American Journal of
Biomedical Science & Research

www.biomedgrid.com
ISSN: 2642-1747

Perspective

Genetic and Epigenetic Influences on Fetal DNA in Utero: Current Concepts and Future Perspectives

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To Cite This article: *Stefan Bittmann*, Elisabeth Luchter, Elena Moschüring-Alieva, Genetic and Epigenetic Influences on Fetal DNA in Utero: Current Concepts and Future Perspectives. Am J Biomed Sci & Res. 2026 31(4) AJBSR.MS.ID.004065,* **DOI:** 10.34297/AJBSR.2026.31.004065

Received: June 29, 2026 **Published:** July 03, 2026

Abstract

Human genome includes 3.1 milliards paired bases in a simple chromosome set. To date, there are known thousands of rare genetic diseases in human being, whereas 70 per cent of them are found exclusively in children. Nearly 10-15 per cent of all children treated in intensive care units have a rare genetic disease. The diagnosis of a rare genetic disease is difficult due to the variability of the diseases. Rare pediatric genetic can be mono-or polygenetic of origin. Most of all these single mutations, no matter in what form, occur in stages of fetal development in pregnancy. From that time, an aberrant fetal development is starting inconspicuous, where the physician nor the mother does not recognize any pathological development during pregnancy. There is a big account of different mutations that occur during pregnancy changing the normal development of the fetus in a serious one. The focus of this perspective article is lying on evaluating possible future research aspects of influencing fetal DNA in utero by genetic and epigenetic approaches from getting vulnerable by mutational changes in any way.

Keywords: Fetal DNA, Prenatal diagnosis, DNA methylation, Gene editing, Vulnerability, Genetics, Epigenetics, Mutation, Rare genetic disease, In utero gene therapy

Introduction

Established Fetal Genetics and Prenatal Diagnosis

In 2012, researchers such as Jay Shendure from the University of Washington developed methods to reconstruct the complete genome of a foetus non-invasively from maternal blood and paternal saliva in order to detect mutations early on, not to protect them [1]. This enables testing for genetic diseases without invasive procedures such as amniocentesis. At the Salk Institute, researchers such as Juan Carlos Izpisúa Belmonte, in 2015, developed gene-editing techniques using nucleases to eliminate mitochondrial mutations in egg cells or early embryos, which could prevent the transmission of hereditary diseases [2]. Such methods aim at preventive editing, but are still experimental and not established as a "protective shield" in the uterus during pregnancy. Studies show that fetal DNA naturally enters the maternal circulation by microchimerism, which could have potential protective effects but does not constitute active protective technology. Advances in CRISPR-based embryo genome editing allow corrections. Concerning target identification mutations were priorized in high-risk genes based on prenatal NIPT diagnostics from cHDNA. Safety tests could be performed in animal embryos, then later in human-equivalent models and safety studies on mosaic effects and immune responses. Current research focuses on prenatal diagnostics rather than active protection.

Epigenetic Regulation and Environmental Interventions

In the womb, fetal DNA is primarily exposed to epigenetic influences. These factors do not alter the underlying genetic sequence itself; instead, they use external stimuli to regulate which genes are switched on or off. Key influencing factors include maternal lifestyle and nutrition. A lack of essential nutrients significantly affects development. Avoiding alcohol, nicotine, and certain medications is also crucial, as these substances directly interfere with embryonic development. Environmental factors are

pollutants, air pollution, pesticides, and other toxins that can impair fetal growth and cellular function. Stress and psychological strain include chronic stress and maternal anxiety trigger the release of stress hormones, which cross the placenta to affect the fetus and shape its development. Infections and inflammation include maternal pathogens or inflammation within the body can directly disrupt the genetic material and organogenesis.

Experimental Prenatal or Embryo Interventions

There are comprehensive overviews of the times when genetic mutations occur most frequently in monogenic diseases. The "moment of mutation" can be de novo or inherited, with most cases occurring in the germ line during meiosis or in early embryogenesis. Mutations in monogenic diseases typically occur in the following phases. Germline mutations most commonly occur during meiosis in the germ cells of the parents, spermatogenesis or oogenesis, leading to hereditary forms. These account for the majority of cases, as they are stably inherited. De novo mutations are new in the affected individual, often in the zygote or early embryonic stages and up to approximately the 8-cell stage. They are prominent in dominant diseases such as neurofibromatosis type 1 or Rett syndrome. Somatic mutations are rarely causal, as they are not inherited; they only affect postzygotic cells and play a role in mosaic forms. Genetic disorders in a fetus can be inherited or occur spontaneously, de novo mutations, as a "one-off" event. Technology integration includes package of CRISPR base editing in liposomal nanoparticles that cross the placental barrier and reach foetal cells without off-target effects. Delivery and activation could be intrauterine injection or intravascular infusion in pregnancy between week 8 to 12.

