DS Reviews of Research in Life Sciences
Volume 2 Issue 14, 1-10, Jan - Mar 2026
ISSN: 3107-975X / https://doi.org/10.59232/RLS-V2I1P101

Review Article

The Role of Epigenetics in Reproductive Biology: A Review of Epigenetic Marks and their Impact on Fertility

Moses Adondua Abah[1,2*], Oloko Oluwasegun Ayodeji[3], Micheal Abimbola Oladosu[2,4], Micah Nnabuko Okwah[5,6], Nathan Rimamsanati Yohanna[1,2]

[1]Department of Biochemistry, Faculty of Biosciences, Federal University Wukari, Taraba State, Nigeria
[2]ResearchHub Nexus Institute, Nigeria.
[3]Department of Animal Breeding and Genetics, Federal University of Agriculture, Abeokuta, Ogun State, Nigeria.
[4]Department of Biochemistry, Faculty of Basic Medical Sciences, University of Lagos, Lagos State, Nigeria.
[5]Department of Internal Medicine, Cardiology Unit, Lagos University Teaching Hospital, Lagos State.
[6]Department of Chronic Disease Epidemiology, Yale University, Connecticut, United States of America.

*m.abah@fuwukari.edu.ng

Received: 12 January 2026; Revised: 06 February 2026; Accepted: 08 March 2026; Published: 30 March 2026

Abstract - From gametogenesis and fertilization to embryonic development and a healthy birth, reproductive biology is essential to population dynamics, individual health, and societal wellbeing. Disruptions in reproductive function, whether brought on by genetic factors, environmental exposures, or clinical interventions like assisted reproductive technologies, have significant personal and societal repercussions. This review explores the role of epigenetics in reproductive biology with emphasis on epigenetic marks and their impact on fertility. Findings have revealed that fertility also supports demographic trends, shapes public health planning, and affects socioeconomic outcomes. DNA methylation, post-translational histone modifications, chromatin remodeling, and noncoding RNA-mediated regulation are examples of biochemical markers and molecular mechanisms that affect gene expression without changing the underlying DNA sequence. Collectively, these markers determine chromatin accessibility and the transcriptional programs that define cell identity and function. During gametogenesis, germ cells undergo substantial reprogramming, and the early embryo undergoes genome-wide waves of demethylation and de novo methylation that create lineage-specific epigenomes. These processes make epigenetics particularly dynamic and crucial in reproductive situations. Because these periods align with the manipulation of gametes and the culture of embryos in assisted reproduction, changes to epigenetic programming can have a significant impact on imprinting, developmental paths, and long-term health. Changes in epigenetic markers have been connected in the last 20 years to a variety of reproductive diseases and fertility problems. Environmental factors such as stress, air pollution, endocrine-disrupting chemicals, and maternal nutrition can alter gamete quality, embryo viability, and placental function. In certain situations, these alterations may have an impact on future generations. Concerns regarding imprinting disorders and subtle epigenetic changes seen in some offspring conceived through in vitro fertilization and related procedures demonstrate the clinical relevance of these mechanisms, which drives both more in-depth mechanistic research and improvements to ART protocols to reduce epigenetic risk. Hence, epigenetic insights offer new avenues for diagnosis and intervention. Epigenomic profiling can identify biomarkers of gamete competence and endometrial receptivity, and targeted modulation of epigenetic regulators holds potential for restoring normal reproductive function in selected settings.

Keywords - Reproduction, Epigenetics, Fertility, Gametogenesis, Healthy Birth.

1. Introduction

Reproductive biology is central to individual health, population dynamics, and societal wellbeing, encompassing processes from gametogenesis and fertilization to embryonic development and successful birth. Fertility underpins demographic trends, influences public health planning, and affects socioeconomic outcomes; disruptions in reproductive function, whether caused by genetic factors, environmental exposures, or clinical interventions such as assisted reproductive technologies, carry profound personal and public consequences. Understanding the mechanistic controls of reproduction is therefore a priority for medicine, agriculture, and conservation, and recent advances reveal that inheritance and developmental outcomes are shaped not only by DNA sequence but also by reversible, heritable modifications that regulate gene activity.

