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Is spermatozoa epigenome a diagnostic tool for assessing male infertility?

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ABSTRACT

Relevance: The sperm epigenome is essential in ensuring sperm quality, including maintaining chromatin integrity. However, despite its importance, a clear link between successful embryo development and clinical outcomes has not been established.
The study aimed to assess the influence of sperm epigenetics on the quality and development of the embryo and identify the molecular mechanisms involved in this process.
Materials and Methods: A search in the PubMed database and the World Health Organization documents for 2012-2023 was conducted using the following keywords: assisted reproductive technologies, in vitro fertilization, male infertility, sperm, spermatozoa, epigenome, and intracytoplasmic sperm injection.
Results: The analysis of current publications revealed that the relationship between the sperm epigenome and embryo development remains the subject of active research. The degree of influence of the sperm epigenome on the fertilization process, early embryo development, and the outcome of the IVF program continues to cause debate.
Conclusion: The study of epigenetic changes in spermatozoa of men who have infertility opens new horizons for understanding the mechanisms affecting fertility and embryo quality. Understanding the epigenetic processes affecting spermatogenesis and embryogenesis may contribute to improving the results of ART and may also offer new approaches to the treatment of male infertility. Future research in this area may provide new insights into the mechanisms underlying male infertility.

Keywords: *assisted reproductive technologies (ART), in vitro fertilization (IVF), male infertility, sperm, spermatozoa, epigenome, intracytoplasmic sperm injection (ICSI).*

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Является ли эпигеном сперматозоидов диагностическим инструментом оценки мужского бесплодия?

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АННОТАЦИЯ

Актуальность: Эпигеном сперматозоидов играет важную роль в обеспечении их качества, включая сохранение целостности хроматина. Тем не менее, несмотря на его значимость, не установлена четкая связь между успешным развитием эмбриона и клиническими результатами.

Цель исследования – оценка влияния эпигенетики сперматозоидов на качество и развитие эмбриона, а также выявление молекулярных механизмов, участвующих в этом процессе.
Материалы и методы: Поиск информации был проведен в базе данных Pubmed и документах Всемирной организации здравоохранения за период с 2012 по 2023 годы. Использовались следующие ключевые слова: вспомогательные репродуктивные технологии, экстракорпоральное оплодотворение, мужское бесплодие, сперма, сперматозоиды, эпигеном, интрацитоплазматическая инъекция сперматозоида.
Результаты: На основе анализа актуальной литературы установлено, что связь между эпигеномом сперматозоидов и развитием эмбриона остается предметом активных исследований. Вопрос о степени влияния эпигенома сперматозоидов на процесс оплодотворения, раннее развитие эмбриона и исход программы ЭКО продолжает вызывать дискуссии.
Заключение: Исследование эпигенетических изменений в сперматозоидах мужчин, страдающих от бесплодия, открывает новые горизонты для понимания механизмов, влияющих на фертильность и качество эмбрионов. Осознание эпигенетических процессов, затрагивающих сперматогенез и эмбриогенез, может способствовать улучшению результатов применения ВРТ, а также предложить новые подходы к терапии мужского бесплодия. Будущие исследования в этой области могут предоставить новые знания о механизмах, стоящих за мужским бесплодием.

Ключевые слова: *вспомогательные репродуктивные технологии (ВРТ), экстракорпоральное оплодотворение (ЭКО), мужское бесплодие, сперма, сперматозоиды, эпигеном, интрацитоплазматическая инъекция сперматозоида (ИКСИ).*

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Сперматозоид эпигеномы ер бедеулігін бағалаудың диагностикалық құралы болып табылады ма?

