НАУЧНЫЕ ОБЗОРЫ / SCIENTIFIC REVIEWS

THE HUMAN ENDOMETRIUM AND EMBRYO DURING IMPLANTATION ADHESIVE ABILITY ENHANCING PERSPECTIVES

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Summary. Infertility is a global problem. According to the data of the World Health Organization, 17.5% of people, or one in six people worldwide, suffer from infertility as of 2023. Experts believe that by 2050, a critical decline in the birth rate will lead to a reduction in the number of children under 15 by 40% or more. In Russia, statistics reflect global trends. Therefore, the search for new, effective infertility treatments is a pressing issue in modern medicine. The objective of this review was to analyze and evaluate current data on the use of a hyaluronic acid-enriched medium during embryo transfer to increase implantation rates in infertility treatment cycles using assisted reproductive technologies. The sources of specialized literature used in this review were electronic libraries of scientific publications and medical databases such as Google Scholar, PubMed, and elibrary.ru. The review included relevant publications found through a search using the following keywords: "assisted reproductive technologies," "hyaluronic acid," "embryo," and "endometrium." The study found that the Russian Federation ranks first among European countries and fourth globally in the number of assisted reproductive technology cycles performed (140,931 cycles in 2020 and 158,893 in 2021). However, according to the Russian Association of Human Reproduction and the European Society of Human Reproduction and Embryology, the effectiveness of assisted reproductive technology programs is no more than 40%. Infertility treatment with assisted reproductive technology can be unsuccessful for a number of key factors, including the lack of effective embryo implantation in the endometrium. One of the leading causes of implantation failure of a competent embryo is the failure to form an adhesive matrix between the embryo and the endometrium. The coordinated differentiation of endometrial cells and their interaction with the embryo play a crucial role in this process. It is hypothesized that the use of hyaluronic acid-enriched culture media during embryo transfer may help address the problem of implantation failure in assisted reproductive technology programs. A systematic review of the literature on the use of hyaluronic acid-enriched culture media during embryo transfer to improve assisted reproductive technology outcomes was conducted. Possible mechanisms of action for this medium during assisted reproductive technology embryo transfer are described.

Keywords: ***assisted reproductive technology, implantation, human embryo, hyaluronic acid, endometrium***

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ПЕРСПЕКТИВЫ ПОВЫШЕНИЯ АДГЕЗИВНОЙ СПОСОБНОСТИ ЭНДОМЕТРИЯ И ЭМБРИОНА ЧЕЛОВЕКА ПРИ ИМПЛАНТАЦИИ

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Резюме. Бесплодие является проблемой глобального масштаба. По данным Всемирной организации здравоохранения за 2023 год бесплодием страдает 17,5 % людей, это каждый шестой человек в мире. По мнению ее экспертов к 2050 году критическое падение рождаемости приведет к сокращению количества детей до 15 лет на 40% и более. В России статистика отражает общемировые тенденции. В связи с чем поиск новых эффективных способов лечения бесплодия является актуальной задачей современной медицины. Цель обзора состояла в анализе и оценке текущих данных относительно использования среды, обогащенной гиалуроновой кислотой, при переносе эмбрионов для увеличения показателей имплантации в циклах лечения бесплодия методами вспомогательных репродуктивных технологий. Источниками специализированной литературы, использованными в данном обзоре, стали электронные библиотеки научных публикаций и медицинские базы данных, такие как Google Scholar, PubMed и Elibrary.ru. Обзор включал публикации, соответствующие тематике, найденные посредством поиска, по следующим ключевым словам - «вспомогательные репродуктивные технологии», «гиалуроновая кислота», «эмбрион», «эндометрий». В результате исследования выявлено, что Российская Федерация занимает 1 место среди европейских стран и 4 место в мире по количеству проведенных циклов вспомогательных репродуктивных технологий (140931 цикл за 2020 год, 158893 за 2021 год). Однако, по данными Российской ассоциации репродукции человека и Европейского общества репродукции человека и эмбриологии, эффективность программ вспомогательных репродуктивных технологий составляет не более 40%. Лечение бесплодия методами вспомогательных репродуктивных технологий может быть неудачным по ряду основных факторов, в том числе в связи с отсутствием эффективной имплантации эмбриона в эндометрий. Одна из ведущих причин неудачи имплантации компетентного эмбриона – отсутствие формирования адгезивного матрикса между эмбрионом и эндометрием. Решающую роль в этом процессе играют скоординированные во времени дифференцировка клеток эндометрия и взаимодействие с эмбрионом. Выдвинута гипотеза, что применение сред, обогащенных гиалуроновой кислотой, при переносе эмбрионов может помочь решить проблему неудачи имплантации в программах вспомогательных репродуктивных технологий. Проведен систематический анализ литературных данных о применении культуральной среды, обогащенной гиалуроновой кислотой, при переносе эмбрионов для улучшения исходов программ вспомогательных репродуктивных технологий. Описаны возможные механизмы ее действия при переносе эмбрионов в программах вспомогательных репродуктивных технологий.