Epigenetics refers to the collection of biochemical marks and molecular mechanisms that influence gene expression without altering the underlying DNA sequence, including DNA methylation, post-translational histone modifications, chromatin remodeling, and noncoding RNA-mediated regulation; together these marks determine chromatin accessibility and the transcriptional programs that define cell identity and function (Huntriss et al., 2018). In reproductive contexts, epigenetic processes are especially dynamic and consequential: germ cells undergo extensive reprogramming during gametogenesis, and the early embryo experiences genome-wide waves of demethylation and de novo methylation that establish lineage-specific epigenomes. Because these windows coincide with gamete manipulation and embryo culture in assisted reproduction, perturbations to epigenetic programming can have outsized effects on imprinting, developmental trajectories, and long-term health (Huntriss et al., 2018; Yu et al., 2024).

Research over the past two decades has linked altered epigenetic marks to a range of fertility issues and reproductive disorders. Environmentally induced epigenetic changes from maternal nutrition and endocrine-disrupting chemicals to air pollution and stress can modify gamete quality, embryo viability, and placental function, and in some cases may have intergenerational consequences (Yu et al., 2024). The clinical relevance of these mechanisms is reflected in concerns about imprinting disorders and subtle epigenetic shifts observed in some offspring conceived through in vitro fertilization and related procedures, motivating both deeper mechanistic study and refinement of ART protocols to minimize epigenetic risk (Huntriss et al., 2018).

At the same time, epigenetic insights offer new avenues for diagnosis and intervention. Epigenomic profiling can identify biomarkers of gamete competence and endometrial receptivity, and targeted modulation of epigenetic regulators holds potential for restoring normal reproductive function in selected settings. Translating these prospects into practice requires rigorous characterization of cause–and–effect relationships, standardization of measurement approaches, and careful assessment of safety and heritability. Overall, this review synthesizes the role of epigenetics in reproductive biology. Integrating epigenetics into reproductive biology enriches our understanding of fertility, clarifies how environment and clinical care intersect with developmental programming, and points to novel strategies for preserving and improving reproductive outcomes.

2. Epigenetic Mechanisms in Gametogenesis

Gametogenesis is governed not only by the DNA sequence but by dynamic epigenetic reprogramming that establishes the heritable regulatory states of sperm and oocytes; these programmed changes ensure genome integrity, transposon silencing, parent-of-origin imprinting, and the correct activation of embryonic gene expression after fertilization (Ben Maamar, Nilsson, & Skinner, 2021). In mammals, two major genome-wide waves of DNA methylation erasure and re-establishment occur during germline development: an early demethylation phase in primordial germ cells that removes most somatic methylation marks, followed by sex-specific de novo

methylation during later stages of spermatogenesis or oogenesis that creates the mature parental epigenomes and establishes imprints (Ben Maamar et al., 2021; Saftić Martinović et al., 2024).

2.1. Spermatogenesis (Paternal Methylation, Imprinting)

During spermatogenesis, the male germ line undergoes progressive chromatin compaction accompanied by extensive DNA methylation and small RNA-mediated regulation; paternal imprinting patterns are largely set during prospermatogonia and spermatocyte stages through de novo DNA methyltransferase activity, and these methylation marks are critical for silencing imprinted loci and transposable elements in the sperm genome (Ben Maamar et al., 2021). In addition to cytosine methylation, sperm carry a distinct epigenetic cargo including specific retained histones at developmental gene promoters, protamine packaging that promotes extreme chromatin condensation, and a rich complement of small noncoding RNAs (miRNAs, piRNAs, tRNA fragments) that can influence early zygotic transcription and paternal epigenetic inheritance (Saftić Martinović et al., 2024). Perturbations in paternal methylation or the small RNA profile, whether from environmental toxicants, heat stress, or lifestyle factors, have been linked to reduced sperm quality and altered offspring phenotypes in animal models and emerging human studies (Ben Maamar et al., 2021).

