MELATONIN EXCHANGE IN INFERTILE WOMEN WITH REPEATED IMPLANTATION FAILURES

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INTRODUCTION

Implantation is the first step in human reproduction [1]. Considering the rate of natural conception, it seems that the chance of conception in one menstrual cycle is quite low and reaches 30%. This means that two-thirds of potential natural conceptions are lost due to implantation failure [2]. Similar observations are also made in the context of *in vitro* fertilization and embryo transfer (IVF-ET) treatment. The probability of implantation failure is approximately 70%, as deduced from the fact that the implantation rate per embryo transfer is 30% [3]. Acknowledging these data, although failure of implantation may result in a pathological condition, it is also, from an evolutionary point of view, a physiological "barrier" leading to the establishment of a full-term pregnancy.

However, there is a special category of infertile patients who have an abnormally increased proportion of consecutive implantation failures in the context of IVF-ET treatment, despite the transfer of high-quality embryos. This phenomenon is known as repeated or recurrent implantation failure (RIF) and affects approximately 10–15% of women undergoing treatment in IVF-ET cycles worldwide [4]. The Preimplantation Genetic Diagnosis Consortium of the European Society of Human Reproduction and Embryology (ESHRE) defined RIF as when more than three quality embryos or ten embryos in several transfer cycles are performed without achieving a clinical pregnancy [5]. According to the latest ESHRE 2023 guidelines, RIF describes a scenario in which the transfer of embryos considered viable does not result in a positive pregnancy test in a particular patient frequently enough to warrant consideration of further investigations and/or interventions [6].

RIF is a multifactorial condition [1, 3, 7]. One of the important factors is the changed morphofunctional state of the endometrium and chronodestruction in the woman's body.

Development of the endometrium is a cyclical event strictly regulated by hormones and factors. Molecular perturbations of the circadian clock by external cues (eg, light pollution) or other environmental processes that affect the oscillations of the internal biological clock are deeply associated with low implantation rates, pregnancy disorders, higher incidence of menstrual irregularities, infertility, and miscarriages in women. These phenomena are often accompanied by a decrease in the level of melatonin (MT) and its receptors in the normal tissue of the uterus and placenta [8].

MT (N-acetyl-5-methoxytryptamine) is a lipophilic indolamine neurohormone derived from the essential amino acid tryptophan. Circulating melatonin exhibits a circadian rhythm with highest levels at night, moderate levels in the morning, and much lower levels in the afternoon. Exposure to light can reduce the duration of MT secretion and the subsequent level of MT in the blood. Thus, MT can be a key biological mediator of chronodestruction [9].

Normally, MT is synthesized and secreted primarily in the pineal gland in response to darkness, acting as a neuroendocrine converter of photoperiodic information during the night [10]. MT is also produced in the mitochondria of all other cells of the human body in a non-circadian way, so the level of MT in mitochondria is approximately 100 times higher than in plasma [11]. It is produced in reproductive organs such as ovaries, testicles, uterus, and placenta. The amount synthesized by the pineal gland is less than 5% of the total amount of MT [12]. Therefore, MT is probably best defined today as a pineal gland hormone and a biologically active amine with cellular targets near the site of its synthesis in some tissues [13].

Among all species, both animals and plants, the chemical structure of MT remains unchanged, and its action becomes more and more diverse. The diverse functionality of MT can be attributed to its evolutionary history of two to three billion years, during which it had enough time to develop complex interactions with other molecules [14]. These interactions allowed MT to exhibit an extremely wide range of functions, as shown in all species [14, 15, 16].

MT has demonstrated an antioxidant function and a key role as a regulator of physiological processes related to human reproduction. MT has been reported to control the expression of genes related to oocyte maturation, including mitochondrial function, antioxidant enzymes, apoptosis, cumulus cell expansion, and oocyte maturation factors [17]. In addition, it is involved in epigenetic mechanisms, such as DNA methylation and histone acetylation [18]. MT partic-

ipates in the normal course of pregnancy, starting with oocyte quality, continuing with embryo implantation, and ending with fetal development and delivery [10, 19–21].

