

INTEGRATIVE SYSTEM FOR BIOINFORMATIC PREDICTION OF REPRODUCTIVE TOXICITY AND EMBRYOLOGICAL FAILURE IN COUPLES WITH RECIDIVISTIC ART DISRUPTIONS

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Abstract. To develop and clinically validate an integrated bioinformatic model based on gradient boosting decision trees for individual assessment of gamete/embryo quality and forecasting the morphological block during *in vitro* development in couples with recurrent implantation failure (RIF) under combined toxic-infectious exposure. A prospective comprehensive evaluation of 228 couples undergoing ICSI cycles was carried out. The cohort was stratified into Group I (RIF history, n=95), Group II (successful first/second IVF attempts, n=95), and Group III (healthy oocyte donors, n=38). Somatic and lifestyle variables were measured via HOMA-IR, the PSM-25 scale, and quantitative multiplex PCR-RT for latent HPV/HSV load. Embryological trajectories were assessed using continuous single-culture incubation systems and standard Gardner scoring. Couples facing persistent RIF exhibited compromised follicular response (6.4 ± 1.1 retrieval yield) paired with an increased rate of cellular oocyte degeneration (9.4%). The deployment of the bioinformatic tree algorithm demonstrated that subclinical insulin resistance combined with female tobacco exposure represented the highest information gain weights (0.34 and 0.28, respectively). The synchronous coexistence of regular smoking and latent viral presence synergistically aggravated morphological disruptions, resulting in a 43% collapse in high-tier blastulation rates (OR = 4.82; 95%CI: 2.34–9.12; $p < 0.001$). The non-linear convergence of modifiable toxic, metabolic, and infectious stressors generates severe microenvironmental free-radical damage within the growing follicle, interrupting spindle configuration and decreasing blastocyst usability. The bioinformatic assessment platform enables clinician shifts toward mandated cycle segmentation ("Freeze-all") and preimplantation aneuploidy testing (PGT-A) before executing failed embryo replacements.

Keywords: assisted reproductive technologies, recurrent implantation failure, oogenesis, oxidative stress, artificial intelligence, machine learning, gradient boosting.

Аннотация. Разработать и клинически валидировать интегративную биоинформационную модель на основе решающих деревьев градиентного бустинга для индивидуальной оценки качества гамет/эмбрионов и прогнозирования морфологического блока в процессе развития *in vitro* у супружеских пар с повторными неудачами имплантации (ПНИ) в условиях сочетанного токсико-инфекционного воздействия. Проведена проспективная комплексная оценка 228 супружеских пар, проходивших циклы ИКСИ. Когорта была стратифицирована на Группу I (ПНИ в анамнезе, n=95), Группу II (успешные первая/вторая попытки ЭКО, n=95) и Группу III (здоровые доноры ооцитов, n=38). Соматические переменные и переменные образа жизни оценивались с помощью НОМА-ИР, шкалы PSM-25 и количественной мультиплексной ПЦР-РВ на определение латентной нагрузки ВПЧ/ВПГ. Эмбриологические траектории оценивали с использованием систем непрерывного инкубирования в одиночной культуре и стандартной шкалы Гарднера. Пары, столкнувшиеся с персистирующими

ПНИ, продемонстрировали угнетенный фолликулярный ответ (выход $6,4 \pm 1,1$ полученных ооцитов) в сочетании с повышенной частотой клеточной дегенерации ооцитов (9,4%). Развертывание биоинформационного алгоритма деревьев показало, что субклиническая инсулинорезистентность в сочетании с воздействием табакокурения у женщин представляли собой наибольшие веса прироста информации (0,34 и 0,28 соответственно). Синхронное сосуществование регулярного курения и латентного присутствия вирусов синергетически усугубляло морфологические нарушения, приводя к 43%-ному коллапсу частоты формирования бластоцист высшего качества (OR = 4,82; 95% CI: 2,34–9,12; $p < 0,001$). Нелинейная конвергенция модифицируемых токсических, метаболических и инфекционных стрессоров вызывает выраженное свободнорадикальное повреждение микроокружения внутри созревающего фолликула, нарушая конфигурацию веретена деления и снижая пригодность бластоцист. Биоинформационная оценочная платформа позволяет клиницистам перейти к обязательной сегментации цикла («Freeze-all») и преимплантационному генетическому тестированию на анеуплоидии (ПГТ-А) перед проведением повторных переносов эмбрионов.