2.2. Oogenesis (Maternal Imprinting, Histone Retention)

Oogenesis follows a related but distinct epigenetic trajectory. Female germ cells initiate de novo methylation later than males and complete many imprinting marks during oocyte growth and maturation; importantly, oocytes retain a characteristic pattern of histone modifications and, unlike sperm, preserve a larger fraction of canonical nucleosomes across the genome, which contributes to maternal regulation of early embryonic transcription (Sindik, Pereza, & Dević Pavlić, 2024). Histone retention in oocytes supports regulatory chromatin states at developmental genes and at imprint control regions, while oocyte-specific transcription and chromatin remodeling establish maternal imprints that are essential for proper placental development and embryonic growth (Sindik et al., 2024). Assisted reproductive technologies and adverse maternal exposures during oocyte maturation can interfere with histone modification patterns or methylation establishment, raising concerns about imprinting errors and long-term developmental outcomes (Saftić Martinović et al., 2024).

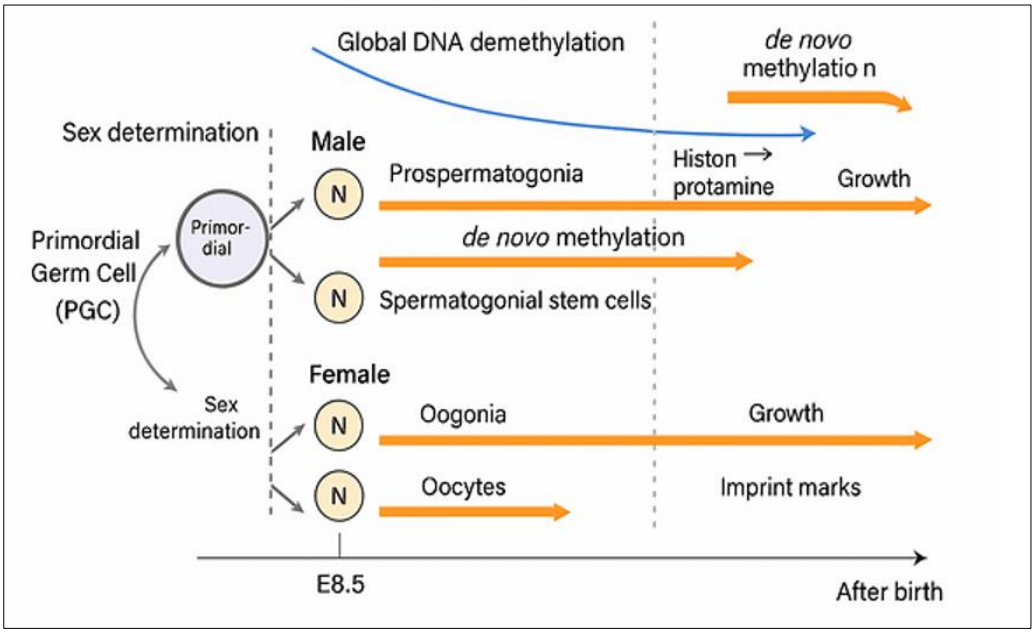

Fig. 1 Epigenetic reprogramming during gametogenesis et al., 2024)

Source: Ben Maamar et al. (2021)

Figure 1 above illustrates these coordinated events: the figure traces primordial germ cells through sex determination into male and female germ lines, highlights the first global wave of demethylation that erases somatic marks, then shows the sex-specific timelines where de novo methylation is completed earlier in males (during prospermatogonia and spermatogenesis) and later in females (during oocyte growth). The diagram also annotates associated chromatin changes, histone to protamine replacement in sperm, partial histone retention in oocytes, and marks the windows when small RNAs and imprinting marks are generated. This schematic emphasizes critical vulnerable periods when environmental or procedural perturbations can alter epigenetic programming and thus fertility or offspring health (Ben Maamar et al., 2021; Sindik et al., 2024).

Together, these mechanisms of DNA methylation dynamics, histone modification and retention patterns, protamine replacement, and noncoding RNA provisioning form an integrated epigenetic program that confers gamete competence and establishes the parental epigenetic contributions to the embryo. Understanding the timing, molecular players, and susceptibility of these processes is essential for diagnosing idiopathic infertility, refining ART protocols to minimize epigenetic risk, and developing interventions that preserve or restore healthy epigenetic states in the germ line (Saftić Martinović et al., 2024).