New data prove that the disruption of circadian rhythm regulation followed by a low level of circulating MT is associated with a low implantation rate and difficulties in maintaining pregnancy [8, 18, 19]. The key role of MT is determined by the fact that the rhythms of its production are subject to all the endogenous rhythms of the body. Exogenous introduction of MT reliably increases endothelial oscillations, which reflects an increase in the metabolic activity of the endothelium. This is probably due to the stimulating effect of MT on the production of NO-synthase by vascular endothelial cells, with subsequent increase in NO production and vasodilation. MT acts as an antioxidant and regulates ovarian function by binding to its receptors [12], which is associated with a decrease in the number of molecules such as cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), as well as an increase in phospholipase C (PLC) [23]. In addition, MT can directly chelate reactive oxygen and nitrogen species, as well as mobilize an intracellular antioxidant enzyme without its receptors [24].

A.A. Mosher et al. (2019) [25] recently showed that melatonin receptors 1A (MTNR1A or MT1) and 1B (MTNR1B or MT2) are expressed in eutopic human endometrium. MTNR1B has been suggested to synergize with oxytocin to promote nocturnal uterine contractions [26]; in late pregnancy, circulating melatonin is fundamental for inducing the timing and extent of contractions, and conversely, its acute suppression by light inhibits myometrial contractions [27]. AANAT (aralkylamine-N-acetyltransferase) is the rate-limiting enzyme of MT synthesis [11]. In an experiment on mice, it was proved that the uterine melatonergic systems AANAT and membrane MTNR1B are important for endometrial receptivity and early implantation in mice [11]. Data on the status of melatonin metabolism in infertile women with RIF are limited.

Objective of the study: to determine the characteristics of melatonin metabolism in infertile women with RIF in IVF-ET cycles.

MATERIALS AND METHODS

The study was conducted at the Department of Obstetrics and Gynecology of the Odesa National Medical University (ONMedU), University Clinic "Center of Reconstructive and Restorative Medicine" of ONMedU, LLC "Clinic of Reproductive Medicine "Nadia Odesa"". The research was carried out for the period from 2021 to 2023, was a fragment of the planned research topic of the Department of Obstetrics and Gynecology of ONMedU "Improving methods of prevention, diagnosis and treatment of diseases reproductive system of a woman using the latest medical technologies" (state registration number 0117U007494). Study was approved by the ONMedU Commission on Bioethics (protocol No. 2/21 dated 08.11.2021). Informed consent was obtained from all patients.

103 women of reproductive age with infertility and RIF who were treated in IVF-ET cycles were under observation.

Depending on the onset of pregnancy in the current cycle of IVF-ET, the examined women were divided into 2 groups:

- group A – 35 women with the onset of pregnancy;
- group B – 68 patients with no onset of pregnancy.

Criteria for the inclusion of patients with RIF in the study: infertility associated with tubal or male factor; regular ovulatory menstrual cycles; basal level of follicle stimulating hormone < 11 mIU/ml; the number of antral follicles on the 3–5th day of menstrual cycle from 7 to 12 in the maximum ultrasound section of the ovaries; treatment of infertility by IVF-ET method; presence of at least two euploid embryo transfers in the past; absence of organic gynecological diseases, endocrine disorders, functional vascular disorders (for example, arterial hypertension) and genital endometriosis; absence of taking hormonal drugs during the last 6 months; no history of smoking.

Control group C consisted of 32 healthy fertile women.

Determination of the level of MT in blood serum, taken at 7–8 o'clock in the morning, was carried out by radioimmunoassay using the Gammamaster analyzer and test systems (Pharmacia LKB Biotechnology AB, Sweden), LDN (Labor Diagnostika Nord GmbH & Co.KG, Germany). Reference values of MT were 8.0–20.0 pg/ml.

The main metabolite of MT in urine 6-sulfatoxymelatonin in urine (aMT6s) was determined by radioimmunoassay using the IBL test system ELISA (Hamburg Germany). Determinations were adjusted for kinetically measured urinary creatinine using the Yaffe test [28], so results were expressed as ng/mg urinary aMT6 (ng/mg Cr).