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АҢДАТПА

Өзектілік: Сперматазоид эпигеномы шәует сапасында, соның ішінде хроматиннің тұтастығын сақтауда маңызды рөл атқарады. Дегенмен, оның маңыздылығына қарамастан, эмбрионның сәтті дамуы мен клиникалық нәтижелер арасындағы нақты байланыс орнатылмаған.
Зерттеудің мақсаты – Қазіргі заманғы әдебиеттердің қолда бар мәліметтерін қолданып, сперматазоид эпигеномының эмбрионның сапасы мен дамуына әсерін бағалау, сонымен қатар осы процеске қатысатын молекулалық механизмдерді анықтау.
Материалдар мен әдістері: PubMed деректер базасында және Дүниежүзілік денсаулық сақтау ұйымының 2012-2023 жылдарға арналған құжаттарында іздеу келесі кілт сөздерді пайдалана отырып жүргізілді: көмекші репродуктивті технологиялар, in vitro ұрықтандыру, ер бедеулігі, сперматозоидтар, сперматозоидтар, эпигеном және интрацитоплазмалық шәует инъекциясы.
Нәтижелері: Заманауи әдебиеттерді талдау негізінде сперматозоид эпигеномы мен эмбрион дамуы арасындағы байланыс белсенді зерттеу нысаны болып қала беретіні анықталды. Шәует эпигеномының ұрықтандыру процесіне, эмбрионның ерте дамуына және ЭКО бағдарламасының нәтижесіне әсер ету дәрежесі туралы мәселе әлі де пікірталас тудыруда.
Қорытынды: Сперматозоидтың эпигенетикалық өзгерістерді зерттеу бедеуліктен зардап шегетін ерлердің фертильділікке және эмбрион сапасына әсер ететін механизмдерді түсіну үшін жаңа көкжиектерді ашады. Сперматогенезге және эмбриогенезге әсер ететін эпигенетикалық процестерді түсіну ҚРТ нәтижелерін жақсартуға көмектеседі, сондай-ақ ер бедеулігін емдеудің жаңа тәсілдерін ұсынады. Бұл саладағы болашақ зерттеулер ер бедеулігінің механизмдері туралы жаңа білім бере алады.

Түйінді сөздер: *көмекші репродуктивті технологиялар (КРТ), экстракорпоралдық ұрықтандыру (ЭКҰ), ер бедеулігі, шәует, сперматозоидтар, эпигеном, интрацитоплазмалық сперматозоид инъекциясы (ИКСИ).*

Introduction: According to the definition made by the World Health Organization (WHO), infertility is a disease of the male or female reproductive system defined as the inability to achieve pregnancy after regular unprotected sexual intercourse for 12 months or more [1].

Infertility continues to be one of the key problems in modern medicine and society in recent decades. It is due to an increase in infertility cases, which in turn results in a decrease in the birth rate and, as a result, in a decrease in the population. Infertility affects millions of people of childbearing age on all continents. According to the data from the WHO, 48 million couples and 186 million people suffer from it [2].

The infertility incidence is growing in Kazakhstan, as in many countries of the world. In 2021, the number of Kazakhstanis registered due to lack of pregnancy increased by 21.8%, reaching 21.4 thousand married couples. Of these, 7.9 thousand patients are the so-called primary patients who came to medical institutions in connection with fertility problems for the first time. 19.9 thousand women who could not get pregnant due to health problems were registered in the country's medical institutions at the end of 2021 (plus 22.8% by 2020). More than 1500 thousand couples failed to become parents due to infertility in men (plus 10.4% compared to 2020) [3].

The study aimed to assess the influence of sperm epigenetics on the quality and development of the embryo and identify the molecular mechanisms involved in this process.

Materials and Methods: A search in the PubMed database and the World Health Organization documents for 2012-2023 was conducted using the following keywords: assisted reproductive technologies, in vitro fertilization, male infertility, sperm, spermatozoa, epigenome, and intracytoplasmic sperm injection.

Results: The analysis of current publications revealed that the relationship between the sperm epigenome and embryo development remains the subject of active research. The degree of influence of the sperm epigenome on the fertilization process, early embryo development, and the outcome of the IVF program continues to cause debate.

Female infertility is a multifaceted problem caused by many factors, including such anatomical disorders as fallopian tube obstruction, polycystic ovary syndrome, and menstrual irregularities. Such hormonal and endocrine diseases as endometriosis and chronic endometritis also play an important role. Besides, genetic factors, such as mutations in the ZP1 gene, can cause defects in oocyte maturation. Understanding these causes is key to successful diagnostics and effective treatment of infertility.

