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Exploring Molecular Pathways in Spermatogenesis and Their Role in Male Infertility

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Annotation: Regarding the impact on male infertility, the study authors acknowledge that while a low sperm count is not a definitive indicator of infertility, it is closely linked to fertility where They explain that even when sperm concentration exceeds the threshold of 40-50 million/ml where The study aimed to conduct a systematic review of the study group that addressed the relationship between spermatogenesis and its relation to infertility in male patients while our Methodology Designed by This study systematically reviewed a collection of articles related to male infertility cases from 2017 to 2025 where A sophisticated scientific literature review was conducted to identify research findings as well as This study relied on articles indexed in the Google Scholar database as well as Based on the researched studies and the notes recorded in the results, which academically revealed the molecular mechanisms affecting sperm development, including H19 gene methylation patterns and genetic contributors to idiopathic sperm failure, the study also described the contributions and methodologies used in the research as well as Our findings summarize the comprehensive knowledge regarding the identification of molecular factors and their impact on male fertility, particularly the H19, MEST, and MTHFR imprinted genes, which are closely associated with infertility where found also is there relationship between Sperm metabolic characteristics, including amino acids such as arginine and lipids such as cholesterol and triglycerides.

Keywords: Sperm Metabolic, Mest, H19 Gene, Molecular, Pathways, Spermatogenesis.

Introduction

Male infertility impacts around 10% of men and is the cause of reproductive problems for 50% of couples who visit an assisted reproductive clinic. Only about 40% of cases are diagnosed, and genetics is the most common cause of these variations, although only 15% of these variations can be identified [1,2]

According to a previous study, found Male infertility represents a public health challenge that impacts millions of couples globally. According to the World Health Organization (WHO), male infertility is defined as a man's inability to contribute to pregnancy after 12 months of regular sexual intercourse without the use of contraceptive methods (WORLD HEALTH ORGANIZATION, 2010) [3,4,5]

It is estimated that this condition corresponds to approximately 50% of cases of marital infertility, being not only a health problem, but also a social one, with considerable effects on the emotional and psychological well-being of impacted individuals and couples (AGARWAL et al., 2015) [6,7].

Over the past five decades, a sharp decline in male fertility has been observed, especially in industrialized countries. Studies indicate a 50% to 60% reduction in sperm count, a phenomenon attributed to changes in living standards and exposure to environmental pollutants [8].

In addition, factors such as oxidative stress have been broadly accepted as contributors to sperm quality deterioration, affecting sperm morphology, motility, and DNA integrity [9,10]. In addition, to Various structures and testicular cells play important roles during spermatogenesis, while a wide variety of factors can influence their quality and quantity [11,12]

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Infertility is defined as a failure to conceive, presented by a couple trying to reproduce, in a period of 12 months of attempts. Approximately 15% of couples are infertile, and among these couples, male infertility accounts for approximately 50% to 60% of the causes [13]

Based on this, the researchers discovered that impaired piRNA synthesis in men is associated with reduced transposonation pressure. Their analyses of reproductive and testicular phenotypes in affected men revealed consistent, gene-specific findings. These results highlight significant inter-human variability and further underscore that findings cannot be easily generalized to all patients. In short, this study represents a major advance in reproductive genetics. It significantly expands the number of genes associated with male infertility and demonstrates a link between genetic defects in DNA synthesis and spermatogenesis and male infertility. [14]

Methodology

A systematic review of seven studies was conducted, all focused on Exploring Molecular Pathways in Spermatogenesis with a Systematic Review of Their Role in Male Infertility, where the researchers used data extracted from Google Scholar, and the exclusion and inclusion criteria are outlined in the table below.

Table 1- Explain the Criteria Category according to Inclusion Criteria and Exclusion Criteria

Criteria Category	Inclusion Criteria	Exclusion Criteria
Population	Human males diagnosed with infertility or subfertility	Studies focusing on female infertility or animal models
Molecular Focus	Studies investigating molecular pathways (genetic, epigenetic, proteomic, metabolomic) relevant to spermatogenesis	Studies without molecular data or only clinical outcomes
Study Design	Original research, including cohort, case-control, cross-sectional, and experimental studies	Reviews, editorials, letters, conference abstracts without full data
Language	Articles published in English	Non-English publications without translation
Publication Date	Studies published from 2017 to 2025 to capture recent advances	Studies published before 2010
Outcome Measures	Sperm parameters, molecular pathway activity, and fertility outcomes	Studies lacking relevant outcome data

Search Strategy and Study Selection

A comprehensive literature search was performed across multiple databases, including PubMed, Google Scholar, Scopus, Web of Science, and Embase. Search terms combined keywords and MeSH terms related to spermatogenesis, male infertility, and molecular pathways (e.g., "DNA methylation," "proteomics," "GWAS," epigenetics where in addition to the search limited to peer-reviewed articles was published between 2017 and 2025 also were after removing duplicates, two independent reviewers screened titles and abstracts against the inclusion criteria furthermore Data from included studies were