Statistical analysis of the results was performed using the Microsoft Excel 2010 program. Quantitative variables were described using the mean (M), standard error of the mean (± SEM), Student's t-test. Values of $p < 0.05$ were considered statistically significant. Correlation and pairwise correlation-regression analysis were used to study stochastic dependence between indicators. For this, the correlation coefficient (r), approximation coefficient (R^2) and their probability were calculated.

RESULTS AND DISCUSSION

The average age of the examined women in group A was 32.20 ± 0.61 years, in group B – 31.31 ± 0.40 years, in group C – 32.45 ± 0.59 years ($p > 0.05$); body mass index – 19.72 ± 0.90 kg/m^2 in group A and 21.94 ± 0.45 kg/m^2 in group B versus 22.25 ± 0.88 kg/m^2 in the group C ($p > 0.05$).

The duration of infertility in group A reached 9.26 ± 0.30 years against 10.00 ± 0.35 years in group B ($p > 0.05$); number of IVF-ET – 4.51 ± 0.20 vs. 4.43 ± 0.14, respectively ($p > 0.05$). The distribution of primary and secondary infertility in the groups was homogeneous: in group A – 48.57/51.43%, in group B – 45.71/54.29% ($p > 0.05$). The average number of pregnancies in the anamnesis was 0.71 ± 0.08 and 1.00 ± 0.14 ($p > 0.05$), respectively.

The study of melatonin metabolism showed that the MT levels in group A (11.38 ± 0.38 pg/ml) and in group B (9.55 ± 0.27 pg/ml) were lower than in group C (13.67 ± 0.65) in 1.20 ($p < 0.01$) and 1.43 ($p < 0.01$) times, respectively. At the same time, the level of MT in women with the onset of pregnancy in the current IVF-ET cycle exceeded the MT value in the group of patients with no pregnancy by 1.19 times ($p < 0.03$). Excretion of aMT6s in urine in group A (5.09 ± 0.19 ng/ml Cr) and in

group B (3.03 ± 0.09 ng/ml Cr) were lower than in group C (6.12 ± 0.21 ng/ml Cr) respectively in 1.20 ($p < 0.01$) and 2.02 ($p < 0.01$) times. The amount of aMT6s in the urine of patients in group A was 1.68 times higher than in group B ($p < 0.01$) (Fig. 1).

A direct relationship was established between the levels of serum MT and urinary aMT6s, which was most adequately approximated by a polynomial dependence: $y = 0{,}0139x^2 - 0{,}1127x + 3{,}2978$, $R^2 = 0{,}2994$, $r = 0{,}51$, $p < 0{,}01$ (Fig. 2).

There is a "window" of endometrial receptivity, defined as a limited period when the receptive state of the uterus is synchronized with the activated state of the blastocyst, which supports attachment. To achieve proper implantation, evidence demonstrates that fine spatiotemporal tuning between various growth factors, cytokines, lipid mediators, and transcription factors mediated by steroid hormones is essential for uterine preparation [21].

According to previous studies, MT stimulates the expression of its own receptors, protein p53 and leukemia inhibitory factor (LIF), activating signaling pathways involved in embryo implantation [29]. At the molecular level, the MTNR1B receptor is more active than MTNR1A during reproduction and is upregulated. Increased MTNR1B expression promotes p21 protein activation. This, in turn, induces p38-mediated phosphorylation of p53, which modulates LIF expression, thus promoting embryo implantation [15, 20].