Ethical and Safety Constraints

Possible developmental steps include the target identification, technology integration, safety tests and evaluation of the overall challenge of these interventions. Ethical hurdles include germline editing, placental passage and long-term risks such as uncontrolled genetic changes make this experimental.

Key Timeframes for Genetic Mutations

Key timeframes for genetic mutations in pregnancy include preconception and conception, which impress as meiosis errors. Parental germ cells may possess mutations due to age or environmental factors, leading to chromosomal abnormalities like trisomies. Mutations or genetic alterations during pregnancy can occur at different stages, ranging from preconception to later developmental phases, with the first trimester being the most critical period.

All or None-Period (weeks 1-2)

The "All or None"-period describes a period after fertilization where extreme damage to the early embryo usually results in miscarriage, or it survives without defects.

First Trimester (0-13 weeks)

The first trimester (weeks 1-13 -crucial stage) include organogenesis. Major structures like the heart, arms, legs, and neural tube are forming. This is the period of highest susceptibility to mutations caused by teratogens or spontaneous replication errors. The highest mutation rate and cell division is highest during early embryogenesis, leading to the highest rate of de novo mutations. The placental formation describes confined placental mosaicism, where mutations exist in the placenta but not the fetus.

Second/Third Trimester (week 14-birth)

In the second and third trimesters functional defects are prominently found while major structural organs are formed in the first trimester, mutations or exposures in later stages are more likely to cause functional deficits rather than structural defects. Another important role includes tissue development. Continued growth allows for mutations in specific somatic tissues to potentially expand. Risk factors and types of events include the role of maternal and paternal age. Advanced age increases the risk of aneuploidy due to meiotic errors. Spontaneous mutations often occur as random events during early cell division, often as a result of a mutation in a single sperm or egg, with a high proportion of these mutations arising during early embryonic growth. Environmental exposures to teratogens (alcohol, medications, infections) during organogenesis can cause developmental abnormalities.

Genetics and Epigenetics

Genetics and epigenetics operate on two different levels: Genetics (mutations) refers to the actual sequence of building nucleotides in DNA. Mutations are copying errors or forms of damage. Epigenetics does not determine whether these errors occur-, do not alter nucleotide sequence directly but can influence genome stability and DNA damage response [3,4]. Epigenetics involves chemical markers, such as methyl groups or histone modifications on the DNA that control whether or not a gene is read, without altering the genetic code itself. Although epigenetics neither triggers nor prevents mutations, it can influence the extent of DNA damage and the repair process. DNA packaging density is an epigenetic mechanism determine how tightly DNA is packed. If DNA is very tightly packed and inactive in certain regions, it is often less accessible to the cell's own repair mechanisms, which can increase the risk of permanent mutations in those areas. Repair genes, if epigenetic processes silence genes responsible for repairing DNA damage, the cell can no longer fix the resulting mutations. Epigenetics controls gene behavior and activity, but not the structure of the DNA sequence itself. However, it can influence susceptibility to mutations by regulating DNA protection and repair. Directly influencing epigenetics to specifically control the proportion of fetal DNA in maternal blood, the fetal fraction, is currently not feasible in a clinical or practical setting. However, the underlying biological processes are highly complex. Cell-free fetal DNA in the mother's blood originates almost exclusively from dying cells in the placenta. It is not produced directly by the fetus but is a byproduct of placental development and cell turnover. Placental development, function, and lifespan, and thus the release of DNA, are heavily regulated by epigenetic mechanisms such as DNA methylation. Theoretically, factors such as maternal diet, extreme stress, environmental toxins,