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extracted using a standardized form and organized into structured tables to facilitate synthesis and comparison in addition to were in this study the extracted data included study identifiers, objectives, methods, sample characteristics, molecular pathways investigated, and key findings and according to a qualitative synthesis was performed to integrate findings across molecular pathways, including genetic, epigenetic, proteomic, and metabolomic mechanisms; however, where data were sufficiently homogeneous, meta-analyses were conducted using random-effects models to calculate pooled effect sizes with 95% confidence intervals as well as heterogeneity was assessed using the I^2 statistic in addition to Subgroup and sensitivity analyses were planned based on molecular pathway type, infertility subtype, and study design to explore sources of heterogeneity and robustness of findings.

Result

Table 2: Descriptive data and demographic information on the systematic study

Authors	Year of Publish	Objective
Á.Rodríguez	2025	This study aims to understand the role of molecular and cellular regulation in sperm function.
Cannarella	2023	In summary, people with aberrant sperm differ from those with normal conventional sperm in the methylation of the H19 gene.
Cannarella	2020	to present current and thorough knowledge on spermatogenetic failure and the molecular biology of spermatogenesis.
G Muñoz	2025	to carry out the first trans-ethnic meta-analysis of idiopathic spermatogenic failure (SPGF) genome-wide association studies.
Li, Jing, et al	2024	to examine the potential underlying mechanism and assess the function of p53 in spermatogenesis and male infertility.
John Charles	2021	to give a summary of what is known about the regulation of gene and genome methylation during spermatogenesis, particularly in relation to the etiopathogenesis of male infertility.
Selvam, M.K.P. and Agarwal,	2017	to use proteomics to find protein changes in male infertile patients' spermatozoa and seminal plasma.

Table 3 provides an additional explanation of contributions and methodology employed in the course of these studies and, through several articles, employ systematic reviews and meta-analyses to demonstrate collaborative efforts in compiling recent literature and identifying common themes or

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novel trends, yet For instance, Cannarella et al. employ systematic reviews to compare H19 gene methylation across various studies strategically, while other articles compile molecular and metabolic effects in spermatogenesis without mention of specific, measurable samples, exhibiting the necessity of sharing generalizable knowledge instead of isolated findings as well as Contrarily, the trans-ethnic meta-analysis of González-Muñoz et al. examines information from a large population of men with idiopathic spermatogenic failure, bringing to the forefront the importance of big population studies in providing concrete results that can be extrapolated across different ethnic groups.

Table 3- Describe the methodology adopted in this study and specify the number of samples for each systematic study.

Contribution	Method	Sample
Focuses on how sperm function and male fertility are regulated at the molecular and cellular levels.	Review of original articles.	Not applicable (review).
Summarizes how male infertility is affected by H19 gene methylation.	meta-analysis	Not specified (pooled data from original studies)
A thorough understanding of spermatogenesis's molecular biology, including its metabolomic components.	Review.	Not applicable (review)
A comprehensive meta-analysis to identify the genome-wide association of sperm failure	meta-analysis	2255 men with idiopathic, 3608 controls.
Examines the complex role that p53 plays in male infertility and spermatogenesis and talks about possible treatment approaches.	Review	Not applicable (review).
Gives a summary of how DNA methylation contributes to the etiopathogenesis of male infertility.	Review	Not specified (discusses findings from various studies).
To detect protein changes in the seminal plasma.	Systematic review	Not specified (pooled data from original studies).

Table 4- Describe the final results of the seven systematic articles.

	Results
1	The summary of the results of this study is that all aspects of the molecular and cellular regulatory mechanisms underlying sperm function and fertility in male patients have been identified.
2	Identifies differences in H19 gene methylation patterns between patients with abnormal and normal conventional sperm parameters.
3	According to the results of this study, arginine supplementation and acylcarnitine concentration show a positive correlation with sperm motility and concentration.
4	In this study, the results provide a comprehensive report on spermatogenesis failure that was of unknown cause, according to GWAS.
5	The tumor suppressor p53 is crucial for various cellular functions, including cell

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	cycle arrest, DNA repair, and apoptosis where It plays multiple roles in spermatogenesis, such as regulating spermatogonial stem cell proliferation, differentiation, and DNA damage repair in addition to found in this study Deregulation of p53-dependent apoptosis in germ cells is strongly associated with male infertility, suggesting p53 as a potential therapeutic target.
6	Sperm DNA methylation defects are associated with altered sperm parameters and infertility, where Specific defects in imprinted genes (MEST, H19) and non-imprinted genes (MTHFR) are repeatedly linked to male infertility.
7	Proteomics is a valuable tool for identifying protein alterations in spermatozoa and seminal plasma in infertile male patients.