Ключевые слова: ***вспомогательные репродуктивные технологии, имплантация, эмбрион человека, гиалуроновая кислота, эндометрий***

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Introduction. Global data indicates that the number of children born through assisted reproductive technologies (ART) has reached ten million [1]. Despite this achievement, the prevalence of infertility continues to rise globally. On average, approximately 10% of married couples experience infertility across different nations, and this percentage escalated to 17,5% by 2023 [2-3]. Contemporary advances in embryological laboratory techniques primarily focus on augmenting pregnancy frequencies and successful live birth deliveries. Current efforts in reproductive medicine center upon discovering novel methodologies to enhance ART efficacy. For conception to occur, a healthy embryo must encounter a receptive endometrium capable of supporting its integration. Among critical determinants governing contemporary ART achievements, embryo implantation within the endometrial lining stands out prominently [4].

The objective of this review is to critically appraise existing information regarding the employment of HA-enriched medium during embryo transfer to boost implantation probabilities in assisted reproductive technologies fertility treatments.

Materials and Methods. Emerging technological advancements aimed at addressing infertility issues in couples include the utilization of culture media supplemented with hyaluronic acid (HA) during embryo transfer into the uterine cavity. Multiple investigations scrutinize diverse elements affecting implantation, encompassing the environmental milieu encircling the embryo. To bolster ART outcomes, certain measures involve incorporating adhesive substances like HA into the transfer medium. Specialized foreign literature spanning from 1987 to 2022 was sourced from digital repositories and prominent medical databases, including Google Scholar, Science Direct, PubMed, and elibrary.ru. Studies directly pertinent to the subject matter were extracted using targeted keywords such as "assisted reproductive technologies," "hyaluronic acid," "embryo," and "endometrium."

Results and Discussion. Randomized controlled trials (RCTs) extensively investigate hyaluronic acid (HA), also referred to as hyaluronan or hyaluronate [5]. Hyaluronate represents a non-sulfated glycosaminoglycan polymer inherently present in various tissues and bodily fluids of mammals, notably within the reproductive systems. Ovarian steroidal hormones modulate its biosynthetic pathways via HAS enzymes (HAS1-3) and its degradation mechanisms through hyaluronidases (HYALs). Functionally, hyaluronan's versatility arises from its dual role serving structurally as a high-molecular-weight compound in tissues or acting dynamically as a signaling molecule in fragmented forms. Interaction with specific cell membrane receptors governs its activity [6].

Hyaluronate belongs to the family of glycosaminoglycans, macromolecules constituting the extracellular matrix in animal tissues. Other members include heparan sulfate, dermatan sulfate, keratan sulfate, and chondroitin sulfate. As the simplest glycosaminoglycan, HA exhibits distinctive characteristics it remains unsulfured, manifests as a linear polysaccharide composed of repeated units of d-glucuronic acid and N-acetylglucosamine, and synthesizes outside the Golgi apparatus on the plasma membrane [6].

Experimental studies employing animal models illustrate hyaluronan's pivotal role in reproduction. Specifically, it amplifies cumulus cell counts during ovulation and stimulates cervical maturation prior to parturition [7-8]. Progesterone administration in ovariectomized mice elevated uterine HA concentrations [9-10]. Additionally, ovarian steroids regulate HA synthase expression patterns, exerting distinct impacts on the generation of varying-sized HA molecules throughout the ovarian-menstrual cycle and gestational phases [11]. Moreover, growth factors (like epidermal growth factor and transforming growth factor-β) and cytokines (interleukin 1-β and interferon-gamma) alongside local mediators (prostaglandins) modulate HA expression profiles [11]. Cell surface receptors CD-44 and RHAMM mediate HA's actions via MAP kinase and Akt signaling cascades [12].

The bioactivity of HA fragments resulting from hyaluronate depolymerization underscores their significance. Binding to CD44 and RHAMM enhances cell proliferation through MAPK-mediated phosphorylation and mitotic stimulation [13]. Observa-

tions from experiments with bovine embryos exposed to HYAL2 revealed heightened MAPK1/MAPK3 levels, augmented blastocyst formation, and enhanced blastocyst quality, evident by increased cell numbers and trophoblastic expansion. Blockade of CD44 negated these benefits, highlighting the indispensable nature of small HA molecules in preimplantation embryogenesis [7].