3. Epigenetics in Fertilization and Early Embryonic Development

3.1. Genome Reprogramming Post-fertilization

Fertilization marks the union of two highly specialized gametes and initiates a rapid and tightly regulated program of epigenetic reprogramming that transforms two differentiated parental genomes into a totipotent zygote capable of directing all subsequent embryonic lineages. Immediately after sperm–oocyte fusion, the paternal and maternal genomes undergo asymmetric reprogramming: the paternal genome experiences rapid, active DNA demethylation mediated in part by oxidation of 5-methylcytosine through TET enzymes, whereas the maternal genome is largely protected from immediate active demethylation and instead undergoes passive demethylation during early cleavage divisions as maintenance methylation is diluted during DNA replication (Guo et al., 2014; Messerschmidt et al., 2014).

These genome-wide methylation dynamics coincide with chromatin remodeling events, protamine-to-histone exchange on the paternal pronucleus, changes in histone post-translational modification patterns, and deposition of maternal histone variants and chromatin regulators all of which together reset transcriptional competence and set the stage for Zygotic Genome Activation (ZGA) and lineage specification (Messerschmidt et al., 2014; O'Neill, 2015).

3.2. Imprinting Control Regions

Imprinting Control Regions (ICRs) form a critical exception to the global waves of demethylation and remethylation in early embryos. Parental-origin-specific DNA methylation marks at ICRs are established in the germ line (spermatogenesis or oogenesis) and must be preserved through the dramatic reprogramming that follows fertilization to maintain parent-of-origin expression patterns of imprinted genes such as H19/IGF2, SNRPN, and KCNQ1OT1 (Reik & Walter, 2001; Messerschmidt et al., 2014). A specialized set of factors, including zinc-finger proteins such as ZFP57 and associated co-factors that recognize methylated ICRs, protect imprints from demethylation and recruit maintenance machinery during early cleavage, ensuring correct imprint transmission and preventing dysregulation that can lead to growth disorders and imprinting syndromes (Reik & Walter, 2001; Messerschmidt et al., 2014). Because proper imprint maintenance is essential for placental development, fetal growth, and postnatal physiology, perturbations at these loci have outsized developmental consequences.

3.3. Epigenetic Barriers in IVF/ART

Assisted Reproductive Technologies (ART), including ovarian stimulation, in-vitro maturation, gamete handling, and embryo culture, intersect with these sensitive reprogramming windows and have been associated in

some studies with altered methylation patterns at specific genomic loci and rare increases in imprinting disorders. Mechanistically, culture media composition, oxygen tension, temperature fluctuations, and hormonal manipulations can influence the activity or availability of DNA methyltransferases, TET enzymes, histone-modifying complexes, and noncoding RNAs that collectively sculpt the early embryonic epigenome (O'Neill, 2015; Ren, Chang, & Qiao, 2017). While the absolute risks to offspring conceived by ART remain low and many ART-conceived children develop normally, these associations motivate careful optimization of ART protocols, standardized culture conditions, and continued epigenomic surveillance in clinical cohorts to reduce any modifiable epigenetic insults during preimplantation development (O'Neill, 2015; Ren et al., 2017).

Table 1 (Key genes regulated epigenetically in early development) highlights representative loci and regulators that are central to early embryogenesis and are subject to epigenetic control or themselves affect epigenetic change. Pluripotency factors such as OCT4 (POU5F1), NANOG, and SOX2 are transcriptionally activated during ZGA and are regulated by promoter and enhancer DNA methylation, histone modifications (H3K4me3 activation marks; H3K27me3 repressive marks), and chromatin-remodeling complexes; their correct epigenetic regulation is essential for maintaining the pluripotent state and directing lineage choice (Guo et al., 2014; O'Neill, 2015).

Epigenetic writers and erasers DNMT3A, DNMT3B, and the oocyte-specific cofactor DNMT3L, together with TET family dioxygenases, control the establishment and removal of cytosine methylation during the waves of de novo methylation and demethylation that define early development; mutations or dysregulation of these enzymes perturb methylation landscapes and can impair embryo viability (Messerschmidt et al., 2014).

