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- 7 Epigenetics in the etiology and management of infertility
Yahaya TO, Bashar DM, Oladele EO, Umar J, Anyebe D, Izuafu A

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Epigenetics in the etiology and management of infertility

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Histone epigenetic dysregulation during oocyte development and histone-protamine replacement in the sperm may also cause reproductive abnormalities. Furthermore, overexpression or repression of certain microRNAs embedded in the ovary, testis, embryo, as well as granulosa cells and oocytes may impair reproduction. Male infertility is characterized by spermatogenesis failure, which includes oligozoospermia, asthenozoospermia, and teratozoospermia, while female infertility is characterized by polycystic ovary syndrome. Some epigenetic modifications can be reversed by deactivating the regulatory enzymes, implying that epigenetic reprogramming could help treat infertility in some cases. For some disorders, epigenetic drugs are available, but none have been formulated for infertility.

CONCLUSION

Some cases of infertility have an epigenetic etiology and can be treated by reversing the same epigenetic mechanism that caused it. As a result, medical practitioners are urged to come up with epigenetic treatments for infertility that have an epigenetic cause.

Key Words: DNA methylation; Gametogenesis; Infertility; Polycystic ovary syndrome; Oligozoospermia; Teratozoospermia

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Core Tip: This article reviews the role of epigenetics in the etiology of infertility, which can be used as a therapeutic target. Some cases of infertility are due to epigenetic disruptions, and this is probably the cause of unknown etiology in some cases of infertility. However, there is little awareness on this subject, hindering its application in mainstream medicine.

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INTRODUCTION

Infertility is defined as a couple's inability to conceive after a year of consistent copulation without the use of contraception[1]. Infertility is becoming more prevalent worldwide and is now a serious public health concern[2,3]. At the very least, roughly 15% of couples are infertile[4], with males accounting for 40%, females also account for 40%; and both jointly contributing to the remaining 20%[5]. The most common feature of male infertility is spermatogenesis failure, which is responsible for half of all human infertility[6]. Spermatogenesis failure is characterized by an abnormal sperm count (oligozoospermia), weak sperm motility (asthenozoospermia), and abnormal sperm morphology (teratozoospermia)[6,7]. The most common features of female infertility are amenorrhea and irregular menstruation[8].

Infertility is often devastating and affects all aspects of life, including physical, mental, and social health[9,10]. Infertility causes enormous psychological problems, poor sexual satisfaction, and a low quality of life[10]. Women are often more affected by the effects of infertility than men

study, therefore, provides an update on the role of epigenetics in the etiology and management of infertility.

MATERIALS AND METHODS

Reputable academic repositories, namely PubMed, Google Scholar, RCA, SpringerLink, and Scopus, were searched separately for peer-reviewed articles on the subject. The keywords used for the search were: "epigenetics," "infertility," "male infertility," "female infertility," "DNA methylation," "histone modifications," "microRNAs," "epigenetic tests for infertility," and "epigenetic drugs for infertility." Other keywords used include "epigenetic mechanisms," "role of DNA methylation in infertility," "role of histone modification in infertility," and "role of microRNAs in infertility." The articles retrieved were sorted using EndNote software, and double citations were removed.

Article inclusion/exclusion criteria

Included articles were those that were available in the English language, those that focused on the epigenetic basis of infertility and management, and those that were published between the years 2000 and 2021, this was to obtain up-to-date information.

Excluded articles were those that were not available in the English language, articles written before the year 2000, and articles for which only abstracts were available.

In all, 702 articles were retrieved from the databases searched (Figure 1), but 220 articles were retained after removing duplicates. The retained articles were subjected to the eligibility test, and 155 passed. Of the 155 eligible articles, 99 fitted the study objectives and thus made the final selection.