As outlined by Girish et al., HA's physiological viscosity facilitates embryo retention and fosters cellular adhesion to matrices, thereby facilitating nutrient diffusion and intrauterine adaptation [14]. Hyaluronate participates actively in cellular homeostasis and tissue reconstruction processes [15]. Human endometrial transformation across the menstrual cycle involves profound alterations. Investigations by Salamonsen et al. utilized histochemistry to track hyaluronate accumulation patterns in the human endometrium, revealing peaks during the proliferative (days 5-10) and secretory (days 19-23) phases. During the proliferative phase, hyaluronate supports unrestrained cellular division, whereas its peak in the secretory phase correlates with implantation readiness [11]. Following menstruation, minimal residual hyaluronate persists in the stroma. Notably, vascular hyaluronate deposits remain consistent throughout the cycle, emphasizing its integral contribution to endometrial dynamics.

Studies by Carson et al. monitored mouse uterine glycoconjugate synthesis during peri-implantation periods using radiolabeled glucosamine [16]. Results indicated a dramatic five-to-six-fold surge in hyaluronate synthesis coinciding with typical embryo implantation timelines. Non-pregnant females exhibited negligible hyaluronate synthesis increments. Contrary to hyaluronate, other glycoconjugates displayed stable synthetic outputs during early gestation. Small oligosaccharides (<5000 Da) predominated, accounting for 85% of newly synthesized products, followed by larger glycoconjugates (~10,000 Da). Exclusively non-epithelial uterine cells accounted for the majority of hyaluronate output. Steroid hormone-induced decidual stimuli provoked marked elevations in hyaluronate synthesis, pinpointing stromal cells as key contributors. Culturing embryos on hyaluronate-coated surfaces facilitated robust embryonic adherence and extension [17].

Cumulus granulosa cells secrete hyaluronate, detectable in follicular, oviductal, and endometrial fluids. Both mice and humans exhibit peak hyaluronate concentrations and maximal CD44 receptor responsivity concurrently with implantation events [18]. CD44 expression characterizes both preimplantation embryos [19] and endometrial stromal tissues [20].

Through CD44 receptors, HA executes autocrine and paracrine regulatory activities. Implicated in cell proliferation, differentiation, migration, gene expression modulation, decidualization, and implantation enhancement, HA’s influence extends beyond embryo competence improvements. Findings from bovine studies demonstrate HA’s capacity to elevate trophectodermal cell numbers and overall blastocyst populations, thus fortifying embryonic developmental capabilities [21].

Investigations by Marei et al. confirmed HYAL2 messenger RNA detection exclusively in oviducts during the early luteal phase and later in embryos at morula and blastocyst stages (post-fertilization days 6 and 7). Introducing HYAL2 into embryo cultures on fertilization day 2 raised MAPK1/MAPK3 phosphorylation levels, promoted blastocyst progression, and multiplied embryonic cellularity. Anti-CD44 antibodies or MAPK inhibitors abrogated these advantages, implying HYAL2 dependence on intact CD44-MAPK signaling for optimal embryonic development [6]. Collectively, these insights justify exploring innovative culture media compositions mimicking native conditions to support morula and blastocyst-stage embryos prior to uterine introduction [22].

Additional reports affirm HA’s protective contributions toward thawed frozen embryos, subsequently linked to elevated implantation potentials [23-25]. Therefore, naturally occurring HA plays a crucial role in implantation, and its incorporation into transfer media augments implantation rates across species-specific experimental settings. Initial demonstrations of HA’s utility in culture media occurred in animal-based research, yielding promising outcomes. Subse-

quent clinical trials ensued, though producing inconsistent results [26].

Among pioneering studies evaluating HA-enriched culture media, the Danish cohort investigation commenced in 2006 [27]. Involving 815 participants receiving ART interventions, subjects were stratified based on embryo transfer medium type. Groups consisted of those utilizing EmbryoGlue® (test group, n=417) and those adhering to conventional, non-HA-enriched mediums (control group, n=398). Results highlighted notable increases in pregnancy rates among individuals with histories of failed ART attempts and recurrent miscarriages. Authors additionally cautioned against excessive reliance on multiple embryo transfers given HA's association with twinning risks.

A 2008 randomized trial conducted by Urman et al. reported heightened implantation and clinical pregnancy rates attributable to HA-containing media. Nevertheless, benefits appeared accentuated in older patients aged >35 years, those harboring suboptimal embryos, or possessing previous IVF failures. Analyzing 1,282 sequential fresh embryo transfer cycles (825 on day 3 and 457 on day 5), participants were randomly assigned to receive either HA-inclusive or standard transfer mediums [28]. Nakagawa et al.'s 2012 study validated this technique solely in cohorts prone to implantation deficiencies [28]. Participants (n=314) younger than 40 years experienced multiple past embryo transfer failures [29]. Cochrane Review analyses (2014) substantiated HA-enriched media's (0.5 mg/ml) favorable influence on implantation metrics and clinical pregnancy outcomes in human ART scenarios [30].