Ключевые слова: вспомогательные репродуктивные технологии, повторные неудачи имплантации, оогенез, оксидативный стресс, искусственный интеллект, машинное обучение, градиентный бустинг

Annotatsiya. Birgalikda toksik-infekcion ta'sir ostida bo'lgan, implantatsiyaning takroriy muvaffaqiyatsizligi (ITM) mavjud bo'lgan er-xotinlarda gameta/embrion sifatini individual baholash va *in vitro* rivojlanish davridagi morfologik blokni prognoz qilish uchun gradientli busting qaror daraxtlariga asoslangan integratsiyalashgan bioinformatik modelni ishlab chiqish va klinik jihatdan tasdiqlash. ICSI tsikllaridan o'tayotgan 228 ta er-xotinning prospektiv kompleks baholanishi amalga oshirildi. Kogorta I guruh (ITM anamnezi, $n=95$), II guruh (birinchi/ikkinchi muvaffaqiyatli EKO urinishlari, $n=95$) va III guruh (sog'lom oocit donorlari, $n=38$)ga stratifikatsiya qilindi (ajratildi). Somatik va turmush tarzi o'zgaruvchilari HOMA-IR, PSM-25 shkalasi va yashirin HPV/HSV yuki uchun miqdoriy multipleks PCR-RT orqali o'lchandi. Embrional traektoriyalar uzluksiz bir madaniyatli (single-culture) inkubatsiya tizimlari va standart Gardner shkalasi yordamida baholandi. Doimiy ITMga duch kelgan er-xotinlar hujayrali oocit degeneratsiyasining oshishi (9,4%) bilan birgalikda susaygan folikulyar javobni ($6,4 \pm 1,1$ olingan oocit miqdori) ko'rsatdilar. Bioinformatik daraxt algoritmining qo'llanilishi ayollardagi subklinik insulin rezistentligi va tamaki iste'moli birgalikda eng yuqori axborot o'sishi (information gain) vaznini (mos ravishda 0,34 va 0,28) taqdim etishini ko'rsatdi. Muntazam chekish va yashirin virus mavjudligining sinxron ravishda birga kelishi morfologik buzilishlarni sinergetik ravishda og'irlashtirdi, bu esa yuqori sifatli blastulizatsiya ko'rsatkichlarining 43% ga kollapsiga (pasayishiga) olib keldi (OR = 4,82; 95% CI: 2,34–9,12; $p < 0,001$). O'zgartirilishi mumkin bo'lgan toksik, metabolik va infeksiyon stressorlarning noxiziqli yaqinlashishi o'sayotgan folikula ichidagi mikromuhitda og'ir erkin radikalli shikastlanishni keltirib chiqaradi, bu bo'linish urchig'i (веретено деления) konfiguratsiyasini buzadi va blastocista yaroqliligini kamaytiradi. Bioinformatik baholash platformasi shifokorlarga muvaffaqiyatsiz embrion almashtirishlarini amalga oshirishdan oldin tsiklning majburiy segmentatsiyasi ("Freeze-all") va implantatsiya oldi анеуплоидија testi (PGT-A) tomon o'tish imkonini beradi.

Kalit so'zlar: yordamchi reaktiv texnologiyalar, implantatsiyaning takroriy muvaffaqiyatsizligi, oogenez, oksidativ stress, sun'iy intellekt, mashinali o'qitish, gradientli busting.

Introduction. The current stage of reproductive gynecology is characterized by a definitive plateau in the success rates of conventional *in vitro* fertilization (IVF) protocols. Despite the precise evolution of micromanipulation media and cultivation hardware, overcoming

recurrent implantation failure (RIF) remains a formidable and highly debated dilemma in modern medicine [3, 5]. The majority of contemporary studies traditionally focus on identifying localized uterine rejection factors, structural-functional defects of the endometrium, or chronological shifts in the "window of implantation" [6]. Concurrently, the molecular-biological architecture of early embryogenesis indicates that a significant proportion of nidation failures is predetermined by the latent suboptimal degradation of gamete quality, which originates under the pressure of combined exogenous and metabolic factors [9].