Imprinted loci listed in the table (for example, H19/IGF2 and SNRPN) are regulated through germline-established ICR methylation and require imprint-protecting factors to prevent erasure after fertilization (Reik & Walter, 2001). Additional developmental regulators, such as CDX2 (trophectoderm specification) and lineage-specific transcription factors, are likewise modulated by DNA methylation and histone state transitions during blastocyst formation and lineage commitment (Guo et al., 2014). The table, therefore, serves as a compact reference linking key developmental genes to the primary epigenetic mechanisms that regulate their timing and level of expression in the preimplantation embryo.

Collectively, the coordinated choreography of DNA methylation dynamics, histone modification changes, chromatin remodeling, and noncoding RNA provision underlies successful fertilization and early embryonic development. Recognizing the molecular actors and their temporal windows of action both informs fundamental developmental biology and guides clinical efforts, particularly in ART, to minimize epigenetic risk while harnessing epigenetic biomarkers to assess embryo quality and reproductive potential.

Table 1. Key genes regulated epigenetically in early development

Gene	Developmental role	Primary epigenetic regulation	Consequence if misregulated	Representative evidence/source
POU5F1 (OCT4)	Maintains pluripotency and drives zygotic genome activation	Promoter/enhancer DNA methylation; H3K4me3/H3K27me3 balance	Loss of pluripotency and failed lineage specification	Reviewed in embryo methylome and pluripotency studies
NANOG	Core pluripotency factor regulating inner cell mass identity	Promoter methylation and histone modification dynamics	Impaired establishment/maintenance of pluripotent cells	Shown in preimplantation epigenetic profiling

SOX2	Works with OCT4/NANOG to maintain pluripotency and ZGA	Enhancer methylation; nucleosome positioning	Defective pluripotency and abnormal lineage commitment	Linked to chromatin remodeling during ZGA
DNMT3A / DNMT3B / DNMT3L	De novo DNA methyltransferases are essential for germline and early embryo methylation	Establishment of germline imprints and de novo methylation patterns	Failed imprinting, embryonic lethality, and developmental defects	Functional genetics and methylation-landscape studies
TET family (TET1 / TET2)	Catalyze active DNA demethylation during early embryo reprogramming	Oxidation of 5-methylcytosine leading to demethylation	Aberrant demethylation, altered ZGA, and lineage outcomes	Demonstrated role in paternal genome demethylation
H19 / IGF2 (imprinted cluster)	Regulate fetal growth via parent-of-origin expression	Germline-established ICR methylation and imprint maintenance	Growth disorders, imprinting syndromes (loss/gain of imprinting)	Classic imprinting locus with conserved ICR regulation
SNRPN (Prader – Willi /Angelman region)	Imprinted control of neural and growth-related genes	Germline imprint establishment and maintenance at ICRs	Imprinting disorders with neurodevelopmental phenotypes	Well-characterized imprint control region
MEST	An imprinted gene implicated in fetal growth and placental function	Germline methylation of ICR; parental-origin expression	Growth and placental development abnormalities	Recurrent finding in sperm methylation studies
CDX2	Trophectoderm specification and early lineage segregation	Promoter/enhancer methylation and histone mark transitions	Failed trophectoderm specification and implantation defects	Epigenetic regulation during blastocyst formation
LINE-1 (retrotransposon)	Genome stability and early embryo transcriptional regulation	DNA methylation and piRNA/piRNA-pathway-mediated silencing	Transposon activation, genomic instability, impaired development	Methylation of repeats is critical in the germline/early embryo

Source: Messerschmidt et al. (2014)

4. Impact on Fertility Disorders

4.1. Male Infertility (Abnormal Sperm Methylation)

Transgenerational inheritance. Epigenetic alterations are increasingly recognized as important contributors to human infertility, acting through changes in DNA methylation, histone modifications, and noncoding RNA profiles that affect gamete quality, embryo competence, and reproductive tract function. In males, abnormal sperm epigenetic marks particularly alter DNA methylation at imprinted loci and genome-wide methylation defects associate with impaired spermatogenesis, reduced sperm motility and morphology, and lower fertilization and

pregnancy rates in clinical cohorts (Rotondo et al., 2021; Hosseini et al., 2024). Key imprinted genes repeatedly implicated include H19 and MEST, while methylation changes in genes linked to folate metabolism (for example, MTHFR) and spermatogenic regulation have also been reported; these methylation anomalies can co-occur with disrupted protamine/histone ratios and abnormal small RNA cargo in sperm, jointly compromising sperm chromatin integrity and early zygotic development potential (Rotondo et al., 2021; Hosseini et al., 2024).