The epigenome of oocytes plays an important role in embryonic development, influencing various processes, from fertilization to early embryogenesis. Studies show that mitochondrial functions, epigenetic modifications, and environmental factors significantly affect this developmental trajectory. Mitochondrial ATP synthesis in oocytes is critical for correct epigenetic programming. Studies on cattle found that a decrease in ATP levels leads to a decrease in DNA methylation and a change in histone modifications, adversely affecting the embryo-splitting rate [4]. Impaired mitochondrial function in oocytes also negatively impacts DNA methylation and embryonic development [5].

Male infertility is registered in 7% of the male population, or 30 men over 18 years of age worldwide, and it is almost half of all infertility cases [5]. The cause of male infertility is associated with abnormal spermogram parameters [6-8]. Numerous studies report declining sperm quality over the past 60 years [9-12]. Poor sperm quality is due to the deterioration of male reproductive health and the associated testicular agenesis syndrome, including testicular cancer, impaired spermatogenesis, cryptorchidism, and hypospadias, which ultimately increases the need for modern treatments, primarily ART [13].

According to some researchers, the etiology of male infertility is complex and includes many potential causes, including anatomical defects, genetic disorders, endocrine imbalance, and immune system disorders [12, 14, 15]. The cause of almost half of cases of male infertility remains unknown [9]. Besides, many social and demographic factors, such as late childbearing and lifestyle, can affect men's reproductive health and be passed on to future generations [9, 12, 16, 17].

At least 2,000 genes are known to be associated with spermatogenesis, and they can be influenced by various factors such as lifestyle (such as tobacco, drugs, stress, diet, obesity) and environmental factors (such as toxic exposure, endocrine disruption, and aging) [18]. Several studies noted the effect of environmental factors on male fertility, especially the epigenome.

Toxins, environmental pollutants, solvents, plastics, oxidative reactions, and drugs alter the methylation profile. Sperm cells constantly receive signals from the environment that can cause changes in gene expression without affecting the DNA sequence. Currently, up to 50% of cases of male infertility remain unexplained. The reason for this remains unclear, and the identification of new genetic factors associated with idiopathic infertility is a serious problem in the field of genetics [19].

Routine semen analysis includes assessment of sperm volume, pH, concentration, motility, and morphology. A modern method of treating male infertility with impaired spermogram parameters is ICSI, conducted after the selection of spermatozoa with mobile and normal morphology. During ICSI, it is important to select morphologically normal sperm to improve implantation and pregnancy rates, as well as reduce the rate of miscarriage [20, 21]. Modern sperm selection methods, such as physiological intracytoplasmic sperm injection (PICSI) and intracytoplasmic morphologic sperm injection (IMSI), have been developed to select the best sperm quality to enhance the ART program's efficacy. The use of PICSI reduces the miscarriage rate but does not have a significant effect on the live birth rate [22]. The IMSI procedure for patients with two unsuccessful previous IVF programs did not show a significant improvement in outcomes compared to traditional ICSI, proving that sperm collection methods may not cope with this problem in full [23]. New methods for the preparation of sperm for the fertilization procedure - microfluidic technologies - have great potential, but additional validation is required to confirm their efficiency in clinical practice [24]. Changes in the sperm genome, chromatin structure, DNA fragmentation, and epigenetic profiles (e.g., DNA methylation and histone patterns) play an important role in normal embryonic development and healthy live births [25]. Therefore, it is extremely important to pay attention to sperm DNA fragmentation and chromatin quality, as these aspects significantly affect the efficiency of the IVF program [26, 27].

The sperm epigenome has unique and highly specialized properties due to its nature and function and the diverse requirements for successful fertilization. In order to ensure motility, sperm chromatin must be tightly packed and organized. Chromatin is compactly packed in the sperm head by replacing most histones with protamines during spermatogenesis. It protects DNA from unfavorable conditions in a woman's reproductive tract. The remaining histones can undergo chemical modifications to their protein tails, activating and inhibiting gene transcription. Epigenetic changes in sperm cells are key to regulating the activity of genes associated with the development of an organism, making them analogous to embryonic stem cells. The combination of activating and suppressing marks in the promoter regions of genes and the hypomethylation of DNA allows these cells to be in a state of "readiness" to activate important genes required for embryogenesis. Abnormalities in the epigenetic structure of spermatozoa can lead to various diseases, such as

male infertility and abnormalities in embryonic development [28].