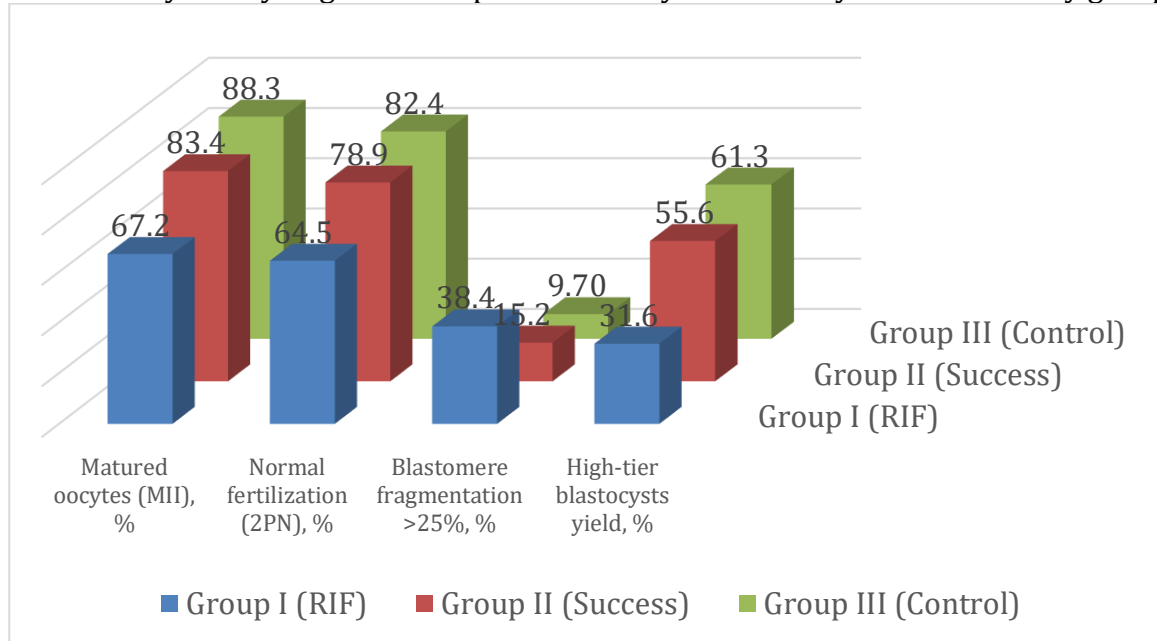
The maturing human oocyte represents a metabolically labile micro-biosystem, the proper functioning of which is strictly dependent on the homeostasis of the follicular fluid. The infiltration of exogenous xenobiotics, subclinical inflammatory pressure, and peripheral insulin resistance are capable of inducing a cascade of cellular oxidative stress, which severely damages the mitochondrial apparatus of the granulosa and triggers long-term epigenetic modifications of the embryonic genome [7]. This pathogenic situation is critically aggravated by the presence of latent viral associations (specifically HPV and HSV) within the reproductive tract of the couple [9]. Unveiling the hidden non-linear relationships between lifestyle triggers, metabolic shifts, and infectious loads requires a major departure from classic linear statistical tools toward the predictive capabilities of machine learning systems and deep neural networks [1, 2, 4, 8].

Materials and methods. A comprehensive clinical and embryological trial was successfully conducted between 2023 and 2026 at a specialized Center for Reproductive Medicine (Tashkent). The digitized dataset accumulated the heterogeneous parameters of 228 infertile couples, representing 228 induced ICSI cycles. The clinical cohort was stratified into three representative groups:

- Group I (n=95): The primary cohort consisting of women with a verified history of RIF (defined as ≥ 3 consecutive failed transfers of morphologically optimal blastocysts).
- Group II (n=95): The active comparative group including patients who successfully achieved a progressive clinical pregnancy during their first or second ART attempt.
- Group III (n=38): The control cohort of conditionally healthy fertile women participating in voluntary oocyte donation programs.