Discussion

Spermatogenesis is a tightly regulated process that is essential to male fertility, involving the proliferation, differentiation, and maturation of the male germ cells where Dysregulation at the molecular level can lead to a variety of male infertility conditions, a condition that in as many as half of all infertile couples around the world6 as well as The recent advances in molecular biology and high-throughput technology have significantly broadened our understanding regarding the pathways and mechanisms of spermatogenesis, shedding new light upon male infertility etiology and therapeutic potential [15,16] where As Spermatogenesis includes mitotic proliferation of spermatogonia, meiotic division of spermatocytes, and spermatid development to mature spermatozoa (spermiogenesis) [17] Infertility represents a significant psychological burden for affected men. A diagnosis not only helps them cope with the situation but also allows them to assess their chances of fathering children. Previous studies have shown that genetic variations that disrupt the piRNA signaling pathway are associated with male infertility. Furthermore, a German study published the results of a study indicating that genetic defects in piRNA synthesis cause transposon inhibition, impaired spermatogenesis, and male infertility. PiRNAs are a subset of DNA molecules that contribute to transposon inhibition through genomic DNA methylation and post-transcriptional silencing, which is essential for maintaining genome integrity. Moreover, these molecules are also involved in regulating gene expression in the adult testes. While the function of piRNAs is well described, their role in human germ cell development remains largely unknown even that the process is tightly controlled by an interplay of genetic, epigenetic, and environmental factors, and at the molecular level, several crucial pathways and mechanisms are known firstly DNA Repair and Genomic Integrity define the integrity of the genome of spermatozoa, which is maintained by multiple DNA repair mechanisms, which include nucleotide excision repair, base excision repair, mismatch repair, and double-strand break repair and while Defects in these pathways have been shown to result in spermatogenic arrest, abnormal recombination, and ultimately, infertility [18] in addition to secondly Epigenetic Regulation were Epigenetic modifications, such as DNA methylation and histone alterations, play crucial roles in the regulation of gene expression in spermatogenesis also In addition to the Alteration of the methylome and differential protamine levels, it has been shown to induce dysfunctional sperm and male infertility [19] while There is a developing consensus that dangerous life-style conduct are at once associated with male infertility. Smoking reduces sperm motility and matter and will increase oxidative stress where Male patients who smoke have a better fee of morphological abnormalities, DNA fragmentation, and molecular apoptosis and Chronic alcohol intake compromises spermatogenesis via way of means of inhibiting testosterone manufacturing and growing oestrogen levels, Illicit capsules together with marijuana, cocaine, and anabolic steroids reason hormonal suppression, testicular atrophy, and an growth in strange germ cells (Lemoine & in addition to Obesity is strongly related to hypogonadism, continual inflammation, and decreased semen quality (Silva et Excess fats results in extended aromatase, changing testosterone into estrogen and disrupting the HPG axis [20] based on Male infertility has been increasingly recognized as a relevant public health issue, affecting approximately 7% of the male population of reproductive age. Although previously attributed to environmental factors, it is now known that genetic aspects play a fundamental role in this context and according to Studies show that mutations, microdeletions, and chromosomal rearrangements are

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frequently associated with spermatogenesis failure and Among the environmental factors, smoking, drug use, obesity, and stress stand out, negatively influencing testicular and hormonal function These factors, in addition to their direct effects, can interact with genetic predispositions, exacerbating infertility. Epigenetics emerges as an important link between environment and gene expression, and is the target of recent investigations, while the genetic causes of infertility include visible chromosomal alterations and mutations in specific genes related to sperm production. Microdeletions in the AZF region of the Y chromosome are among the main genetic causes identified where Current research focuses on sperm. The epigenome is defined as the sum of epigenetic elements in a cell, responsible for the expression of genes specific to each cell type, and thus for the cell's overall function. These include DNA-binding proteins and their modifications, DNA methylation patterns, and short, highly conserved, non-coding microRNAs. Researchers suspect that certain errors in the sperm genome can cause serious developmental disorders after egg fertilization, and thus represent one of the main causes of idiopathic male infertility. The project investigates open questions about sperm genome function and alterations in men with fertility disorders.

Molecular reproductive biology is a relatively new field of research, addressing germ cell development, early embryonic development, and all molecular aspects of infertility and assisted reproduction. Dr. Yu's current research project builds upon this foundation. Shajdarsuringen, "Nucleosome Conservation in Mammalian Sperm: A Genetic Program for Maintaining Male Reproductive Health," based on findings obtained within the clinical research group "Mechanisms of Male Infertility."

Conclusion

Causally, male infertility may be linked to genetic and/or non-genetic factors, while non-genetic causes include certain lifestyle habits (such as lack of exercise, smoking, and drug use), chemical products, and some medications. Genetic causes include numerical and structural abnormalities of the sex chromosomes, mutations in the CFTR gene, and microchromosomal abnormalities. In addition, numerous other causes of male infertility have been identified, ranging from hormonal imbalances to genetic disorders.

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