It is assumed that MT contributes to blastocyst activation and endometrial receptivity by modulating the expression of hormones in the uterus [30]. On the one hand, it induces the

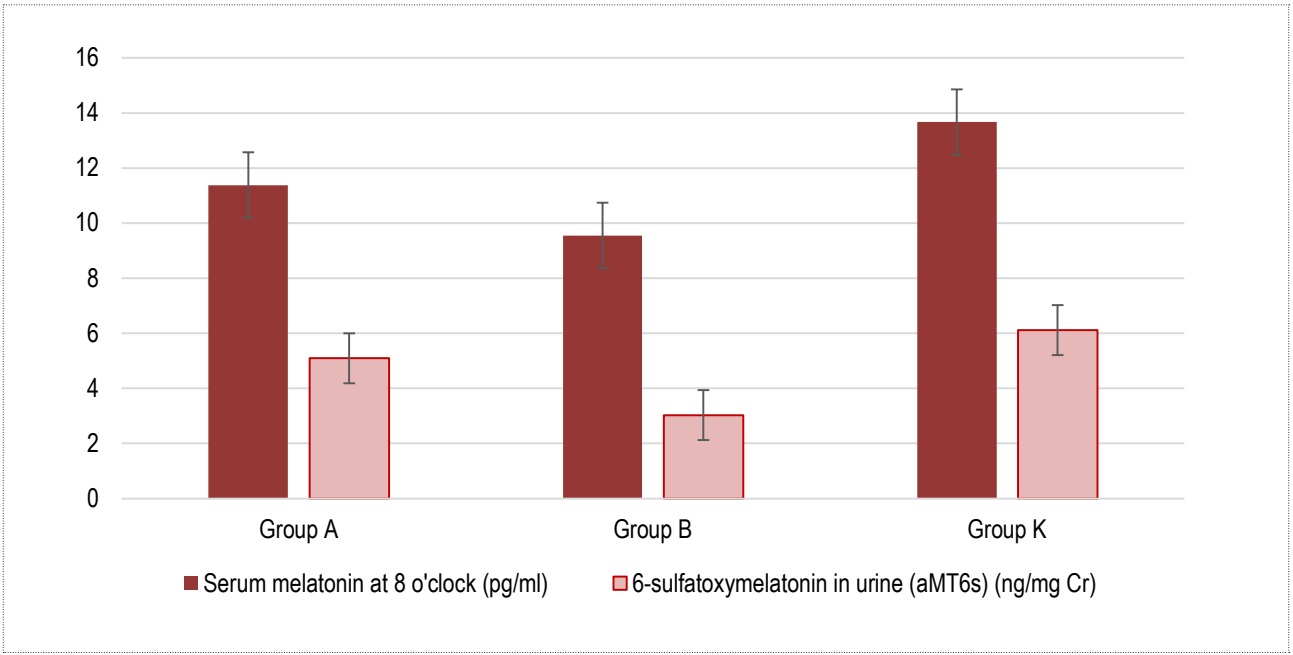

Figure 1. Indicators of MT metabolism in the studied groups

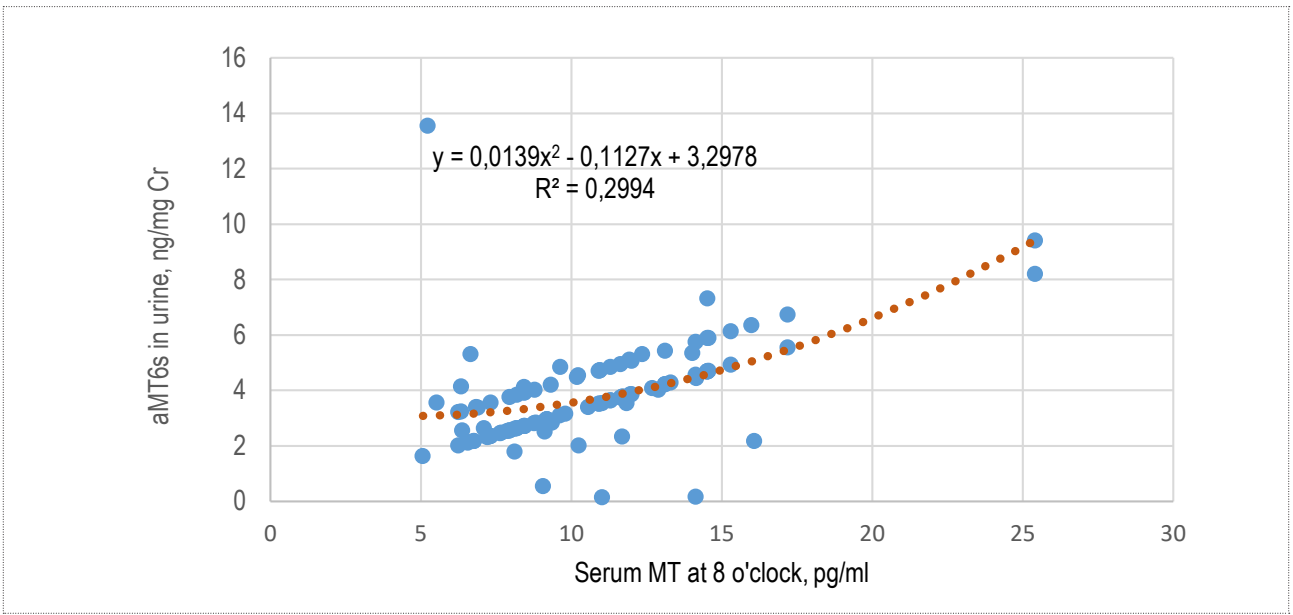

Figure 2. Correlation field, regression formula and coefficient of approximation of serum MT and urinary aMT6s levels in women with repeated implantation failures

expression of progesterone and progesterone receptor A on day 6 after fertilization, promoting endometrial luminal epithelium differentiation, stromal cell proliferation, and decidualization. On the other hand, MT reduces the secretion and activity of estradiol to avoid premature uterine contractions. Estradiol is likely produced and secreted by the blastocyst itself around day 4, allowing the acquisition of implantation competence necessary to initiate the implantation process [21].

Our study showed that women with RIF are characterized by disruption of the internal circadian biological clock, which is accompanied by a decrease in the level of MT in blood serum and its main metabolite aMT6s in urine. Of course, the local production of MT in the endometrium is extremely important for the protection of cells and tissues from oxidative damage; for this, mitochondria, as the main source of its synthesis, must retain their function. It is documented that MT, acting as a multifunctional agent, interacts with endometrial cells, has anti-apoptotic, antioxidant and anti-inflammatory effects. MT certainly sends these cells a signal to organize their physiological functions. Since implantation occurs periodically, MT signaling may be necessary for synchronizing daily molecular rhythms of cells, i.e. secretion of hormones and factors, control of proliferation and apoptosis, regulation of metabolic status and absorption of free radicals, differentiation and activation of immune cells, maintenance of vascular dynamics, etc. [8, 12, 25].

CONCLUSIONS

Women with RIF are characterized by a decrease in the level of MT in blood serum and its main metabolite 6-sulfatoxymelatonin in urine, which may be one of the key factors of implantation failure.

Conflict of interest

There is no conflict of interest.