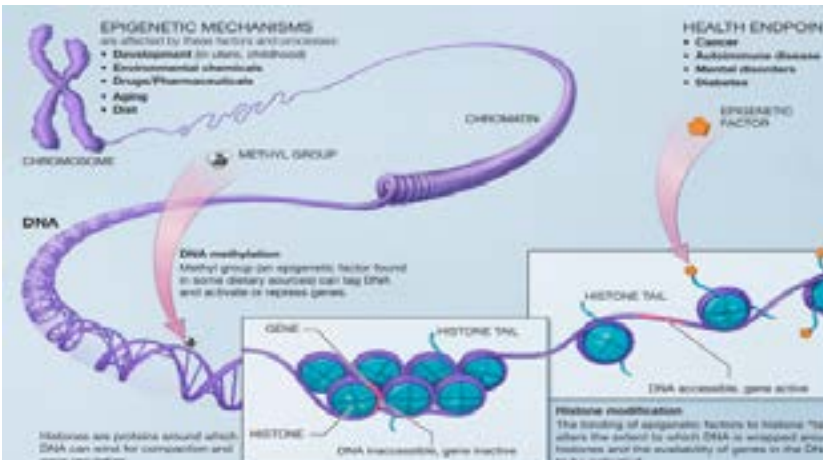
or lifestyle choices can alter epigenetic patterns in the placenta. These influences cannot be manipulated to increase the fetal DNA fraction but could play a role in prenatal diagnostics. Instead, they may lead to placental dysfunction or pregnancy complications. In such cases, increased release of fetal DNA is often a symptom of placental impairment rather than a desired optimization. The absolute amount and percentage of fetal DNA are determined primarily by purely biological factors like gestational age. The fetal fraction rises steadily from early pregnancy, reaching its peak in the second trimester. The mother's body mass index is the most significant influencing factor; significant excess weight dilutes the fetal DNA due to the higher volume of maternal DNA present.

Epigenetic Factors on Fetal DNA

Fetal DNA methylation does not alter the genetic sequence itself but protects the genome by silencing transposable segments, such as transposons [5]. This prevents these elements from replicating or jumping to new locations within the genome, thereby averting insertional mutations and preserving chromosomal stability during embryonic development. This essential protective mechanism operates through the following processes by silencing of "jumping genes" (transposons). Approximately 45% of the human genome consists of mobile genetic elements and remnants of ancient viruses. Fetal DNA methylation inactivates these sequences in the germline and the embryo, minimizing the risk of DNA breaks, deletions, or the disruption of vital genes. Maintenance of genomic stability will be performed by methylation of repetitive DNA sequences that prevent chromosomes from misaligning or breaking. This inhibits structural mutations and the unequal distribution of genetic material during rapid cell division. Epigenetic programming and protection against environmental influences is established by methylation patterns during the fetal period protects developing pluripotent cells from sustaining DNA damage in response to cellular stress or external factors. Deficient methylation can compromise this protection, leading to aberrant programming or an increased mutation rate.

