

Epigenetics and fertility

Abstract

More than 200 genes have been identified that cause infertility in mice, while many of the genes involved in human fertility remain unknown. The completion of the genomic sequencing project and the hap map project can facilitate the identification of effective genes in fertility. Many infertility forms seem to be complex diseases. The causes of infertility can be male (40%), female (40%), or both male and female factors (20%). For each couple or individual, more than one factor may be the cause of infertility. Epigenetics is a series of hereditary changes that alter the pattern of expression of genes without altering DNA sequences. Recently, epigenetics has been studied in areas such as diabetes, heart disease, autoimmune disease, and fertility. Among the factors that cause epigenetic implications for the reproductive health of women and men, the influence of the environment is mostly considered. Besides the genetic causes, Epigenome of fertility, Smoking, age, obesity or diabetes mellitus, Mother Pregnancy PKU, men's genital abnormalities, Imprinted genes are included in the list of effective factors on fertility physiology and biology.

Keywords: fertility, epigenome, male factor, female factor

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Introduction

Infertility is a genetically heterogeneous disease that has multifactorial etiology, and affects approximately 22% of couples of the reproductive age group and has a major effect on reproductive health.¹ In about 50% of these cases, the infertility problem is in association with a male factor or cooperation of male and female factors.² In men, the main cause of infertility is anatomical defects, gametogenesis impairment, endocrinopathies, immunological problems, perineal duct deficiency and peripheral toxicity.³ Infertile men may exhibit phenotypic abnormalities or sperm abnormalities.⁴ Phenotypic abnormalities include Klinefelter syndrome (KFS),⁵ Congenital and Vascular Disorders (CAVD),⁶ Kalman Syndrome (KS),⁷ cryptorchidism,⁸ Hypospadias,⁹ Obscuration Outpatient Genitalia, and Androgenic Depression Syndrome (AIS).¹⁰ On the other hand, infertility in infertile men with abnormal sperm parameters is considered idiopathic infertility.¹¹ Infertility in infertile men who do not have abnormal sperm parameters is defined as without explanation infertility.^{12,13} The present studies have shown that CNVs of duplicates and/or microscopic deletions affect approximately 20% of the human genome.¹⁴ Except for changes in the number of Y chromosome genes, CNVs are not yet known as the cause of male infertility.¹⁵

Epigenome of fertility

The Epigenome is the structural changes in the genome with unchanged nucleotide sequences that affect the gene expression.¹⁶ Although it is considered that the genetic code is stable in all cells for the whole life except for disease, aging and personal traits,¹⁷ the dynamic epigenetic code is specific to a tissue that adapts the individual's phenotype to the environment and other factors.^{18,19} Among the epigenetic processes, DNA methylation, histone modification, and chromatin remodeling are the most common mechanisms.²⁰ CpG islands within the promoter region form approximately 40% of the mammalian genes and are susceptible genomic sites for environmental factors influences on gene behavior.²¹ The N terminus of histones includes amino acids that are affected by methylation, acetylation, phosphorylation, ubiquitylation, and sumoylation.²² The human

sperm nucleus, which retains 10-15% of its original histone content, can distribute histones in a heterozygous state within the genome.^{22,23} Several studies have shown that histones that are stored in the sperm DNA are bound to specific regions to convey epigenetic information to the embryo.²⁵ It has been proven that the production of reactive oxygen species in semen is positively related to the fragmentation of DNA and is negatively related to DNA methylation.²⁶ In addition, there is a negative relationship between DNA methylation and fragmentation of DNA.^{27,28} Infertile men have more fragmentation of DNA and higher levels of reactive oxygen species than fertile men.²⁹ The results indicate that DNA damage caused by oxidative stress may facilitate abnormal DNA methylation.^{28,30} There is an epigenetic instability during gametogenesis and embryogenesis that alters gene expression pattern in primordial cells through changes in DNA methylation levels which are high in embryonic stem cells (73.2% to 85%), but in female primordial germ cells (PGCs) is less than 10% on day E13.5.³¹

Smoking and fertility

Studies of women who had IVF have shown that smoker women need higher doses of gonadotropins to stimulate their ovaries,¹ and rates of abortion are higher in these women.² Smoker men have lower sperm count and lower sperm motility.³ In these individuals, abnormalities increase in the shape and function of the sperm.^{4,5} Moreover, it is identified that smoking has a direct impact on DNA methylation in cancer, heart disease and respiratory diseases, as well as on the development of normal fetuses during pregnancy. Preparing the methylation profile (methyl) and comparing it between smokers and non-smokers can help to predict the onset of a disease.⁶

Age related fertility

The most commonly observed relationship between genetics and reduced fertility in women is the effect of maternal age. Trisomy associated with maternal age is usually the most common factor in the loss of pregnancy. Approximately 25% of all spontaneous abortions of the first trimester are trisomy. Most of the other aneuploid pregnancies

(like monosomies and autosomal trisomies of chromosomes 1 and 19) will be lost before reaching the clinical diagnosis. Genome-wide Association Studies (GWAS) is trying to understand biological pathways which are linked to the effectiveness of age for fertility and its health outcomes.⁶