ЛІТЕРАТУРА/REFERENCES

1. Ma J, Gao W, Li D.
Recurrent implantation failure: A comprehensive summary from etiology to treatment. Front Endocrinol (Lausanne). 2023 Jan 5:13:1061766. doi: 10.3389/fendo.2022.1061766
2. Kim S. M, Kim JS.
A Review of Mechanisms of Implantation. Dev Reprod. 2017 Dec;21(4):351–9. doi: 10.12717/DR.2017.21.4.351
3. Sun Y, Zhang Y, Ma X, et al.
Determining Diagnostic Criteria of Unexplained Recurrent Implantation Failure: A Retrospective Study of Two vs Three or More Implantation Failure. Front Endocrinol (Lausanne). 2021 Jul 22:12:619437. doi: 10.3389/fendo.2021.619437
4. Cimadomo D, Craciunas L, Vermeulen N, et al.
Definition, diagnostic and therapeutic options in recurrent implantation failure: an international survey of clinicians and embryologists. Hum Reprod. 2021 Jan 25;36(2):305–17. doi: 10.1093/humrep/deaa317
5. Thornhill AR, deDie-Smulders CE, Geraedts JP, et al.; ESHRE PGD Consortium.
ESHRE PGD Consortium 'Best practice guidelines for clinical preimplantation genetic diagnosis (PGD) and preimplantation genetic screening (PGS). Hum Reprod. 2005 Jan;20(1):35–48. doi: 10.1093/humrep/deh579
6. ESHRE Working Group on Recurrent Implantation Failure; Cimadomo D, de Los Santos MJ, Griesinger G, et al.
ESHRE good practice recommendations on recurrent implantation failure. Hum Reprod Open. Jun 15;2023(3):hoad023. doi: 10.1093/hropen/hoad023
7. Pantos K, Grigoriadis S, Maziotis E, et al.
The Role of Interleukins in Recurrent Implantation Failure: A Comprehensive Review of the Literature. Int J Mol Sci. 2022 Feb 16;23(4):2198. doi: 10.3390/ijms23042198
8. Chuffa LGA, Lupi LA, Cucielo MS, et al.
Melatonin Promotes Uterine and Placental Health: Potential Molecular Mechanisms. Int J Mol Sci. 2019 Dec 31;21(1):300. doi: 10.3390/ijms21010300
9. Hsing A. W, Meyer TE, Niwa S, et al.
Measuring serum melatonin in epidemiologic studies. Cancer Epidemiol Biomarkers Prev. 2010 Apr;19(4):932–7. doi: 10.1158/1055-9965.EPI-10-0004
10. Zou H, Chen B, Ding D, et al.
Melatonin promotes the development of immature oocytes from the COH cycle into healthy offspring by protecting mitochondrial function. J Pineal Res. 2020 Jan;68(1):e12621. doi: 10.1111/jpi.12621
11. Ma X, Wang J, Wang L, et al.
The Uterine Melatonergic Systems of AANAT and Melatonin Membrane Receptor 2 (MT2) Are Essential for Endometrial Receptivity and Early Implantation in Mice. Int J Mol Sci. 2023 Apr 12;24(8):7127. doi: 10.3390/ijms24087127
12. Reiter RJ, Sharma R, Rosales-Corral S, et al.
Melatonin and Pathological Cell Interactions: Mitochondrial Glucose Processing in Cancer Cells. Int J Mol Sci. 2021 Nov 19;22(22):12494. doi: 10.3390/ijms222212494
13. Olcese JM.
Melatonin and Female Reproduction: An Expanding Universe. Front Endocrinol (Lausanne). 2020 Mar 6:11:85. doi: 10.3389/fendo.2020.00085
14. Zhao D, Yu Y, Shen Y, et al.
Melatonin Synthesis and Function: Evolutionary History in Animals and Plants. Front Endocrinol (Lausanne). 2019 Apr 17:10:249. doi: 10.3389/fendo.2019.00249
15. Zhao D, Yao Z, Zhang J, et al.