Yet, in contrast, Fancsovits et al. 2015 study failed to document any appreciable HA-related gains in implantation rates [31]. Enrolling 581 IVF cycles, equivalent clinical pregnancy rates (42.4% vs. 39.2%), implantation rates (23.3% vs. 23.2%), and live birth rates (31.0% vs. 29.2%) characterized the study and control arms. Birth weights differed significantly favoring the HA group (3,018±598 g vs. 2,724±698 g, p=0.001) [32-33]. Heymann et al.'s meta-analysis (2020) established HA-medium enrichment as tripling clinical pregnancy chances in women with adverse IVF predictions yet offering merely marginal (16%) improvements in better-prognosis patients [34]. Adeniyi et al.'s 2021 review explored varied hyaluronic acid concentrations in ART-associated transfer media. Comparing outcomes across 1,018 low-level and 1,175 high-level HA recipients, HA inclusion consistently enhanced implantation and live birth rates irrespective of embryo culture durations [35].

Russian investigators at the Kulakov National Medical Research Centre for Obstetrics, Gynecology, and Perinatology (2021) documented comparable clinical pregnancy and delivery rates irrespective of HA usage [36]. Nonetheless, trends suggested HA-positive influences on pregnancy courses derived from euploid embryo transfers, particularly advantageous for older women. Study enrolment comprised 309 married couples. Distinctively, preimplantation genetic testing for aneuploidy (PGT-A) enabled selection of chromosomally sound embryos. Average participant ages stood at 34 (women) and 38 (men). Selective singleton embryo transfers defined study protocols. Clinical pregnancy rates differed marginally between control (43.7%) and comparative (32.0%) groups.

Large-scale meta-analytical updates in June 2022 corroborated the salutary influence of HA-enriched media on implantation outcomes [37]. Of 357 reviewed studies, only 15 qualified for final analysis involving 4,686 female participants. Randomization validity hinged on predefined statistical algorithms. Outcomes focused on live births, pregnancy occurrences, and miscarriage incidences. Transfers encompassed embryos at developmental stages ranging from days 2-6, embracing both freshly harvested and cryopreserved specimens. Analysis parameters homogenized differing HA concentrations (functional: 0.5 mg/mL; low: 0.125 mg/mL; absent: 0.0 mg/mL) across brands. Functional HA concentrations yielded superior results. Live birth rates climbed from 32% to 39% in autologous oocyte cycles. Correspondingly, clinical pregnancy and multiple pregnancy rates ascended by 5% and 8%, respectively. Donor oocyte cycles remained unaffected by HA additions. Emergent data reinforced HA's pivotal role in rectifying impaired implantation propensities, especially prevalent in suboptimal IVF candidates [33, 38].

Collectively, available evidence affirms HA's utility in improving ART success, especially for autologous oocyte users. Enhanced embryo-endometrial adhesion, optimized cellular signaling, migratory efficiency, gene expression modulation, and decidualization processes collectively contribute to HA's therapeutic potency. Concurrent reductions in miscarriage risks provide additional incentives for HA adoption. Economic considerations underscore HA's affordability, balancing modest incremental ART costs against substantial societal returns from achieving live term births [39-41].

Conclusion. The findings from extensive randomized trials and meta-analyses suggest that hyaluronic acid (HA) can enhance the efficacy of assisted reproduction technologies (ART) programs utilizing one's own eggs. Incorporating it into the transfer medium may augment the probability of successful live births, boost clinical pregnancy rates through improved embryo adherence to the endometrium, modulating cellular signaling pathways, promoting cell migration, altering gene expression patterns, and facilitating decidualization processes. Additionally, data have emerged suggesting that supplementing the transfer medium with HA might lower the risk of miscarriages. Moreover, when employing autologous oocytes and transferring only one embryo per cycle, optimal outcomes including higher clinical pregnancy and live-birth rates are noted among older women with complicated reproductive histories. Using a hyaluronate-enriched medium diminishes the necessity for multi-embryo transfers, thereby reducing the risks linked to multiple gestations and related complications. Given the increasing reliance on ART procedures worldwide, there is an urgent requirement to explore methods for improving their effectiveness. Notably, enriching the transfer medium with straightforward substances like HA offers both enhanced pregnancy and live-birth rates while remaining cost-effective. Although incorporating these specialized media marginally raises the expense of ART treatments, the long-term benefits-namely, delivering healthy term babies-ultimately justify the additional expenditure based on actuarial evaluations. Consequently, ongoing research underscores the importance of refining techniques aimed at optimizing embryo implantation within the uterus. Standardizing protocols for utilizing HA-enriched media becomes essential. Equally critical is continuing efforts to define specific indications and targeted patient populations who would most benefit from this intervention within ART settings designed to address infertility challenges.

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