Based on these data, we can agree that the epigenome plays an important role in the fertilization process and the early development of the embryo, leading to the successful outcome of the IVF program. However, the opinions of the authors on this issue are divided: some argue that there is no correlation between the epigenetics of male sperm and the efficiency of IVF programs, while others argue the opposite [28-31].

Some studies suggest no consistent or clear correlation between the sperm epigenome and embryonic quality. For example, although different patterns of sperm DNA methylation and other epigenetic markers have been found, their prognostic significance for embryonic development remains unclear. For example, Jenkins and Carrell reviewed the impact of paternal epigenetics on embryogenesis but noted that there was no convincing evidence to support a direct link between epigenetic changes in sperm and adverse embryonic outcomes in vitro fertilization [29].

However, according to M.M. Denomme et al., the epigenetic profile of sperm can have an impact on the quality of embryos. Men with high embryo quality had a mostly hypermethylated profile of CpG sites, while men with low embryo quality had significant abnormalities in methylation. These changes concerned genes associated with sperm-oocyte fusion, embryonic genome activation and implantation, and miRNA profiles that affected embryonic development [28].

On the other hand, according to F. Giacone et al., standard morphological parameters of sperm are not always a reliable indicator of successful fertilization, and it indicates that epigenetic factors may not be universal [32].

M. Hua et al. found differences in tsRNA, rsRNA, and miRNA expression in 87 men with normozoospermia who underwent the IVF procedure. Participants were divided into groups based on the incidence of good-quality embryos. As a result, 10 differentially expressed tsRNAs, 7 rsRNAs, and 5 miRNAs were found, and made it possible to classify sperm samples with high predictive accuracy (AUC 0.87–0.7), emphasizing their importance in predicting embryo quality [33].

N. Garrido et al. note the effect of epigenetic changes in sperm on reproduction, but their direct impact on embryonic quality remains unclear [34].

According to K.I. Aston et al., the epigenetic patterns of sperm DNA methylation in men are stable and may differ in patients with different fertility as well as those undergoing the IVF procedure. The study found more than 8500 CpG sites with different levels of methylation associated with embryogenesis outcomes and the likelihood of a successful pregnancy. It makes sperm methylation a potential biomarker for predicting IVF success [35].

N.G. Cassuto and colleagues also found an association between spermatozoid head morphology and DNA methylation levels. Sperm samples with different morphologies showed differential DNA methylation and changes in gene expression in men undergoing ICSI. Analysis of the expression of 10 genes related to spermatogenesis (such as HDAC4, AURKA, and CFAP46) showed that their levels were higher in samples with normal morphology, indicating their potential role as biomarkers of sperm morphology and possible therapeutic targets [36, 37].

Discussion: The analysis of modern literature highlighted the influence of the sperm epigenome on the quality of spermatozoa, including chromatin integrity. However, there is no convincing correlation between successful embryonic development and clinical outcomes. The link between the sperm epigenome and embryonic development remains an open topic, and further research is required to fully understand the molecular mechanisms involved. The debate about the extent to which the sperm epigenome influences fertilization and early embryonic development is ongoing, with most researchers acknowledging it.

The study of epigenetic changes in the spermatozoa of men with infertility opens up new perspectives for understanding the mechanisms that affect fertility and embryo quality. Understanding the epigenetic mechanisms affecting spermatogenesis and embryogenesis can not only improve the results of ART (IVF, ICSI) but also offer new therapeutic strategies for the treatment of male infertility. Further research in this area may provide new knowledge about the mechanisms of male infertility.

Conclusion: The study of epigenetic changes in the spermatozoa of men suffering from infertility opens up new horizons for understanding the mechanisms affecting fertility and embryo quality. Understanding the epigenetic processes affecting spermatogenesis and embryogenesis can contribute to the improvement of ART results and offer new approaches to the therapy of male infertility. Future research in this area may provide new insights into the mechanisms behind male infertility.

The Republic of Kazakhstan has accumulated considerable experience in improving the population's reproductive health. However, a comprehensive analysis of modern factors affecting public fertile health, especially male health, is required, considering the rapidly changing social and economic conditions. In this regard, the development of new strategies for assessment, monitoring, and implementation of comprehensive measures aimed to strengthen the reproductive health of infertile couples, in particular men's health, as well as raising awareness of the importance of preventing infertility.

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