Melatonin synthesis genes N-acetylserotonin methyltransferases evolved into caffeic acid O-methyltransferases and both assisted in plant terrestrialization. J Pineal Res. 2021 Oct;71(3):e12737. doi: 10.1111/jpi.12737
16. Cipolla-Neto J, Amaral FGD.
Melatonin as a Hormone: New Physiological and Clinical Insights. Endocr Rev. 2018 Dec 1;39(6):990–1028. doi: 10.1210/er.2018-00084
17. Jiang Y, Shi H, Liu Y, et al.
Applications of Melatonin in Female Reproduction in the Context of Oxidative Stress. Oxid Med Cell Longev. 2021 Jul 29:2021:6668365. doi: 10.1155/2021/6668365
18. Tamura H, Jozaki M, Tanabe M, et al.
Importance of Melatonin in Assisted Reproductive Technology and Ovarian Aging. Int J Mol Sci. 2020 Feb 8;21(3):1135. doi: 10.3390/ijms21031135
19. Pilehvari S, Yavangui M, Paknahad E, et al.
The Boosting Effects of Melatonin on the In Vitro Fertilization (IVF) of Women with Polycystic Ovary Syndrome. Chonnam Med J. 2023 Sep;59(3):188–93. doi: 10.4068/cmj.2023.59.3.188
20. Carlomagno G, Minini M, Tilotta M, Unfer V.
From Implantation to Birth: Insight into Molecular Melatonin Functions. Int J Mol Sci. 2018 Sep 17;19(9):2802. doi: 10.3390/ijms19092802
21. Russo M, Forte G, Oliva MM, et al.
Melatonin and Myo-Inositol: Supporting Reproduction from the Oocyte to Birth. Int J Mol Sci. 2021 Aug 5;22(16):8433. doi: 10.3390/ijms22168433
22. Man GCW, Zhang T, Chen X, et al.
The regulations and role of circadian clock and melatonin in uterine receptivity and pregnancy-An immunological perspective. Am J Reprod Immunol. 2017 Aug;78(2). doi: 10.1111/aji.12715
23. Jockers R, Delagrange P, Dubocovich ML, et al.
Update on melatonin receptors: IUPHAR Review 20. Br J Pharmacol. 2016 Sep;173(18):2702–25. doi: 10.1111/bph.13536
24. Amara, FGD, Cipolla-Neto J.
A brief review about melatonin, a pineal hormone. Arch Endocrinol Metab. 2018 Aug;62(4):472–9. doi: 10.20945/2359-3997000000066
25. Mosher AA, Tsoulis MW, Lim J, et al.
Melatonin activity and receptor expression in endometrial tissue and endometriosis. Hum Reprod. 2019 Jul 8;34(7):1215–24. doi: 10.1093/humrep/dez082
26. Sharkey J. T, Puttaramu R, Word RA, Olcese J.
Melatonin synergizes with oxytocin to enhance contractility of human myometrial smooth muscle cells. J Clin Endocrinol Metab. 2009 Feb;94(2):421–7. doi: 10.1210/jc.2008-1723
27. Olcese J, Beesley S.
Clinical significance of melatonin receptors in the human myometrium. Fertil Steril. 2014 Aug;102(2):329–35. doi: 10.1016/j.fertnstert.2014.06.020
28. Bejarano I, Monllor F, Marchena A. M, et al.
Exogenous melatonin supplementation prevents oxidative stress-evoked DNA damage in human spermatozoa. J Pineal Res. 2014 Oct;57(3):333–9. doi: 10.1111/jpi.12172
29. Zhang L, Zhang Z, Wang F, et al.
Effects of melatonin administration on embryo implantation and offspring growth in mice under different schedules of photoperiodic exposure. Reprod Biol Endocrinol. 2017 Oct 2;15(1):78. doi: 10.1186/s12958-017-0297-7
30. He C, Wang J, Li Y, et al.
Melatonin-related genes expressed in the mouse uterus during early gestation promote embryo implantation. J Pineal Res. 2015 Apr;58(3):300–9. doi: 10.1111/jpi.12216