RESULTS

Epigenetic mechanisms

The word "epigenetics" was previously employed to describe the relationship between the genome and the environment that takes part in the development of mammals and some other organisms[14]. However, it is currently defined as heritable alterations in DNA accessibility and chromatin structure, affecting gene expression without changing the DNA sequence[14,15]. Epigenetics plays an important role in normal development, cell differentiation, and disease pathologies[14,15]. There are several epigenetic mechanisms. However, the most common epigenetic mechanisms are DNA methylation, histone modifications, and microRNA (miRNA) interference[12,16]. These mechanisms may alter gene expressions individually or interact to control gene expressions[12]. Figure 2 depicts interactions among epigenetic mechanisms, and Table 1 summarizes the mechanistic links between epigenetic disruptions and infertility.

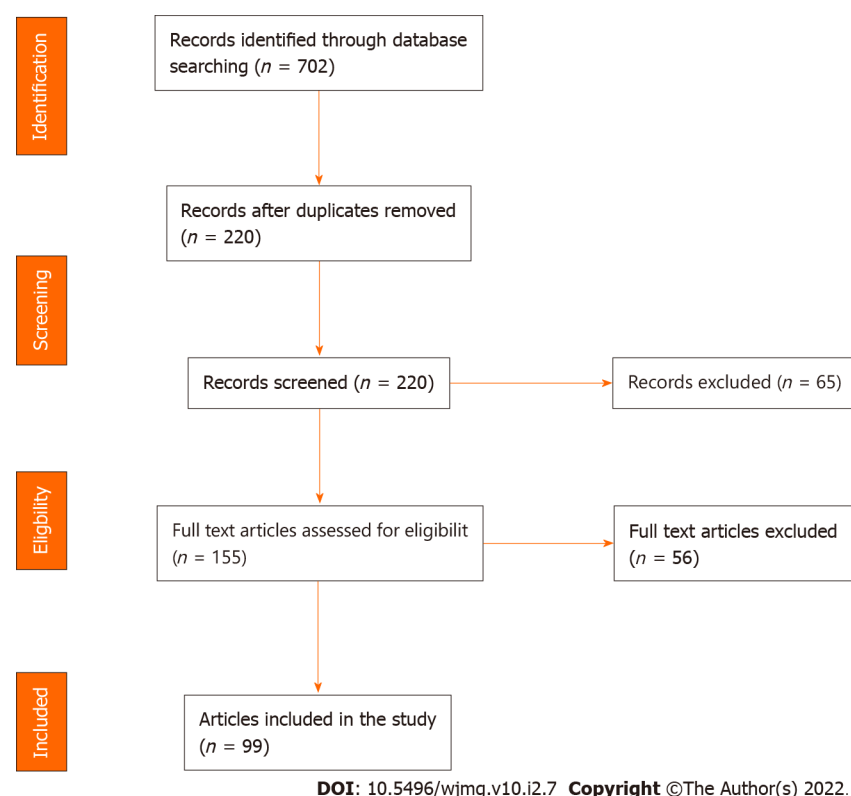
DISCUSSION

DNA methylation in the etiology of infertility

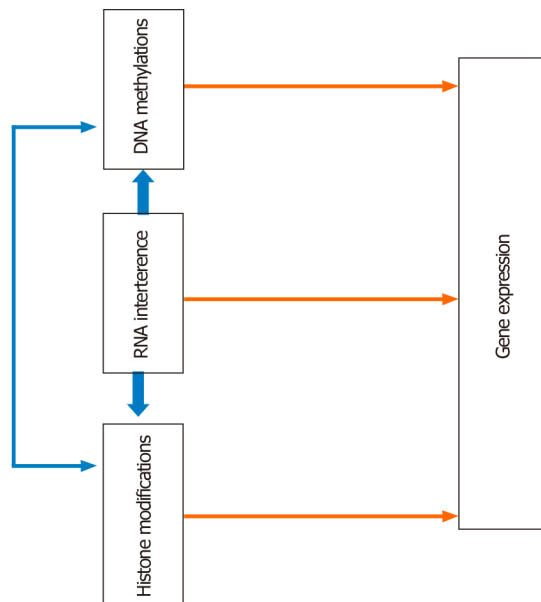
DNA methylation is the most researched epigenetic mechanism and often results in gene silencing[17, 18]. DNA methylation involves the binding of a methyl group to the DNA, resulting in a change of the expression and functions of the embedded genes (Figure 3).