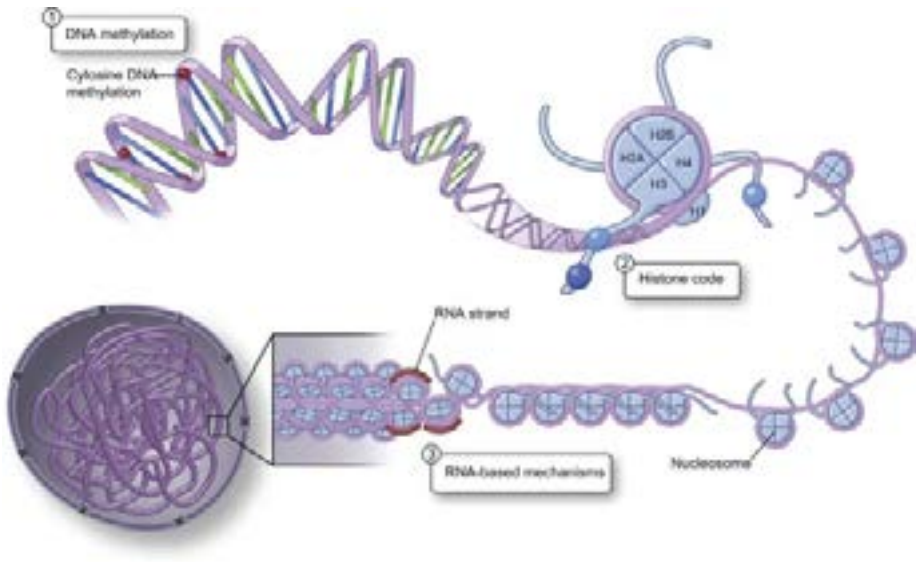
Epigenetic Techniques to Silence a Gene

The most advanced epigenetic technique to silence a gene is CRISPR epigenome Editing [6,7]. Unlike traditional gene editing, it does not cut the DNA [8]. Instead, it uses a deactivated Cas enzyme to attach methyl groups to the gene's promoter [9-11]. This adds chemical "decorations" that fold the chromatin tightly and turn the gene off. Here is a breakdown of the leading techniques used to silence genes epigenetically (Figure 1-3). CRISPR-dCas9 epigenetic editors uses a catalytically dead Cas9 (dCas9) guided to a specific gene [12]. It does not edit the genetic code. Instead, it is fused to a repressor domain and DNA methyltransferases (like DNMT3A/3L). It adds repressive histone modifications and DNA methylation to the gene's promoter, shutting down transcription. Advantages are highly specific, leaves the DNA sequence unharmed, heritable through cell division, and to a different degree reversible if a demethylase enzyme is used. RNA interference (RNAi) /siRNA techniques introduce Small, Double-Stranded RNA molecules (siRNA) into the cell [13]. These molecules guide the RNA-Induced Silencing Complex (RISC) to the target messenger RNA. The effect is to destroy the mRNA before it can be translated into a protein. It can also recruit proteins that cause long-term, localized chromatin silencing. Advantage is highly efficient for knocking down gene expression and very straightforward to design and administer. The silencing is typically transient, meaning the cell must constantly produce or be re-administered the siRNA to maintain the effect. Zinc Finger or TALEN epigenetic repressors work similar to CRISPR, this technique relies on engineered Zinc Finger proteins or TALENs that bind to a precise DNA sequence, rather than a guide RNA. The DNA-binding protein is fused to a repressor domain which physically blocks transcription factors and induces local heterochromatin formation. The advantage is it can be smaller in size than CRISPR machinery, which is useful for certain viral vector deliveries.



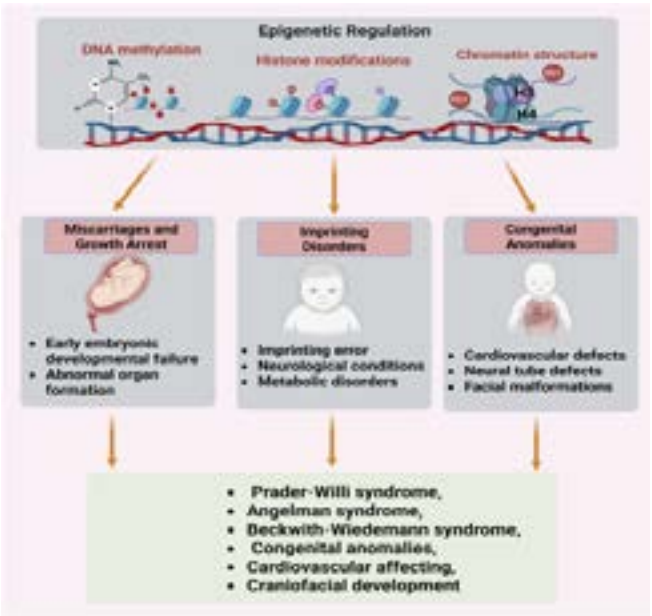
Note*: Epigenetic mechanisms are affected by several factors and processes including development in utero and in childhood, environmental chemicals, drugs and pharmaceuticals, aging, and diet. DNA methylation is what occurs when methyl groups, an epigenetic factor found in some dietary sources, can tag DNA and activate or repress genes. Histones are proteins around which DNA can wind for compaction and gene regulation. Histone modification occurs when the binding of epigenetic factors to histone "tails" alters the extent to which DNA is wrapped around histones and the availability of genes in the DNA to be activated. All of these factors and processes can have an effect on people's health and influence their health possibly resulting in cancer, autoimmune disease, mental disorders, or diabetes among other illnesses. National Institutes of Health - http://commonfund.nih.gov/epigenomics/figure.aspx; Reuse is verified.

