. Nevertheless, it should be remembered that with the application of ART for the treatment of infertility there is always a chance for parentage and but 100%. The pioneer of ART. treatment Edwards R. wrote in 2006 [5] that human implantation is the last barrier in assisted reproductive technology. In this review we will present the easiest and useful methods for clinicians of assessing endometrial receptivity, as well as how to improve the implantation rate that in consequence will give the highest cumulative live birth rate.

ASSESEMENT OF ENDOMETRIAL RECEPTIVITY

There are two major goals for clinicians who deal with infertility The efficiency of the treatment, considered as the home taken healthy baby, and not as "clinical or biochemical surrogate end points," presented in many publications, and safety of the procedures proposed to solve the case of childlessness must be always kept in mind. In comparing fecundability in people with other species, the fecundity of human being is much smaller and the probability of a woman becoming pregnant in a cycle is approximately 20–25%, depending on her age. When in cases of infertility there is a proposition of assisted reproductive technology (IVF/ET) and when about 25–35% is obtained in the live birth per cycle [6] it sounds as the "good success rate". The treatment of infertility is expensive, and one must realize that if the success rate is 25 to 35%, it means 65–75% is the "failure rate". No doubt such situation is distressing for couples undergoing both heavy financial as well as psychological costs of the procedure [6]. During last decades the protocols of the controlled ovarian hyperstimulation has been improved and the optimal number of mature follicles has been obtained, there are new equipment for the culture of embryos but efficiency of ART has gained some "plateau". It appeared that implantation of embryos is the most limiting factor in the treatment of infertility and hence, quite understandable interest in so called endometrial receptivity. This receptivity, besides normal and good quality of blastocyst, plays a crucial role in the process of implantation and finally decides about the life birth ratio as well as about the cumulative life birth ratio, the truest results of infertility treatment [7–9]. The implantation of embryos is a very complex process which involves both the embryo and maternal endometrium and the key to this process is the cascade of molecular mechanisms regulated by endocrine, paracrine and autocrine modulators both of embryonic and maternal origin [10–13]. There is a commonly accepted opinion that implantation process depends on the three basic conditions: normal "receptive" endometrium, normal functional blastocyst and on „propter" dialogue and communication between the above-mentioned structures [14–17]. Endometrial receptivity is described as the temporary and exceptional sequence of events and factors which allow for the embryo to implant in the uterus. The "implantation window", which occurs 6–10 days after ovulation is the proper time for embryos implantation [14]. For the clinicians dealing with ART it is significant to diagnose the best time for the embryo transfer. As the endometrial receptivity plays the significant role in the results of the infertility treatment by ART there are commonly employed in clinics methods of its evaluation: morphology, ultrasonography, investigation of the vagino-cervical fluid, assessment of the single biomarkers and OMICs. Morphological assessment of the endometrial receptivity relays on the using of Noyes criteria and on the formation of pinopodes [18]. These methods are considered as controversial because they require the biopsy of an endometrium. Ultrasonography — 2/3D power Dopler allows, however, in the non-invasive method, evaluates the thickness, structure and volume of endometrium. Moreover, this method enables the measurement of the pulsatile, vascular resistance, and flow indexes. The ultrasonographic assessment enables the identification of couples with the bad implantation prognosis however it is not possible to foresee the result of ART in the infertility treatment [19]. There are two possibilities to obtain of the fluid to investigate of the excretion of cytokines, interleukins and growth factors: washing with the results changed by the dilution and aspiration with the components of cervical mucus and blood. The further investigations are necessary to identify the markers speaking for the favourable endometrial receptivity [20]. The most promising are investigations of the single marker showing the best time for embryo transfer. The observation of many proteins with the temporary expression during the "implantation window" allowed for preparing the list of candidates: glikodelina, aVb3 integrina, osteopontina, LIF, colony stimulating factor (CSF-1). Regrettably, at the moment the results of these studies do not allow for proposing the molecule as the positive single endometrial receptivity marker [21]. Another endometrial marker is MAG considered to be the substance excreted by the endometrium just before the implantation and regarded as the endometrial function test (ETF). It is based on the expression of cycline C and p27 and recommended in same cases before the ART treatment [22]. The molecular conception of the implantation is the hope for the better understanding of the pathological processes of this significant step in infertility treatment and great improvement the effectiveness of ART as well as diminishing the percentage of the recurrent implantation failure (RIF) [23, 24].