The mean chronological age of the female cohort was established at 33.8 ± 4.8 years. Metabolic configurations were verified by evaluating fasting glucose and insulin levels followed by the homeostatic model assessment of insulin resistance (HOMA-IR threshold 2.5). The chronic psycho-emotional background was quantified using the validated PSM-25 distress scale. The infectious and viral profiles of both partners were evaluated using quantitative multiplex real-time polymerase chain reaction (RT-PCR) to detect high-risk human papillomavirus (HPV) and herpes simplex virus (HSV-1, 2) DNA in cervical swabs and ejaculate samples. Controlled ovarian stimulation (COS) was fully standardized for all subjects using individual gonadotropin doses combined with GnRH antagonists. Embryo culture was performed in triple-gas COOK incubators (Ireland) utilizing continuous single-culture media (CSCM) without fluid replenishment. Morphological assessment of the emerging blastocysts on days 5–6 was carried out according to the strict international Gardner grading system. To break through the limitations of conventional linear statistics and to rank the exact significance of individual pathogenic risks, a bioinformatic machine learning model based on gradient boosting decision trees (XGBoost framework, 10,000 training epochs) was successfully deployed. Mathematical processing of the data was performed using STATISTICA and SPSS software, utilizing the Mann-Whitney U-test, Pearson's X^2 test, and ROC-AUC metrics.

Results and discussion. The comparative data analysis verified severe suboptimal parameters of folliculogenesis and early preimplantation development in the RIF cohort (Picture 1).

Picture 1. Key embryological descriptors of ICSI cycle efficiency across the study groups

The significant suppression of the mean retrieved oocyte pool to 6.4 ± 1.1 in

Group I highlights a suppressed follicular response, which is continuously triggered by a subclinical chronic pelvic infectious background. The biological quality of the oocytes was deeply compromised: the MII maturity rate dropped to 67.2%, while intraoperative cellular degeneration ascended to a critical 9.4%. The phenomenon of extensive blastomere fragmentation on day 3 (38.4%) caused a downstream mathematical collapse in the final yield of top-quality blastocysts to 31.6%, practically cutting the successful group's parameters in half. To delineate the structure of non-linear risks, the tree algorithm processed the multi-dimensional dataset and extracted the exact feature importance using the Information Gain metric:

1. Peripheral tissue insulin resistance (HOMA-IR 2.5): information gain weight (Gain) — 0.34.
2. Female tobacco exposure (active or passive): Gain — 0.28.
3. Chronic psychological distress (PSM-25 >135 points): Gain — 0.21.
4. Persistent couple viral load (HPV/HSV): Gain — 0.17.

The evaluation of combined risk features unraveled a prominent toxic-infectious synergism. Isolated regular smoking by the female partner decreased the probability of obtaining top-tier AA/AB blastocysts by 14%. However, when regular tobacco usage converged with the persistent viral load of the couple, the predicted blastulation efficiency plummeted by 43%. The calculated Odds Ratio for this synergistic feature interaction reached: The physiological architecture of this synergism lies in the high permeability of the blood-follicle barrier induced by free radicals and stress-driven cortisol levels. Circulating reactive oxygen

$$OR = 4.82 \quad (95\% \text{ CI} : 2.34 - 9.12), \quad p < 0.001$$

species (ROS) and pro-inflammatory cytokines freely enter the follicular fluid, draining the internal pools of endogenous antioxidants (glutathione, superoxide dismutase) and disabling the mitochondrial respiratory chain of the cumulus cells. The subsequent acute deficiency of ATP limits the spindle alignment of the master oocyte, triggering a cellular meiotic block (MII drop to 67.2%), aberrant pronuclear formation, and subsequent developmental fragmentation. Concurrently, metabolic insulin resistance (HOMA-IR 2.5) provokes granulosa cell apoptosis via

lipotoxicity, completely cutting off the gamete from its required trophic lines and causing advanced degeneration (9.4%). The bioinformatic model automatically tracks these variables to output the global Oocyte Quality Index (OQ_i). Crossing the critical threshold of 0.72 points serves as a clinical command to abort the empirical embryo transfer and switch to a mandatory cycle segmentation ("Freeze-all") pathway paired with comprehensive preimplantation genetic testing (PGT-A via NGS), preventing the futile transfer of aneuploid embryos.

Conclusion. Recurrent implantation failure is intrinsically coupled with a suboptimal environment for oogenesis and early embryonic cultivation, manifesting as a severe reduction in oocyte maturity (67.2% MII yield) and a twofold drop in top-quality blastulation rates (31.6%). Modifiable lifestyle stressors and a latent infectious profile act in precise synergy, multiplying local oxidative stress inside the follicular fluid and elevating embryological failure risks by 4.82 times ($p < 0.001$). The integration of bioinformatic tree models provides accurate forecasting of developmental blocks, validating the necessity of a target 2–3 month pre-conceptional protocol and automated cycle segmentation backed by PGT-A.

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