Journal of Obstetrics, Gynecology and Cancer Research | ISSN: 2476-5848

Evaluation of Epigenetic Factors in Surrogacy: A Mini-Review

Samira Negahdari[1], Maede Nilechi[2], Seyed Farzad Hosseini[1], Mehdi Forouzesh[1], Azin Samimi[1], Mohsen Maleknia[3,4], Samira Valiyari[1]*

1. *Legal Medicine Research Center, Legal Medicine Organization, Tehran, Iran*
2. *Department of Biology, School of Basic Science, Science and Research Branch, Islamic Azad University, Tehran, Iran*
3. *Thalassemia and Hemoglobinopathy Research Center, Health Research Institute, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran*
4. *Student Research Committee, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran*

Article Info

10.30699/jogcr.8.2.95

Received: 2022/10/17;
Accepted: 2023/01/13;
Published Online: 22 Feb 2023;

Use your device to scan and read the article online

Corresponding Information:
Samira Valiyari,
Legal Medicine Research Center, Legal Medicine Organization, Tehran, Iran

Email: samiravaliyari@yahoo.com

ABSTRACT

Surrogacy is an assisted reproductive technology in which the intended parents allocate the gestation and birth to another woman named the surrogate mother. From this view of surrogacy, although there is no genetic relationship between surrogate mother and fetus, this approach is faced with some issues such as the epigenetic effect, which is the environmental influence on gene expression. Epigenetics plays a critical role in ovulation, spermatogenesis, and embryonic growth, development, and health. DNA methylation, histone modification, and non-coding RNAs activity are the major epigenetic mechanisms. In this mini-review, we focus on the possibility of epigenetic alterations during in vivo embryo culture and intrauterine life.

Keywords: DNA methylation, Epigenetic, Reproductive techniques, Surrogate mother

Introduction

Surrogacy is one of the Assisted Reproductive Technologies (ARTs) in which the intended parents, who are unable to conceive in usual ways, allocate the gestation and birth to another woman known as the surrogate mother. The surrogate mother carries the fetus during the pregnancy, gives birth to the child, and then delivers the baby to the intended parents. There is no genetic link between the surrogate mother and the child. The embryo entering the surrogate mother's uterus is results from the sperm and oocytes of the original parents or donors using the In Vitro Fertilization (IVF) **(1-4)**. Infertility, medical conditions, sexual identity disorders, similar problems, and social issues are important factors in selecting this method. Women with severe Mullerian duct anomalies or congenital uterine or vaginal anomalies are the main candidates for this method. Other potential candidates include individuals with Mayer-Rokitansky-Küster-Hauser syndrome, who have a female genotype but phenotypically, have congenital uterine or vaginal ageneses or anomalies, and patients with androgen insensitivity syndrome. Also, women who have had a previous hysterectomy, women with Turner syndrome, women with a history of multiple miscarriages, and women who have not benefited from long-term infertility treatments. A history of severe cardiovascular disease or medical conditions that expose the fetus to high teratogen levels are other reasons for selecting this method **(5, 6)**.

The surrogacy process includes ovarian hyperstimulation, ovulation induction, oocyte retrieval, IVF, embryo (blastocyst) culture, embryo selection, and embryo transfer into the uterus of the surrogate mother. This process is closely related to the IVF technique. Epigenetic means beyond genetic that involves multiple processes of hereditary alterations in gene expression without DNA sequence changes. DNA methylation, histone modification, and changes in non-

coding RNAs (ncRNAs) are the central epigenetic mechanisms **(7)**. Epigenetic alterations by internal and external factors can also be inherited by future generations. In mammals, embryogenesis cannot be adequately done without epigenetic mechanisms. Embryonic cells are prone to epigenetic alterations because gametes' epigenetic programming occurs during early differentiation in gametogenesis and before implantation **(8)**. In the present mini-review, we intended to briefly mention the various studies and effective aspects of epigenetic alterations in ARTs, especially surrogacy, as well as reviewing the available studies in this field.