4.2. Female Infertility (PCOS and Endometriosis)

Female infertility frequently reflects underlying epigenetic dysregulation, and the diagram's pathway from upstream causes to molecular changes and clinical outcomes helps explain how conditions such as Polycystic Ovary Syndrome (PCOS) and endometriosis develop and impair reproduction. PCOS is characterized by differential DNA methylation and altered microRNA expression in ovarian tissue and granulosa cells that modify genes controlling steroidogenesis, insulin signaling, and folliculogenesis, producing anovulation and subfertility (Crafa et al., 2024).

Endometriosis shows promoter methylation and histone-modification changes at genes involved in inflammation, estrogen signaling, and cell adhesion, which reduce endometrial receptivity and raise implantation failure risk (Crafa et al., 2024). The diagram positions these disease-linked epigenetic signatures as downstream consequences of upstream modifiers, environmental toxicants, metabolic disturbance, age, and ART procedures that alter one-carbon metabolism, epigenetic-enzyme activity, and chromatin states during vulnerable windows such as oocyte growth and preimplantation development (Messerschmidt et al., 2014; Ben Maamar et al., 2021).

Mechanistically, the schematic highlights (Figure 2) specific lesions relevant to female infertility: failure to establish or maintain maternal imprints, aberrant histone-mark retention in oocytes, and maladaptive noncoding-RNA provisioning from the oocyte and surrounding somatic cells. Because maternal de novo methylation occurs late in oocyte growth, nutritional deficits, endocrine disruption, or inflammatory signals during this period can cause locus-specific hypomethylation or hypermethylation at genes required for follicle maturation and endometrial signaling, directly linking exposures to anovulation, poor oocyte competence, and implantation problems (Messerschmidt et al., 2014; Sindik et al., 2024). The diagram's arrows from epigenetic changes to fertility outcomes therefore map the plausible causal chain observed in molecular and clinical studies: altered promoter/enhancer methylation and histone marks change expression of receptivity genes (for example, HOXA10, LIF) and metabolic regulators, producing measurable declines in cycle fecundity and ART success (O'Neill, 2015; Crafa et al., 2024).

Transgenerational considerations in the diagram are especially pertinent: animal models demonstrate that ancestral exposures (endocrine disruptors, nutritional imbalance, stress) can reprogram the germ line via persistent sperm or oocyte DNA-methylation changes, altered small-RNA payloads, or modified histone retention to produce reproductive dysfunction and developmental abnormalities across multiple generations (Ben Maamar et al., 2021). Human data remain more circumstantial because social and genetic confounders complicate inference, yet epidemiologic links between grandparental exposures and descendant outcomes and exposure-associated sperm epigenetic changes in men support the concern that germline epimutations could influence fertility transgenerationally (Hosseini et al., 2024).

The diagram therefore integrates clinical phenotypes (PCOS, endometriosis, implantation failure) with molecular mechanisms and temporal vulnerability, reinforcing translational priorities: targeted epigenomic profiling of ovarian and endometrial tissues and reproductive biofluids, interventions that restore one-carbon and metabolic balance, and ART protocol refinements to avoid perturbing oocyte maturation or preimplantation epigenetic programming (O'Neill, 2015; Ren et al., 2017). Longitudinal human cohorts with paired exposure, tissue-specific epigenomic, and reproductive outcome data, together with mechanistic models testing reversibility

and heritability, are required to move from association to causation and safe clinical application (Ben Maamar et al., 2021).