Table 1 Mechanistic links between epigenetic disruptions and infertility

Epigenetic mechanisms	Links (Pathophysiology)	Ref.
DNA methylation	Hypermethylation or hypomethylation disrupts genomic imprinting and parental epigenetic mark erasure, resulting in abnormal expression of some genes and imprinted genes involved in gametogenesis and embryogenesis	[3,4,12,13,17,20,25,29-42,44-49]
Histone post-translational modification	Abnormal histone modification alters the expression of certain genes important in gametogenesis and embryogenesis. Also, it disrupts sperm DNA protamination, causing sperm abnormalities	[7,43,56-63]
miRNA	Up-regulation or down-regulation alters the expression of certain genes important in gametogenesis and embryogenesis	[15,68-75]

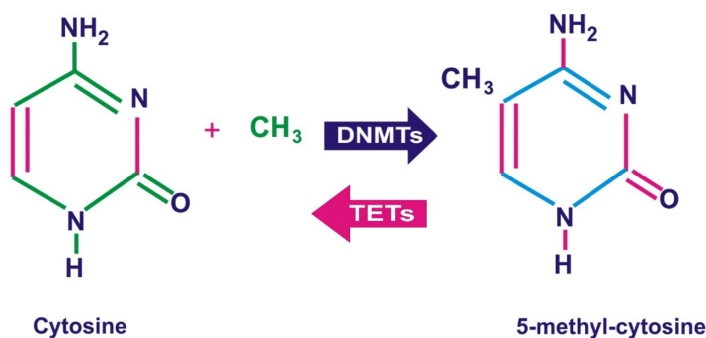
**Figure 1** Flow chart of article selection.

the other allele is imprinted or silenced[25]. Thus, genomic imprinting maintains the parent-of-origin expression of genes. However, some genes may not be fully imprinted; instead of one allele being completely expressed and the other repressed, the two alleles show varied expressions[26]. As of 2019, 228 imprinted genes have been reported in the human genome[27]. Normal imprinting of some genes is necessary for healthy development as it protects the genome's integrity[25,28]. Abnormal imprinting, often caused by alterations in DNA methylation, is associated with many diseases, including impaired spermatogenesis and infertility[3,29]. In a study that analyzed the DNA methylation patterns of seven differently methylated regions (DMRs), in the sperm of 97 infertile men, 14 showed abnormal paternal DNA methylation at H19 and GTL2, and 20 had abnormal maternal DNA methylation at PEG1, LIT1, ZAC, PEG3, and SNRPN[30]. These DMRs contain imprinted genes that regulate spermatogenesis, and at least half of the genes show maternal and paternal imprint abnormalities in infertile men[30]. In another study, methylation and imprinting errors were observed in the IGF2/H19 imprinting control region 1 (ICR1) and MEST DMRs in the spermatozoa of 148 idiopathic infertile men compared with 33 normozoospermic controls[31]. The idiopathic infertile men (sperm motility below 40% and normal sperm morphology below 5%) displayed hypermethylation of the MEST DMRs and hypomethylation of the IGF2/H19 ICR1, while the control showed the opposite. Thus, in the study, infertility was clearly linked with IGF2/H19 ICR1 hypomethylation and MEST hypermethylation[32,33]. In another study, seven out of 15 (46.7%) individuals with low sperm count (below 10×10^6 /mL) showed defective methylation of H19 and/or MEST imprinted genes[34]. Of the seven patients that expressed imprinting errors, two had both H19 hypomethylation and MEST hypermethylation, while five had only one of the impaired imprinted genes[34]. This again proved that imprinted genes in H19 and MEST play an



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Figure 2 Epigenetic mechanisms.