Methods

In this mini-review, all the data were compiled from electronic databases including Google Scholar, PubMed, Scopus, and Web of Science (ISI). The search was conducted without a time restriction, up to February 2021 using the following keywords: "Reproductive Technologies", "Surrogacy", "Epigenetic", "DNA methylation" and "embryo".

Results and Discussion

Epigenetic Alterations in Prenatal Life

Epigenetics plays a critical role in ovulation, spermatogenesis, and embryonic growth, development, and health. Epigenetic dysregulation can result in silencing or improper expression of certain genes, thereby leading to disturbances. Human studies have shown that the biology of the surrogate mother can reprogram the embryo's epigenome and that any disturbance in the early stages of life, especially the critical period of prenatal life, will have programmed effects on lifelong health **(9)**. This fact proves the biological link between the surrogate mother and the child in addition to the proven emotional relationship, and the surrogate mother can alter the child at the epigenetic level. Epigenetic alterations in ARTs may lead to clinical problems, including failure in embryo implantation, miscarriage, intrauterine growth retardation with placental dysfunction, phenotypical changes, and even genomic imprinting syndromes **(2, 10)**.

Prenatal DNA Methylation

Conserved non-exon elements rich in CpG dinucleotides in the human genome are the main targets for epigenetic alterations. DNA methylation is the most common epigenetic alteration, in which a methyl group is added to the C5 position of the nucleotide cytosine **(11)**. This alteration does not change the DNA sequence. If this methylated region is close to the gene, it can lead to underexpression or even silencing **(12, 13)**. In the active mitotic cells, DNA methyltransferases (DNMTs) perform the methylation using donor groups, including methionine, S-adenosyl methionine, choline, vitamin B6, vitamin B12, zinc, betaine, folic acid, etc. **(14)**. Methylated CpG dinucleotides condensate and inactivate the chromatin and subsequently suppress the transcription. These effects are directly exerted by interfering with the activities of transcription factors and indirectly exerted by using the Methyl-CpG-Binding Domains (MBDs), which adsorbs the Histone Deacetylases (HDACs) and Histone Methyltransferases (HMTs) **(15)**. In early embryogenesis, epigenetic silencing of genes from paternal or maternal origins is mediated by the maintenance methylation activity of DNMT1, while the tissue-specific gene expression and postnatal DNA methylation require spontaneous methylation activity of DNMT3a and DNMT3b **(16, 17)**.

Genetic imprinting is an epigenetic alteration that causes the preferential rather than definitive expression of the parental allele. During the critical period of genomic imprinting, which is from conception to 2 yr old age and is known as the 1000 days, epigenetic alterations can play a critical role in development, thereby influencing the risk of future development of chronic diseases such as cardiovascular diseases, diabetes, obesity, etc. **(18)**. The imprinted genes are often tissue-specific and are abundantly found in regions close to CpG islands or CG-rich sequences. Genomic imprinting is removed in primordial gametes during gametogenesis and is then re-established gender-specifically in the next stages. This reprogramming is essential for maintaining the inheritance pattern in imprinted loci **(19)**.

DNA of the spermatozoa is methylated differentially at several maternal and paternally imprinted sites, and also has a unique pattern of general methylation. ARTs such as Intra Cytoplasmic Sperm Injection (ICSI) and IVF may increase the risk of epigenetic abnormalities and impact embryonic growth and development by using immature spermatozoa, which may not be appropriately imprinted or may not have a maintained methylation pattern (Figure 1) **(20)**.