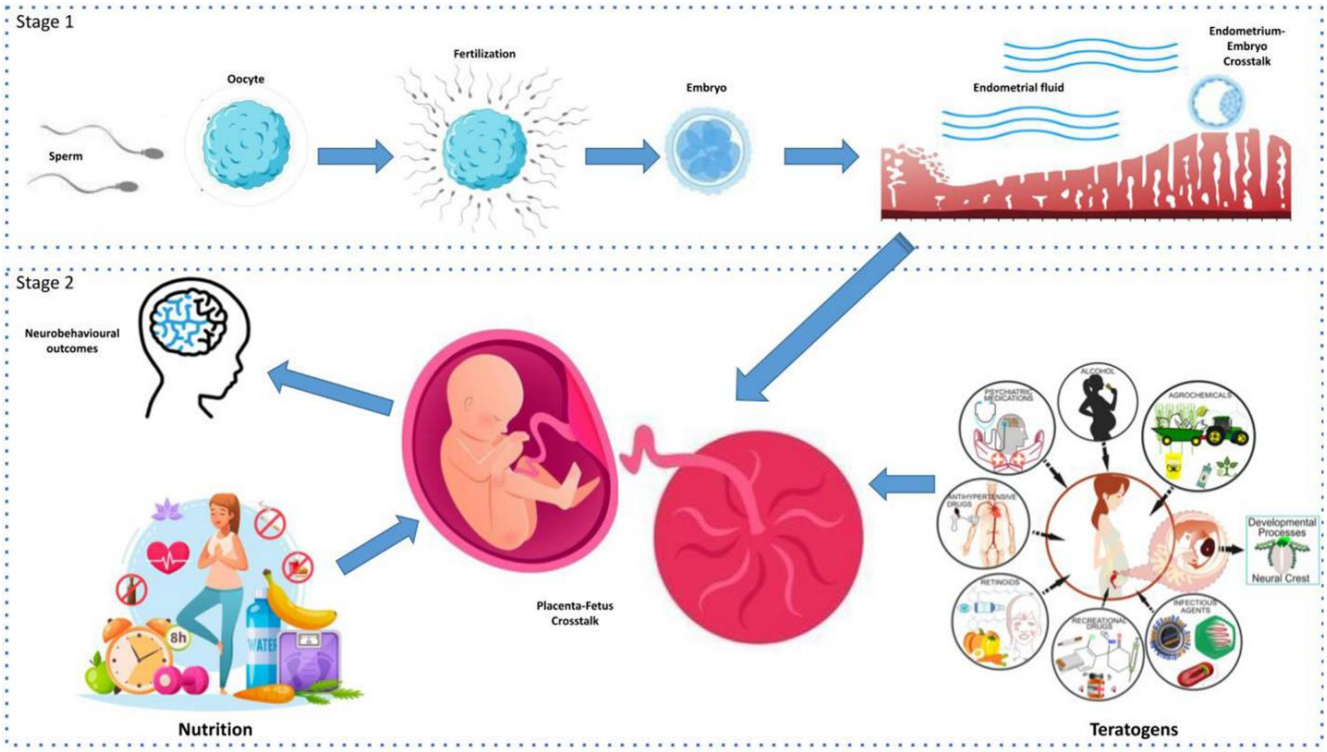

Fig. 2 Epigenetic alterations affect fertility outcomes

Source: Messerschmidt et al. (2014)

5. Clinical and Therapeutic Implications

5.1. Biomarkers for Fertility

Epigenetic drugs. Epigenetic biomarkers hold substantial promise for improving fertility diagnosis, prognosis, and treatment monitoring by providing molecular readouts that reflect gamete quality, endometrial receptivity, and embryo competence beyond what standard semen analysis or morphological assessment can reveal. DNA methylation signatures in sperm at imprinted loci (e.g., H19, MEST) and at genes involved in spermatogenesis correlate with sperm count, motility, and fertilization success, and panels combining targeted methylation markers with sperm small-RNA profiles have shown enhanced discriminatory power for male factor infertility in research cohorts (Rotondo et al., 2021). In women, endometrial DNA methylation and histone-modification patterns at receptivity genes (for example, HOXA10, LIF) vary across the implantation window and between fertile and infertile cycles, supporting methylation- or chromatin-based assays as adjuncts for timing embryo transfer and diagnosing endometrial causes of implantation failure (Clinical Epigenetics Consortium, 2024). Cell-free fetal and reproductive-tissue epigenetic markers detectable in blood or uterine fluid are emerging as minimally invasive options to track reproductive health and ART outcomes, with the potential to stratify patients for tailored interventions and to monitor responses to lifestyle or pharmacologic treatments (e.g., folate supplementation, metabolic control) that influence epigenetic state (Yu et al., 2024).