STRATEGY FOR THE IMPROVEMENT OF ENDOMETRIAL RECEPTIVITY

The clinicians dealing with the problem of infertility and having in mind that endometrial receptivity plays a crucial role in the effectiveness of ART treatment, can find in the scientific literature hundreds of different attempts to improve both LBR as well CLBR. Below, there is the list of different strategical attempts to gain the above-mentioned goal. The first step in IVF/ET methods is controlled ovarian hyperstimulation (COH). In these protocols there are proposals which do not diminish the endometrial receptivity and even could increase it. In such protocols there is no place for a clomiphene, but the addition of an exogenous oestradiol can have the positive effect, diminishing concentration of an oestradiol in preimplantation phase recommending step-down protocols in high responders, elimination of the high concentrations of progesterone adding of antiprogestogens and finally the strategy of the transfer of the high quality three embryos [25, 26]. There is a significant progress in the freezing of embryos using vitrification techniques, which do not damage their biological activity and hence the strategic proposal is to delay of the transfer in the natural cycle [27, 28]. The improvement of the uterus blood flow is the goal for numerous clinical trials. The administration of small doses of aspirin for blocking the synthesis of thromboxane and to induce the synthesis of prostacyclin, employment of L-arginine (donor of nitric oxide NO) as well as nitro-glycerine (donor of NO too) and intravaginal sildenafil they are aimed at improving uterus blood flow in cases suspected for diminished endometrial receptivity [29–32]. In the strategy for the improvement of an endometrial receptivity the important role plays treatment of the functional and anatomical conditions. It has appeared that progesterone is the most effective way to support luteal phase insufficiency. The application of progesterone is better than injections of choriogonadotropin mostly due to the less frequent OHSS [33]. In the cases of hyperprolactinemia the addition of dopamine agonists gave positive effect [34]. It has been also recommended to perform myomectomy in cases deforming uterus cavity [35], hysteroscopic incision of intrauterine adhesions [36], and laparoscopic elimination of the fallopian tube hydrosalpinxes [37].The very controversial subject in the strategy of an improvement of an endometrial receptivity is the endometrial scratching /injury/ in the cycle before embryo-transfer [38, 39].There are data suggesting that such scratching might cause the increase of chance for pregnancy in cases of RIF, but there are also information that endometrial scratching is without any positive effect [40]. There are also suggestion of using, as an alternative strategy in women with thin endometrium and recurrent implantation failure, intrauterine infusion of autologous platelet-rich plasma (PRP) in assisted reproductive technology (ART) leads to better results. For better results the authors stated that these findings need further confirmation in large prospective and high quality controlled, randomised trials [41]. Finally, the mode of transferring also can influence the effectiveness of infertility treatment. In clinical practice the precise evaluation of the uterine cavity, avoiding contractions of this organ by administering Valium or atosiban, extraction of cervical mucus and proper placing of embryo with the help of USG, are all ways which should not be omitted when looking for the increase of the effectiveness infertility treatment [42, 43].

CONCLUSIONS

There is no doubt that implantation of embryos and endometrial receptivity, mostly during well-defined implantation window plays the crucial role in the expected results of infertility treatment by ART. In the literature devoted to this subject one can meet different proposals however it should be emphasized that they are described as the proven and unproven methods of infertility treatment [44]. While analysing available proposals clinicians should remember that none of the receptivity markers has sufficient discriminating value to act as a diagnostic test for an endometrial receptivity which allows for prediction pregnancy and delivery of the live, healthy baby. Nevertheless, there is some hope that further investigations, involving modern molecular tests of an endometrial receptivity (ERA, ER Map/ER) allow clinician's obtaining of awaited tools for the personalized infertility treatment. Minimizing ineffective attempts and increasing value of the obtained results it is a great challenge for the investigators dealing with infertile couples [45, 46].

Conflict of interests

The authors report no conflict of interest.