Epigenetic and fetal evolution

Type 1 or type 2 diabetes occurs during pregnancy in 6% to 9% of pregnant women.⁷ Mother's obesity or her lack of mobility have been identified as having epigenetic causes for pregnancy type 2 diabetes (T2D)⁸ which increases the fetal sickness potential by altering the embryonic environment and the gene programming.^{9,10} Change in some cellular receptors in preeclampsia,¹¹ GDM,¹² and intrauterine growth retardation¹³ has been observed. In addition to the mother diseases that influence fetal health, the stress of parents who undergo IVF is reportedly associated with changes in the gene expression and effect on the birth weight of the baby.¹⁴

Maternal pregnancy diseases

Maternal diabetes in pregnancy increases 2-3 times the risk of congenital anomalies.¹⁵ Significant increases in premature births have been reported in mothers with autoimmune diseases, especially those with type 1 diabetes mellitus.¹⁶ Also, mothers with Phenylketonuria (PKU) are at increased risk of microcephaly and intellectual impairment.¹⁷ Maternal pregnancy epilepsy increases the risk of NTD from 5% to 10% due to anti-epileptic drugs (AED),¹⁸ and elevation of genitourinary anomalies like hypoplasia, fetal heart disease and limb defects risks.¹⁹ Smoking in almost 14% of pregnant women have exposed the fetus to 450 harmful substances in cigarette smoke and increased pregnancy complications like abortions, still births, and postpartum deaths.²⁰

Epigenetics and infertility in men

Recent studies have shown that at least 30 million men worldwide are infertile including the highest rate of African and Eastern European.²¹ Genetic factors account for 15% to 30% of male infertility with the most involvement of *DAZ* (Yq11.23),²² *RBMY* (Yq11.223), *USP9Y* (Yq11.2) mutations, *SYCP3*, *PLK4*.²³ Some cases of male sterility are attributed to epigenetic events of spermatogenesis such as chromosome condensation, genomic packaging in the spermatid nucleus, and the presence of retro-transposons.²⁴ Genital abnormalities found in 80% of children with a gender-related syndromic α -thalassemia are a disturbance in the new type of DNA methyltransferase and thus an expression change dependent on methylation.²⁵ Hypermethylation of promoter regions of tumor suppressor genes²⁶ and the consequence silencing, and oncogenes hypomethylation,²⁷ alter the behavior and function of germ cells²⁸ that do not naturally imply methylation²⁹ and imprinting of DNA and are Totipotent, therefore cause tumorigenesis of the testicular germ cells through molecular changes, such as CpH (CpA/CpC/CpT) methylation.³⁰ These tumors are 98% of all the testicular neoplasms and also the most common malignancy among young men.³¹

Imprinted genes and fertility

14.4% of 92 men with low spermatid parameters had abnormal paternal imprinting and 20.26% of them had abnormal maternal imprinting in maternally imprinted genes *PLAG1*, *DIRAS3* and *MEST*.³² Hypermethylation of *MEST* has been observed in infertile men with less than 40% sperm motility and less than 5% normal

sperm morphology, indicating the effect of abnormal methylation patterns on spermatogenesis.³³ Men with idiopathic infertility had 9.6% methylation compared with controls that contained only 4.3% *MEST* methylation.³³ The results of the research show that increasing methylation has a linear relationship with reduced sperm motility.³⁴

With the help of the antiprotamin antibody, it has been shown that infertile men with natural spermatogenesis have 90% of immunopositive spermatids, while infertile men with abnormal spermatogenesis have 75% of immunopositive spermatids. In the second group, the transfer of nuclear protamines was earlier and caused impaired development of spermatids.³⁵ Given that about 45% of the human genomes are transposons that induce insertion mutations, and genomic instability resulting in gene expression variation and performing genetic innovation.³⁶ The TEs have a silencing power before the onset of spermatogenesis that can damage the chromatin during the movement, so they themselves will be methylated to avoid proliferation.³⁷

Conclusion

When talking about an organ system and confronting it with various environmental and maternal factors, there are certainly numerous genetic and non-genetic changes that can affect the normal development of the placenta and the fetus. The role of the imprinted genes in the development and function of human placenta and the implications of assisted reproductive technology (ART) such as IVF on the regulation of these genes should be taken into account more than before.^{38,39} Recent investigations show that the causes of most female infertility such as PCOS, endometriosis, and idiopathic cases, as well as the failure of implantation and the related consequences that ultimately affect the mother and the embryo, are affected by the physiological environment of pregnancy.¹⁴ The critical changes leading to infertility can be identified by examining the entire genome and epigenome in empirical studies, and determining the precise mechanisms of environmental effects in the manipulation of epigenetic marks.⁴⁰ Understanding the nature of gametic epigenome pattern has been considered as a new insight for infertility treatment through the modification of the epigenome code in specific genetic elements without changing the heritage of nucleotides.⁴¹ The study of epigenetic changes during gametogenesis, fertilization, after birth to maturation and puberty with the utilization of NGS and expression profiles are being completed and identified.^{42,43} Determining the transcriptome of progenitor cells by NGS, introduces active or inactive genes that are responsible for the timely differentiation and translation of normal developmental adjustment that can also be used as a reference for targeted environmental changes of genes in the benefit of the individual and reproductive health.⁴⁴ In addition, the results of these studies can help in the management and treatment of a number of reproductive disorders. Also, finding the normal pattern of Epigenome in germ cells can help in the production of normal gametes from other tissues of the body via IPs or from isolated somatic cells originated from the gonads.^{45,46}

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Conflicts of interest

The author declares there is no conflict of interest.

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