Translating epigenetic biomarkers into clinical practice requires rigorous analytical validation, reproducible biomarker panels, and prospective evaluation of clinical utility. Important technical considerations include tissue heterogeneity (sperm vs. seminal plasma; endometrium vs. decidua), standardization of sample collection and processing, and selection of robust loci that are minimally confounded by age, smoking, or medication use. Large,

multicenter studies that pair epigenomic readouts with longitudinal reproductive outcomes will be essential to move from promising associations to actionable tests that improve live-birth rates while avoiding overdiagnosis or unnecessary interventions (Clinical Epigenetics Consortium, 2024).

Epigenetic drugs (epidrugs) offer both opportunity and caution for reproductive medicine. In oncology, inhibitors of DNA methyltransferases (DNMT inhibitors such as 5-azacytidine and decitabine) and histone deacetylase inhibitors (HDAC inhibitors) have demonstrated the ability to reactivate silenced genes and remodel chromatin, validating epigenetic modulation as a therapeutic strategy (Johnstone, 2002; Jones & Baylin, 2007). In reproductive contexts, conceptual applications include using targeted epigenetic modulators to restore normal imprinting, rescue aberrant promoter methylation linked to poor gamete function, or improve endometrial receptivity by resetting maladaptive chromatin states. Preclinical models show that transient modulation of epigenetic enzymes can influence folliculogenesis, spermatogenesis, and implantation biology, but the germline and embryo are uniquely sensitive to epigenetic perturbation, and off-target or heritable effects are major safety concerns (Rotondo et al., 2021).

Consequently, current therapeutic prospects in fertility emphasize indirect and precision approaches rather than systemic epidrug exposure. These include: (a) nutritional and metabolic interventions (e.g., optimized folate, methyl donor balance, and weight management) that modulate one-carbon metabolism and thereby influence DNA methylation in gametes and endometrium; (b) localized topical or intrauterine delivery strategies under investigation to minimize systemic exposure; and (c) highly selective small molecules or RNA-based modulators that target specific epigenetic readers, writers, or noncoding-RNA pathways implicated in reproductive dysfunction, with careful preclinical reproductive-toxicity assessment and transgenerational surveillance before clinical application (Rotondo et al., 2021; Yu et al., 2024).

6. Conclusion

Understanding how DNA methylation, histone modifications, and noncoding RNAs influence gamete quality, embryo competence, uterine receptivity, and long-term offspring health is made possible by incorporating epigenetic perspectives into reproductive biology. This helps us understand why certain fertility phenotypes can be produced by environmental exposures, metabolic disorders, aging, and ART interventions, as well as identifying the windows of vulnerability for prevention and intervention. Epigenomic biomarkers provide a clinical pathway to more accurate diagnosis, patient classification, and tissue-specific, targeted approaches. Improved ART culture and handling, dietary optimization of one-carbon metabolism, and reduction of hazardous exposures offer viable, short-term ways to lower epigenetic risk without exposing the germ line to widespread systemic epigenetic medications.

Priority research directions in science include mechanistic models to test the causality and reversibility of defined epigenetic lesions, longitudinal human cohorts that establish a link between reproductive outcomes and well-characterized exposures to tissue-specific epigenomic changes, and a thorough assessment of transgenerational effects to identify which germline changes persist and by what mechanisms. Advancement along these paths promises to translate epigenetic insights into practical strategies that improve fertility, optimize ART outcomes, and promote healthier offspring. However, sustained progress will require harmonized epigenomic assays, interdisciplinary clinical–basic research consortia, and careful ethical and safety frameworks that balance innovation with protection of future generations.

Acknowledgement

We thank all the researchers who contributed to the success of this research work.

Conflict of Interest

The authors declared that there are no conflicts of interest.

Funding

No funding was received for this research work.

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