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Figure 3 DNA methylation (arrow pointing right) and de-methylation (arrow pointing left) via DNA methyltransferase and ten-eleven translocation, respectively. DNMTs: DNA methyltransferase; TETs: Ten-eleven translocation.

important role in spermatogenesis, fetal growth and development, and placental function[35,36]. Similarly, in a study that compared the DNA methylation at DMRs of maternally imprinted genes extracted from stillborn pups and control embryos, hypermethyations were observed at *Zac1* imprinting genes in the stillborn pups[37]. *Zac1* regulates an imprinted gene network that is important in the regulation of embryonic growth[38]. Aberrant DNA methylation has also been implicated in some genomic imprinting disorders, which, in severe cases, can cause recurrent molar pregnancy, miscarriage, or infertility[39]. These disorders include Prader-Willi syndrome and Angelman syndrome, which are caused by loss of function of imprinted genes on chromosome 15 in females and males, respectively[40]. Beckwith-Wiedemann syndrome and Russell-Silver syndrome are two others. Both are caused by the loss of function of imprinted genes on chromosomes 7 or 11[41,42].

Aside from genomic imprinting, DNA methylation is also involved in parental epigenetic mark erasures in which DNA methylation undertakes two rounds of epigenetic reprogramming during gametogenesis and embryogenesis[13]. One reprogramming occurs immediately after fertilization, in which sperm and oocyte DNA are stripped of the parental methylation marks (DNA demethylation)[4]. Some DNA demethylation occurs specifically in paternally inherited imprinted genes[43]. The erasure of DNA methylation continues until new imprints are formed[43]. The stripping allows the totipotent zygote to start new gene transcription and new cell methylation[4]. Because of this, most epigenetic modifications that occur in sperm and egg cells when the two merge to form a fertilized egg are removed[3]. Thus, epigenetic reprogramming enables the fetus's cells to start afresh and determine their own epigenome[3]. However, some of the epigenetic modifications in parents' sperm and egg cells may escape the reprogramming and be transmitted to the next generation[3]. Another genome-wide stripping of DNA methylation and subsequent new DNA methylation occurs in the primordial germ

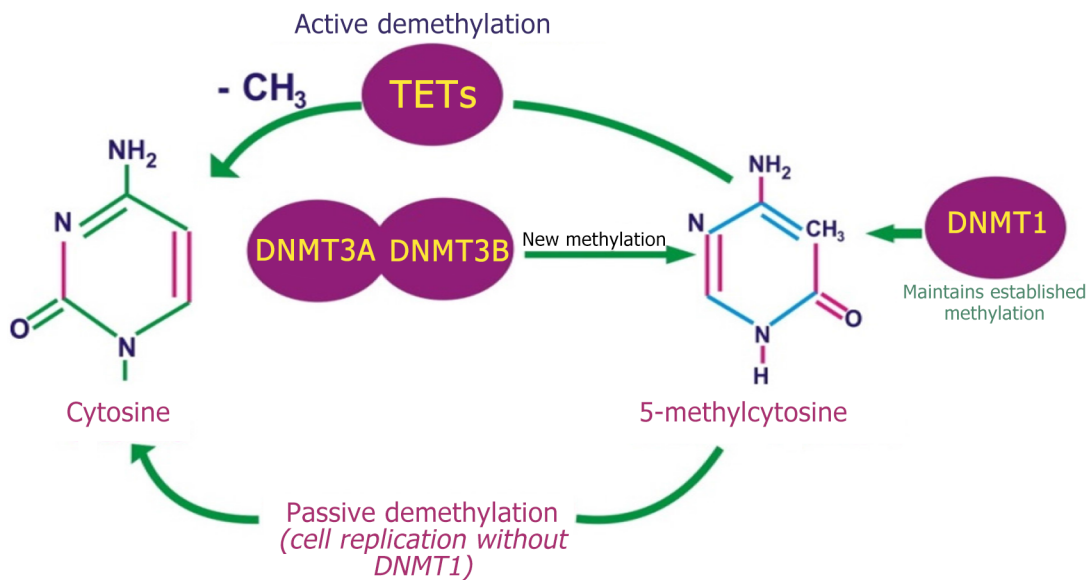


Figure 4 DNA methylation and de-methylation processes, showing the roles of each modulating enzyme; DNMT1, DNMT3A, and DNMT3B stand for DNA methyltransferases 1, 3A, and 3B, respectively; TET2 is short for ten-eleven translocation. DNMTs: DNA methyltransferase; TETs: Ten-eleven translocation.