Figure 1: Epigenetic Mechanism and Influence on Genes.\



Note*: Three fundamental mechanisms of epigenetic gene regulation. Epigenetic mechanisms of gene expression are subserved by three distinct, yet highly interrelated, mechanisms. 1) DNA methylation refers to the addition of a methyl group to the 5-position of cytosine in the context of CpG dinucleotides to define the "fifth base of DNA." 2) The fundamental repeating unit of chromatin is the nucleosome comprised of an octamer of core histone proteins. Posttranslational modifications of the amino-terminal tails of histone proteins (light and dark blue balls) and the density of these proteins per unit length of DNA, can importantly affect chromatin structure and constitute a putative "histone code." 3) RNA-based mechanisms have also recently been shown to impact on the higher-order structure of chromatin. From: Epigenetics in the Vascular Endothelium, Journal of Applied Physiology; Respiratory, Environmental and Exercise Physiology 109(3):916-26, 2010. **DOI:***10.1152/japplphysiol.00131.2010*; Reuse is verified.

Figure 2: Three fundamental mechanisms of epigenetic gene regulation



Note*: From: Front. Cell Dev. Biol., 08 May 2026 Sec. Epigenetics and Genome Architecture. Volume 14 - 2026 | *https://doi.org/10.3389/fcell.2026.1791177*, Reuse is verified.

Figure 3: Epigenetic regulation in early embryogenesis: mechanisms, developmental programming, and transgenerational implications.

Future Perspectives and Limitations

Theoretically, it is conceivable to protect the DNA of a developing fetus from mutations [14,15]. Modern biomedicine, genetics and epigenetics are already exploring approaches in this direction, albeit within strict ethical and scientific limits [16-18]. The combination of preimplantation genetic diagnosis and CRISPR/Cas9 technology could have a role in the future instead of treating the fetus in the womb [19]. Embryos created via in vitro fertilization can be screened for genetic defects prior to implantation or, theoretically, corrected using gene editing. Protection against external influences include protecting fetal DNA in the womb from mutations that damage genetic material, caused by ionizing radiation, X-rays, or chemical substances, is currently achieved through precautionary measures. These include abstaining from alcohol and nicotine, as well as avoiding infections and certain medications. Genetic interventions on the fetus are purely in theory. In utero gene therapy is an innovative new area of research. However, attempts to date have aimed to cure existing, severe genetic diseases rather than to prevent mutations across the board. There is a strong global scientific consensus prohibiting interventions in the germline, genetic changes that would be passed on to future generations.

Ethical and Regulatory Constraints

There is a fundamental ethical distinction between interventions involving somatic cells and those affecting the germline. Modifications to human embryos or germ cells irreversibly alter the genetic makeup of all subsequent generations. Future generations cannot provide informed consent for genetic alterations. The boundary between curing hereditary diseases and enhancing human traits (e.g., intelligence, muscle mass) becomes blurred. Acceptance of people with disabilities or illnesses could diminish if these conditions come to be viewed as “preventable.” The high cost of CRISPR therapies threatens to genetically cement the divide between rich and poor. Artificially accelerated genetic changes in animals and plants could wipe out entire species or cause ecosystems to collapse. Erroneous cuts (off-target effects) can trigger cancer or create new genetic defects.

Conclusion

The fetal DNA in pregnancy is influenced by varies environmental, nutritional, psychological, genetic and epigenetic influences, that could play an important role in the beginning of a serious genetic pediatric disease by mutational shifts in the DNA sequence as well as from epigenetic viewpoint and their role in activating or silencing genes by DNA methylation or histone modification on the DNA. Future research efforts have to evaluate further epigenetic influences on switching genes on or off. Epigenetic approaches could play an important part of curing a disease by silencing a nucleotide sequence on the DNA. The questionis, when you can silence a gene completely, is it possible to silence only single nucleotide sequences, where especially spontaneous point mutations occurred. The question is, can we silence single regions of mutational impairment prenately by epigenetic approaches to repair serious regions on the DNA by DNA-methylation of histone modifications. A very early diagnosis, better prenatally, is necessary to introduce epigenetic curing options as early as possible to prevent the fetus from silent ongoing genetic disease in pregnancy without treating it.

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Consent and Ethical Approval

It is not applicable.

Competing Interests

Author has declared that no competing interests exist.

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