REFERENCES

1. Boivin J, Bunting L, Collins JA, et al. International estimates of infertility prevalence and treatment-seeking: potential need and demand for infertility medical care. Hum Reprod. 2007; 22(6): 1506–1512, doi: 10.1093/humrep/dem046, indexed in Pubmed: 17376819.
2. Inhorn MC, Patrizio P. Infertility around the globe: new thinking on gender, reproductive technologies and global movements in the 21st century. Hum Reprod Update. 2015; 21(4): 411–426, doi: 10.1093/humupd/dmv016, indexed in Pubmed: 25801630.
3. Balen AH, Morley LC, Misso M, et al. The management of anovulatory infertility in women with polycystic ovary syndrome: an analysis of the evidence to support the development of global WHO guidance. Hum Reprod Update. 2016; 22(6): 687–708, doi: 10.1093/humupd/dmw025, indexed in Pubmed: 27511809.
4. Ray A, Shah A, Gudi A, et al. Unexplained infertility: an update and review of practice. Reprod Biomed Online. 2012; 24(6): 591–602, doi: 10.1016/j.rbmo.2012.02.021, indexed in Pubmed: 22503948.
5. Edwards RG, Edwards RG. Human implantation: the last barrier in assisted reproduction technologies? Reprod Biomed Online. 2006; 13(6): 887–904, doi: 10.1016/s1472-6483(10)61039-5, indexed in Pubmed: 17169215.
6. Fathalla MF. Current challenges in assisted reproduction. In: Vaegter E, Rowe PJ, Griffin PD. ed. Current Practices and Controversies in Assisted Reproduction. Report of a Meeting on „Medical and Social Aspects of Assisted Re-production". Hel dat WHO Headquarters in Geneva 2001: 17–21.