cells (gamete precursors), which subsequently differentiate into the gametes (sperm and eggs)[17,44]. Overall, this showed the importance of DNA methylation in gametogenesis and embryogenesis and, hence, fertility. In fact, DNMT1, DNMT3a, and DNMT3b have been shown to be highly expressed in the early embryonic stage[20]. Furthermore, it has been shown that more than 150 genes are associated with mammalian spermatogenesis, and if the normal expression of any of these genes is altered, the reproductive success of males could be compromised[25]. Thus, aberrant DNA methylation may cause dysfunctional gametogenesis and embryogenesis, resulting in infertility[4,25]. In a study, 696 differentially methylated CpGs, comprising 184 (26%) hypomethylations and 512 (74%) hypermethylations associated with 501 genes, were identified between the spermatozoa of 19 fertile men and 42 infertile men[45]. The CpGs are home to 13 processes related to spermatogenesis. Moreover, 17 differentially methylated genes related to spermatogenesis were observed between the fertile and infertile groups [45]. In another study that compared 46 sperm samples obtained from 17 normospermic fertile men and 29 normospermic infertile men, 2752 CpGs showing aberrant DNA methylation patterns were observed in the sperm of infertile men[46]. Importantly, these differentially methylated CpGs were significantly associated with CpG sites that are involved in spermatogenesis[46]. Additionally, 48 imprinted genes were abnormally methylated in the altered CpGs of the infertile patients. In a related study that compared the sperm of 12 fertile and 45 infertile men, reactive oxygen species were found to cause DNA fragmentation and abnormal methylation in the infertile group's sperm

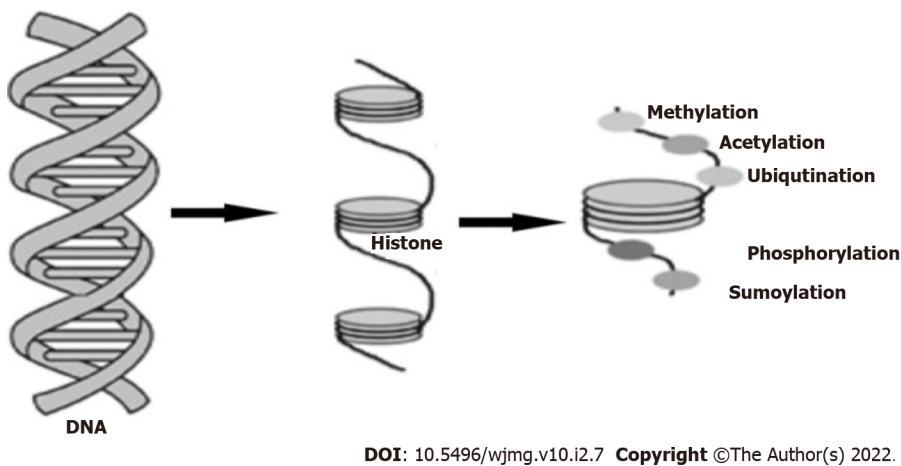


Figure 5 Histone post-translational modification processes, showing mechanisms.