Delayed oocyte growth and maturation, which prevents imprinting maintenance at the right time, ovulation induction, or use of older oocytes, which are abundantly acetylated during mitosis, can result in epigenetic impairments **(21)**. Human and murine studies have suggested that gonadotropins used in ART can release metaphase II oocytes with defective or unstable imprinting patterns and induce molecular changes in oocytes with adverse effects on genomic imprinting maintenance in embryogenesis **(22, 23)**. Oocytes from ovarian hyperstimulation are immature and require in vitro culture to achieve maturity. Genomic imprinting analyses in oocytes from ovulation induction showed abnormalities in 4 imprinted murine genes of PEG1 (paternally expressed genes 1), KCNQ1OT1 (KCNQ1 opposite strand/antisense transcript 1), Zac (Zinc-activated ion channel), and H19 mice in comparison with the oocytes from natural ovulation **(24)**. In addition, human studies have reported that imprinted genes, including SNRPN

(small nuclear ribonucleoprotein polypeptide N), H19, PEG1/MEST (mesoderm-specific transcript), KCNQ1OT1, and their regulatory regions are prone to abnormal changes in methylation or gene expression pattern in some pre-implanted embryos **(25, 26)**.

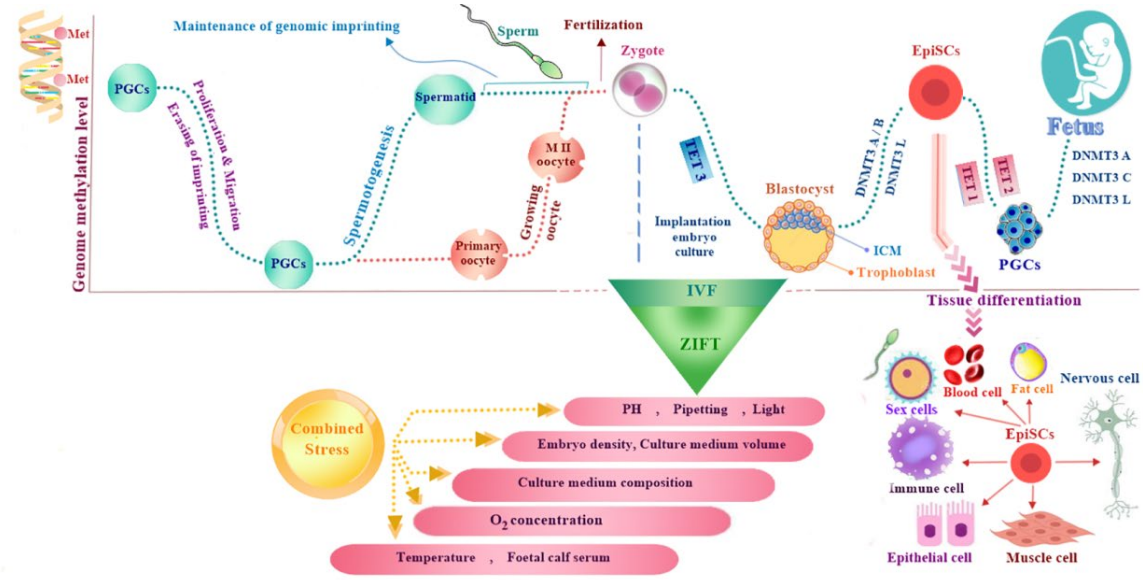

Figure 1. DNA methylation changes in the gametogenesis and the ART procedure. PGC, primordial germ cell; TET, tubal embryo transfer; DNMT, DNA methyltransferase; ICM, inner cell mass; EpiSCs, epiblast stem cells; IVF, in vitro fertilization; ZIFT, zygote intrafallopian transfer.

A previous study showed hypomethylation in the group using ARTs compared to the group with natural conception by investigating several genomic arrays **(27)**. Also, while investigating ovulation induction in human models, another study reported that oocytes from ovulation induction in ARTs showed hypomethylation of PEG1 and H19, which was compatible with murine models **(28)**. Also, there are other similar findings including the abnormal methylation of the differentially methylated regions (DMRs) in gene H19, which are normally methylated in the maternal allele, the demethylation of DMRs in the maternal LITI locus, which is normally methylated, in Beckwith-Wiedemann syndrome, and the decreased level of HDAC and incomplete acetylation of H3K9 in in-vitro-cultured oocytes **(29, 30)**.