ОБМІН МЕЛАТОНІНУ В БЕЗПЛІДНИХ ЖІНОК ІЗ ПОВТОРНИМИ НЕВДАЧАМИ ІМПЛАНТАЦІЇ

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Обґрунтування. Повторна невдача імплантації спостерігається приблизно в 10–15% жінок, які проходять лікування у циклах запліднення *in vitro* та ембріотрансферу (IVF-ET). Одним із важливих чинників при цьому є змінений морфофункціональний стан ендометрія та хронодеструкція в організмі жінки.

Мета дослідження: визначити особливості обміну мелатоніну (МТ) у безплідних жінок із повторними невдачами імплантації в циклах IVF-ET.

Матеріал та методи. Спостереження охоплювало 103 жінки репродуктивного віку з безпліддям та повторними невдачами імплантації, які проходили лікування у циклах IVF-ET. Залежно від настання вагітності у поточному циклі IVF-ET жінки були розділені на 2 групи: група А – 35 жінок з настанням вагітності, група Б – 68 пацієнток без настання вагітності. До групи контролю (група К) увійшли 32 здорових фертильних жінки. Визначався рівень МТ у сироватці крові та 6-сульфатоксимелатоніну (аМТ6s) у сечі.

Результати. Початковий рівнень МТ у пацієнток групи А (11,38 ± 0,38 пг/мл) і групи Б (9,55 ± 0,27 пг/мл) був нижчим за аналогічний показник в групі К (13,67 ± 0,65 пг/мл) відповідно у 1,20 ($p < 0,01$) і у 1,43 ($p < 0,01$) раза. Водночас рівень МТ у жінок групи А перевищував аналогічний у пацієнток групи Б у 1,19 раза ($p < 0,03$). Екскреція аМТ6s у сечі в групі А (5,09 ± 0,19 нг/мл Кр) і в групі Б (3,03 ± 0,09 нг/мл Кр) були нижчими за аналогічний показник у групі К (6,12 ± 0,21 нг/мл Кр) відповідно в 1,20 ($p < 0,01$) й у 2,02 ($p < 0,01$) раза. Концентрація аМТ6s у сечі у пацієнток групи А була більша за цей показник у групі Б в 1,68 раза ($p < 0,01$). Між рівнями сироваткового МТ та сечового аМТ6s було встановлено прямий зв'язок, який найбільш адекватно апроксимувався поліноміальною залежністю: $y = 0,0139x^2 - 0,1127x + 3,2978$, $R^2 = 0,2994$, $r = 0,51$, $p < 0,01$.

Висновки. Жінкам із повторними невдачами імплантації притаманне зниження рівня МТ у сироватці крові та його основного метаболіту аМТ6s в сечі, що може бути одним з ключових чинників імплантаційної недостатності.

Ключові слова: безпліддя, повторна невдача імплантації, ендометрій, мелатонін, 6-сульфатоксимелатонін.

MELATONIN EXCHANGE IN INFERTILE WOMEN WITH REPEATED IMPLANTATION FAILURES

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Background. Repeated implantation failure occurs in approximately 10–15% of women undergoing *in vitro* fertilization and embryo transfer (IVF-ET) cycles. One of the important factors is the changed morpho-functional state of the endometrium and chronodestruction in the woman's body.

Objective of the study: to determine the characteristics of melatonin (MT) metabolism in infertile women with repeated implantation failures in IVF-ET cycles.

Material and methods. 103 women of reproductive age with infertility and repeated implantation failures who were treated in IVF-ET cycles were observed. Depending on the onset of pregnancy in the current IVF-ET cycle, women were divided into 2 groups: group A – 35 women with the onset of pregnancy, group B – 68 patients without the onset of pregnancy. The control group (group C) included 32 healthy fertile women. The MT level in blood serum and 6-sulfatoxymelatonin (aMT6s) in urine was determined.

Results. The initial levels of MT in patients of group A (11.38 ± 0.38 pg/ml) and in group B (9.55 ± 0.27 pg/ml) were lower than in group C (13.67 ± 0.65 pg/ml) in 1.20 ($p < 0.01$) and 1.43 ($p < 0.01$) times, respectively. At the same time, the level of MT in women of group A was 1.19 times higher than in the group B ($p < 0.03$). Excretion of aMT6s in urine in group A (5.09 ± 0.19 ng/ml Cr) and in group B (3.03 ± 0.09 ng/ml Cr) were lower than in group C (6.12 ± 0.21 ng/ml Cr) respectively in 1.20 ($p < 0.01$) and 2.02 ($p < 0.01$) times. The aMT6s concentration in urine in patients of group A was 1.68 times higher than in group B ($p < 0.01$). A direct relationship was established between the levels of serum MT and urinary aMT6s, which was most adequately approximated by a polynomial dependence: $y = 0.0139x2 - 0.1127x + 3.2978$, $R^2 = 0.2994$, $r = 0.51$, $p < 0.01$.

Conclusions. Women with repeated implantation failures are characterized by a decrease in the level of MT in blood serum and its main metabolite aMT6s in urine, which may be one of the key factors of implantation failure.

Keywords: infertility, repeated implantation failure, endometrium, melatonin, 6-sulfatoxymelatonin.