modified through several mechanisms, such as methylation, acetylation, phosphorylation, sumoylation, and ubiquitylation (Figure 5). However, methylation and acetylation are the most common mechanisms [15,55]. Acetylation binds an acetyl group to the amino acid lysine in the histone, while methylation binds a methyl group to the amino acids of histone proteins, primarily lysine and arginine residues [15, 55]. As lysine and arginine are the most abundant amino acids in histones, they are frequently acetylated and methylated [50]. Acetylation ideally takes place in non-condensed chromatin, while deacetylation usually takes place in condensed chromatin [15]. Histone methylation can take place in both forms of chromatin. Histone acetyltransferases and histone methyltransferases catalyze histone acetylation and methylation, respectively [12], whereas histone deacetylases (HDACs) and histone demethylases catalyze deacetylation and demethylation [12]. Aside from the structural state of chromatin mentioned earlier, the effects of histone post-translational modifications on gene expression also depend on the mechanisms and degree of methylation or acetylation, which could be mono-, di-, or tri-methylated [12]. Sometimes, both DNA methylation and histone post-translational modification combine to cause epigenetic changes [12]. DNA methylation plays a part in ensuring high levels of chromatin structure [45].

Histone modifications play an important role in gametogenesis and embryogenesis, as well as in fertility [56]. To successfully transfer a sperm's genetic and epigenetic materials to an egg, the chromatin must be very condensed for proper motility and protection of the paternal DNA and epigenome from external stimuli [56,57]. This is guaranteed by the replacement of histones with protamines (a unique, sperm-specific protein) by sperm DNA protamination [56,57]. Despite this, some regions, particularly the sperm head, retain histones, which are prone to modifications [56,57]. Protamination and some other biological events during spermatogenesis are controlled by epigenetic mechanisms in which abnormal histone modifications may cause the sperm to lose its oocyte fertilizing capacity [7]. Defects in either the replacement or the modification of histones might

miscarriage in 3 pregnant women, 81 genes were overexpressed in the chorionic villous of the affected compared with controls[61]. These genes take part in several important physiological processes, such as cell proliferation, nuclear division, chromatic assembly, DNA packing, and modification[61]. Furthermore, 231 genes that are functionally involved in histone modifications and cell cycle control were down-regulated in the chorionic villous of the affected women compared with controls[61]. In a study of histone locations and modifications, in the semen of seven infertile patients, unlike fertile men, five infertile men had non-programmatic (randomly distributed) histone retention genome-wide[62]. Although the methylation patterns of H3K4me and H3K27me in infertile men were similar to those in the control group, the amounts of histones retained by developmental transcription factors and certain imprinted genes were decreased[62]. In a study that monitored the effects of chlordecone exposure on the epigenome of the ovaries of mice, compared with the control, reduced H3K4me3 and H4ac in fully grown oocytes were observed. This reduction caused repression of genes associated with estrogen signaling and oocyte maturation in adult ovaries[63]. Furthermore, gene expression analysis revealed that RCBTB2 and RBPMS genes were not expressed in the embryonic gonads[63]. Reproductive abnormalities observed in the exposed mice included compromised meiotic double-strand break repair in female embryos, puberty delay, decreased primordials, and increased atretic follicles[63]. The study showed that exposure to a low dose of chlordecone during pregnancy impaired female reproductive functions, which are mediated by abnormal histone modifications[63].

MicroRNAs in the etiology of infertility

MicroRNAs (miRNAs) are small, single-stranded non-coding RNA molecules of between 19 and 25 nucleotides[15,64]. MicroRNAs interact with transcriptional and epigenetic regulators in cells to maintain lineage-specific gene expression[15,65]. Specifically, miRNAs control the expression of genes during transcription by disrupting the translation of target messenger RNA. However, in diseased cells, miRNA expression is changed, leading to altered expression, mostly overexpression of the target genes [15,66]. Approximately 1% of the human genome is made up of genes that contain miRNAs[67], which shows how