There is defective SNRPN imprinting in the Prader-Willi and Angelman syndromes. The SNRPN methylation level is higher in children conceived with ISCI than IVF and normal conception. However, the difference in the methylation level is slight in children born with IVF compared to spontaneous pregnancies **(31)**. The glucose tolerance gene expression level is different in children born with IVF and normal pregnancy, and children born with IVF have different lipid profiles, fasting blood sugar, body fat distribution, and cardiovascular performance. These findings confirm the relationship between epigenetic alterations and increased risk of cardiovascular diseases **(32, 33)**.

Prenatal Histone Modifications

Post-translational histone modifications are other epigenetic mechanisms that have been widely studied. The variability of alterations and amino acid sequences of histones, including lysine and arginine methylation and acetylation, serine and threonine phosphorylation, and ubiquitination, can be considered as a type of coding **(34)**. The enzyme HDAC1, which plays a critical role in the chromatin restructuring, is significantly decreased in oocytes, the first stage of cleavage, and two-cell embryos that have undergone in vitro maturation. This suggests that in vitro maturation results in decreasing transcription in genes such as HDAC1 **(35)**. A previous study reported a defective chromatin restructuring due to impaired histone acetylation in in-vitro-cultured oocytes **(36)**. Another study showed that in vitro culture caused alteration at the histone levels and in the expression of the genes Igf2 (insulin-like growth factor 2) and Oct4 (octamer-binding transcription factor 4) in mice, confirming the impact of culture media **(37)**. The same group reported in another study that expression of human imprinted genes H19 and 3MEST and histone H3 lysine 9 (H3K9) acetylation in in-vitro-cultured blastocysts was significantly increased compared to in-vivo-cultured blastocysts. However, the histone H3 lysine 9 (H3K9) methylation was significantly decreased **(38)**.

Prenatal Functions of ncRNAs

NcRNAs control many aspects of the activities of gene regulatory networks, including transcription and post-translational regulations. MicroRNAs (miRNAs) are a major group of these RNAs. They are small, non-coding endogenous molecules that are approximately 21 to 23 nucleotides in length and suppress gene expression by mRNA translation inhibition or mRNA

degradation (39, 40). The surrogate mother is related to the embryo through the transplacental transfer of microchimeric molecules (small chemical molecules), nutrients, and antibodies (41, 42). During embryonic development, there are several miRNAs in the endometrial fluid of women carrying an embryo from a donated oocyte. These molecules encode information on the expression regulation of embryonic and, eventually, fetal genes. This indicates the impact of the surrogate mother's genome on the embryo's genetic development. This effect determines which of the child's genes will be expressed (43).

There are several reports of the remarkable effect of maternal lifestyle, including smoking, nicotine or caffeine addiction, alcohol consumption, psychological stress, etc., on the epigenetic alterations in neurological disorders (44-46). A previous study compared the miRNA expression levels in 25 placentas obtained at birth from women with a history of tobacco use during pregnancy and reported a significant decrease in miR-16, miR-21, and miR-146a levels due to maternal tobacco use (47). Their result suggested that the lower expression of miR-16 and miR-21 in the placenta does associate with reduced birth weight. In addition, miR-146a was significantly reduced following nicotine use in the immortal human trophoblastic cell lines (a cell line derived from villi cells in the third-trimester), while levels of other miRNAs were not changed. Down regulation of these miRNA upregulates the targets of these miRNA and may have further effects downstream for both placenta and fetus. Another study compared levels of miR-233 and miR-155 in the placentas and umbilical cords of a group of mothers with nicotine exposure and found increased levels of miR-233 (48). Ovarian hyperstimulation in mice was associated with decreased expression of miRNAs, including miR-122, miR-144, and miR-211, which are involved in neuronal migration and differentiation. However, further studies are needed to illustrate the relationship between epigenetic alterations and the risk of neurological disorder development in ARTs.