7. Malizia BA, Hacker MR, Penzias AS. Cumulative live-birth rates after in vitro fertilization. N Engl J Med. 2009; 360(3): 236–243, doi: 10.1056/NEJMoa0803072, indexed in Pubmed: 19144939.
8. Paul R, Fitzgerald O, Lieberman D, et al. Cumulative live birth rates for women returning to ART treatment for a second ART-conceived child. Hum Reprod. 2020; 35(6): 1432–1440, doi: 10.1093/humrep/deaa030.
9. Høyer S, Kesmodel U, Aagaard J. Conditional and cumulative live birth rates after blastocyst transfer. Eur J Obstet Gynecol Reprod Biol. 2021; 261: 46–51, doi: 10.1016/j.ejogrb.2021.03.037.
10. Guzeloglu-Kayisli O, Kayisli U, Taylor H. The Role of Growth Factors and Cytokines during Implantation: Endocrine and Paracrine Interactions. Semin Reprod Med. 2009; 27(01): 062–079, doi: 10.1055/s-0028-1108011.
11. Fox C, Morin S, Jeong JW, et al. Local and systemic factors and implantation: what is the evidence? Fertil Steril. 2016; 105(4): 873–884, doi: 10.1016/j.fertnstert.2016.02.018.
12. Kim SM, Kim JS. A Review of Mechanisms of Implantation. Dev Reprod. 2017; 21(4): 351–359, doi: 10.12717/DR.2017.21.4.351, indexed in Pubmed: 29359200.
13. Hernández-Vargas P, Muñoz M, Domínguez F. Identifying biomarkers for predicting successful embryo implantation: applying single to multi-OMICs to improve reproductive outcomes. Hum Reprod Update. 2020; 26(2): 264–301, doi: 10.1093/humupd/dmz042.
14. Acosta A, Elberger L, Borghi M, et al. Endometrial dating and determination of the window of implantation in healthy fertile women. Fertil Steril. 2000; 73(4): 788–798, doi: 10.1016/s0015-0282(99)00605-6.
15. Achache H, Revel A. Endometrial receptivity markers, the journey to successful embryo implantation. Hum Reprod Update. 2006; 12(6): 731–746, doi: 10.1093/humupd/dml004, indexed in Pubmed: 16982667.
16. Lessey B, Young S. What exactly is endometrial receptivity? Fertil Steril. 2019; 111(4): 611–617, doi: 10.1016/j.fertnstert.2019.02.009.
17. Massimiani M, Lacconi V, La Civita F, et al. Molecular Signaling Regulating Endometrium-Blastocyst Crosstalk. Int J Mol Sci. 2019; 21(1), doi: 10.3390/ijms21010023, indexed in Pubmed: 31861484.
18. Alfer J, Fattahi A, Bleisinger N, et al. Endometrial Dating Method Detects Individual Maturation Sequences During the Secretory Phase. In Vivo. 2020; 34(4): 1951–1963, doi: 10.21873/invivo.11992, indexed in Pubmed: 32606167.
19. Kupesic S, Bekavac I, et al. Assessement of endometrial receptivity by transvaginal color Doppler and three-dimensional power Doppler ultrasono-graphy in patients undergoing in vitro fertilization procedures. J Ultrasoun Med. 2001; 20(2): 125–134.
20. Craciunas L, Gallos I, Chu J, et al. Conventional and modern markers of endometrial receptivity: a systematic review and meta-analysis. Hum Reprod Update. 2019; 25(2): 202–223, doi: 10.1093/humupd/dmy044, indexed in Pubmed: 30624659.
21. Mirkin S, Arslan M, Churikov D, et al. In search of candidate genes critically expressed in the human endometrium during the window of implantation. Hum Reprod. 2005; 20(8): 2104–2117, doi: 10.1093/humrep/dei051, indexed in Pubmed: 15878921.
22. Hafiz P, Nematollahi M, Boostani R, et al. Predicting Implantation Outcome of In Vitro Fertilization and Intracytoplasmic Sperm Injection Using Data Mining Techniques. Int J Fertil Steril. 2017; 11(3): 184–190, doi: 10.22074/ijfs.2017.4882, indexed in Pubmed: 28868840.
23. Cicinelli E, Matteo M, Tinelli R, et al. Prevalence of chronic endometritis in repeated unexplained implantation failure and the IVF success rate after antibiotic therapy. Hum Reprod. 2015; 30(2): 323–330, doi: 10.1093/humrep/deu292, indexed in Pubmed: 25385744.
24. Makrigiannakis A, Makrygiannakis F, Vrekoussis T. Approaches to Improve Endometrial Receptivity in Case of Repeated Implantation Failures. Front Cell Dev Biol. 2021; 9: 613277, doi: 10.3389/fcell.2021.613277, indexed in Pubmed: 33796523.
25. Levi AJ, Drews MR, et al. Controlled ovarian hyperstimulation does not adversely affect endometrial receptivity in in vitro fertilization cycles. Fertil Steril. 2001; 76(4): 670–674.
26. Masschaele T, Derris J, et al. Does transfering three or more embryos make sense for a wlldefined population of infertility patients undergoing IVF/ICSI? Facts Views Obgyn. 2012; 4(1): 51–58.
27. Dieamant FC, Petersen CG, Mauri AL, et al. Fresh embryos versus freeze-all embryos - transfer strategies: Nuances of a meta-analysis. JBRA Assist Reprod. 2017; 21(3): 260–272, doi: 10.5935/1518-0557.20170048, indexed in Pubmed: 28837037.