Table 2 Status of some microRNAs in infertile men and women

miRNAs	Status	Effect	Ref.
miR-34b	Up-regulated	Asthenozoospermia	[73]
miR-122	Up-regulated	Asthenozoospermia	[73]
miR-1973	Up-regulated	Asthenozoospermia	[73]
miR-15b	Up-regulated	Asthenozoospermia	[73]
miR-34c-5p	Up-regulated	Oligoasthenozoospermia	[73]
miR-449a	Up-regulated	Oligoasthenozoospermia	[73]
miR-16	Up-regulated	Oligoasthenozoospermia	[73]
miR-19a	Up-regulated	Oligoasthenozoospermia	[73]
miR-17-92	Deficient	Abnormal oogenesis	[74]
miR-145	Up-regulated	Implantation failure	[75]
miR-23b	Up-regulated	Implantation failure	[75]
miR-99a	Up-regulated	Implantation failure	[75]
hsa-miR-32	Down-regulated	Implantation failure	[75]
hsa-miR-628-5p	Down-regulated	Implantation failure	[75]
hsa-miR-874	Down-regulated	Implantation failure	[75]

miRNAs: MicroRNAs.

endometrium of patients with repeated implantation failure with controls, 13 differentially expressed miRNAs that regulate 3800 genes were identified in the affected patients[75]. Ten of the miRNAs were overexpressed (including miR 145, 23b, and 99a), and three were repressed (Table 2). These miRNAs target genes are involved in important implantation processes, such as adherens junctions, cell adhesion molecules, Wnt-signaling, p53 signaling, and cell cycle pathways[75].

EPIGENETIC-BASED TESTS FOR INFERTILITY

Currently, there is no standard epigenetic-based test for infertility. This could

Table 3 Selected epigenetic drugs and their activities

Epigenetic drug	Target	Effect	Ref.
Choline	HDAC3	Increases DNA methylation	[15]
Betaine	HDAC3	Increases DNA methylation	[15]
Bobcat339	TETs and TET2	Increases DNA methylation	[15]
C35	TET	Increases DNA methylation	[91]
Zebularine	DNMTs	Reduces hypermethylation	[92]
Disulfiram	DNMTs	Reduces hypermethylation	[92]
Decitabine	DNMTs	Reduces hypermethylation	[92]
Azacitidine	DNMTs	Reduces hypermethylation	[92]
Chaeton	DNMTs	Reduces hypermethylation	[92]
RGFP966	HDAC3	Inhibits histone modification	[95,96]
RG108	Anti-miRNA	Reduces gene expression	[98,99]

DNMTs: DNA methyltransferase; HDAC: Histone deacetylases; TETs: Ten-eleven translocation; miRNA: MicroRNA.

diseases that have an epigenetic etiology[77-81]. This can be achieved by blocking or deleting the enzymes that modulate the epigenetic alterations in the affected individuals, thereby preventing or reversing the associated disease[82-84]. Complementary single-stranded oligonucleotides (otherwise called anti-miRNAs) can also be used to silence overexpressed genes or boost repressed genes[85-87].

Currently, there is no particular epigenetic drug for treating infertility. However, epigenetic drugs have been developed for some diseases, such as cancer and diabetes mellitus (Table 3). Notably, a HDAC3 inhibitor known as RGFP966 has been shown to reverse Type 1 diabetes and its complications in

including Choline, Betaine, Zebularine, Disulfiran, Decitabine, Azacitidine, Chaeton, RGFP966, and RG108, but none have been formulated specifically for infertility. It is theorized that some of the available epigenetic drugs could be helpful in infertility as epigenetic mechanisms are the same in all disease pathologies. Epigenetic drugs for infertility can also be formulated from the bioactive compounds of existing epigenetic drugs or from entirely different bioactive substances.

ARTICLE HIGHLIGHTS

Research background

Medical practitioners are advised to formulate treatment procedures and epigenetic drugs for infertility having an epigenetic etiology.

Research motivation

Epigenetic disruption is involved in some cases of infertility.

Research objectives

Epigenetic disruptions in genes that control gametogenesis and embryogenesis, such as *DDX3X*, *ADH4*, *AZF*, *PLAG1*, *D1RAS3*, *CYGB*, *MEST*, *JMJD1A*, *KCNQ1*, *IGF2*, *H19*, and *MTHFR* may result in infertility.

Research methods

Relevant information was collected from notable academic repositories and the articles collected were sorted using Endnote software.

Research results

The study was aimed at articulating and disseminating the epigenetic basis of infertility to raise public awareness.

P-Editor: Liu JH

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