28. Singh B, Reschke L, Segars J, et al. Frozen-thawed embryo transfer: the potential importance of the corpus luteum in preventing obstetrical complications. Fertil Steril. 2020; 113(2): 252–257, doi: 10.1016/j.fertnstert.2019.12.007, indexed in Pubmed: 32106972.
29. Ruopp MD, Collins TC, Whitcomb BW, et al. Evidence of absence or absence of evidence? A reanalysis of the effects of low-dose aspirin in in vitro fertilization. Fertil Steril. 2008; 90(1): 71–76, doi: 10.1016/j.fertnstert.2007.06.033, indexed in Pubmed: 17889863.
30. So S, Yamaguchi W, Murabayashi N, et al. Beneficial effect of l-arginine in women using assisted reproductive technologies: a small-scale randomized controlled trial. Nutr Res. 2020; 82: 67–73, doi: 10.1016/j.nutres.2020.08.008.
31. Ohl J, Lefèbvre-Maunoury C, Wittemer C, et al. Nitric oxide donors for patients undergoing IVF. A prospective, double-blind, randomized, placebo-controlled trial. Hum Reprod. 2002; 17(10): 2615–2620, doi: 10.1093/humrep/17.10.2615, indexed in Pubmed: 12351537.
32. Moini A, Zafarani F, Jahangiri N, et al. The Effect of Vaginal Sildenafil on The Outcome of Assisted Reproductive Technology Cycles in Patients with Repeated Implantation Failures: A Randomized Placebo-Controlled Trial. Int J Fertil Steril. 2020; 13(4): 289–295, doi: 10.22074/ijfs.2020.5681, indexed in Pubmed: 31710189.
33. Mizrachi Y, Horowitz E, Ganer Herman H, et al. ESHRE Capri Workshop Group. An update of luteal phase support in stimulated IVF cycles. Hum Reprod Update. 2007; 13(6): 581–590, doi: 10.1093/humupd/dmm021, indexed in Pubmed: 17626114.
34. Tang H, Mourad SM, Wang A, et al. Dopamine agonists for preventing ovarian hyperstimulation syndrome. Cochrane Database Syst Rev. 2021; 4: CD008605, doi: 10.1002/14651858.CD008605.pub4, indexed in Pubmed: 33851429.
35. Ojo-Carons M, Mumford SL, Armstrong AY, et al. Is Myomectomy Prior to Assisted Reproductive Technology Cost Effective in Women with Intramural Fibroids? Gynecol Obstet Invest. 2016; 81(5): 442–446, doi: 10.1159/000443391, indexed in Pubmed: 26990761.
36. Catena U, Campo R, Bolomini G, et al. New approach for T-shaped uterus: Metroplasty with resection of lateral fibromuscular tissue using a 15 Fr miniresectoscope. A step-by-step technique. Facts Views Vis Obgyn. 2021; 13(1): 67–71, doi: 10.52054/FVVO.13.1.003, indexed in Pubmed: 33889862.
37. Strandell A, Lindhard A. Hydrosalpinx and ART. Salpingectomy prior to IVF can be recommended to a well-defined subgroup of patients. Hum Reprod. 2000; 15(10): 2072–2074, doi: 10.1093/humrep/15.10.2072, indexed in Pubmed: 11006175.
38. Nastri CO, Ferriani RA, Raine-Fenning N, et al. Endometrial scratching performed in the non-transfer cycle and outcome of assisted reproduction: a randomized controlled trial. Ultrasound Obstet Gynecol. 2013; 42(4): 375–382, doi: 10.1002/uog.12539, indexed in Pubmed: 23754314.
39. van Hoogenhuijze NE, Kasius JC, Broekmans FJM, et al. Endometrial scratching prior to IVF; does it help and for whom? A systematic review and meta-analysis. Hum Reprod Open. 2019; 2019(1): hoy025, doi: 10.1093/hropen/hoy025, indexed in Pubmed: 30895265.
40. Mackens S, Racca A, Van de Velde H, et al. Follicular-phase endometrial scratching: a truncated randomized controlled trial. Hum Reprod. 2020; 35(5): 1090–1098, doi: 10.1093/humrep/deaa018, indexed in Pubmed: 32372078.
41. Mouanness M, Ali-Bynom S, Jackman J, et al. Use of Intra-uterine Injection of Platelet-rich Plasma (PRP) for Endometrial Receptivity and Thickness: a Literature Review of the Mechanisms of Action . Reprod Sci. 2021; 28(6): 1659–1670, doi: 33886116, indexed in Pubmed: 10.1007/s43032-021-00579-2 .
42. Larue L, Keromnes G, Massari A, et al. Transvaginal ultrasound-guided embryo transfer in IVF. J Gynecol Obstet Hum Reprod. 2017; 46(5): 411–416, doi: 10.1016/j.jogoh.2017.02.015, indexed in Pubmed: 28428123.
43. Bortoletto P, Bakkensen J, Anchan RM. Embryo transfer: timing and techniques. Minerva Endocrinol. 2018; 43(1): 57–68, doi: 10.23736/S0391-1977.17.02649-9, indexed in Pubmed: 28381082.
44. Szamatowicz M, Szamatowicz J. Proven and unproven methods for diagnosis and treatment of infertility. Adv Med Sci. 2020; 65(1): 93–96, doi: 10.1016/j.advms.2019.12.008, indexed in Pubmed: 31923772.
45. Sadeghi MR. Low Success Rate of ART, an Illusion, a Reality or Simply a Too High Expectation? J Reprod Infertil. 2012; 13(3): 123, indexed in Pubmed: 23926535.
46. Miravet-Valenciano JA, Rincon-Bertolin A, Vilella F, et al. Understanding and improving endometrial receptivity. Curr Opin Obstet Gynecol. 2015; 27(3): 187–192, doi: 10.1097/GCO.0000000000000173, indexed in Pubmed: 25827647.