Effective Factors on Epigenetic Alteration in Surrogacy

For the first time, Barker suggested the fetal programming hypothesis. He reported that intrauterine events are much more important than postnatal events in terms of gene expression patterns and that chronic diseases, including cardiovascular diseases, obesity, diabetes, etc. are not often caused by only genetic or lifestyle factors. However, they are affected by intrauterine events during pregnancy (49). The fetus receives genetic material from the parents or gamete donors, but the surrogate mother can also affect the fetus. For example, she exerts these effects via diet, and physical activity is done as working or daily activities, the air she breathes, and surrounding sounds. Xenochemicals, including alcohol, tobacco smoke, biophenol, etc. are considered teratogens and can cross the placenta and cause fetal functional defects. Also, it has been reported that endogenous factors such as maternal stress in pregnancy and hypoxia have a significant effect on children's health during childhood and possibly adulthood (50, 51). All these factors should be considered when choosing the ideal surrogate mother. There are reports that mothers using donated oocytes have a significant effect on the fetus, and there are similarities between the child and other family members in families using donated oocytes.

Since there is a close relationship between monocarbon metabolism and diet, DNA methylation can be influenced by the maternal diet (52). It has been reported that children from mothers with a low-calorie diet during pregnancy have a higher risk of diabetes development later in life (44, 53). It has also been found that gestational diabetes alters the embryo/fetus's methylation pattern, placental tissue, and umbilical cord blood (54). Genes with altered methylation patterns due to maternal diabetes are involved in pathways of metabolic diseases, and it was suggested that maternal diabetes alters the child's metabolism epigenetically. It was reported that carbohydrate intake in early pregnancy and childhood obesity are associated with the DNA methylation level of the RXRA (retinoid X receptor alpha) gene promoter in the fetal umbilical cord (55).

Maternal pre-pregnancy obesity and gestational diabetes can significantly increase leptin gene methylation (56). A previous study showed that the normally methylated maternal gene MEST is significantly hypomethylated in fetuses from mothers with gestational diabetes (57). Pre-pregnancy folate intake was associated with several serum biomarker levels, including methionine, choline, and S-adenosyl methionine, and plays an essential role in lymphocyte DNA methylation (58, 59). Evaluation of the methylation levels of imprinted genes in umbilical cord blood from women taking folate supplementation after 12 weeks of gestation showed that the supplementation was associated with increased methylation of IGF2 and decreased methylation of PEG3 and LINE1 (60).

Various studies have discovered a second genome. This genome includes the human microbiome genomes actively interacting with sperm and oocyte genomes through metabolites and causes epigenetic alterations (61, 62). Microbial colonization, especially the microbial flora of the amniotic fluid, placenta, and uterus, can prenatally affect fecal microbial flora development (63). The postnatal impaired microbiome can be due to skin contact, route of delivery, diet, and antibiotic use. These effects play significant roles in the development of disease risk, including chronic cardiovascular diseases, diabetes, obesity, allergic diseases, asthma, and autoimmune diseases through epigenetic alterations (64, 65). Environmental factors, including chemical pollution, tobacco use, alcohol, radiation, temperature changes, and other external stresses can affect growth, metabolism, risk of disease development in future generations, and behavioral

disorders such as schizophrenia through epigenetic programming **(66, 67)**. These environmental factors can impair DNA methylation and DNA fragmentation, as in infertile men in whom DNA damage by oxidative stress leads to DNA methylation **(68-70)**.

Antepartum exposure to high levels of stress, including environmental pollutions, physiological stress, or depression, can increase the risk of fetal somatic system growth retardation or adulthood disturbances. The effects of prenatal stress on fetal and childhood developments, including immune system performance, brain development, and behavior development, have been extensively investigated in animal studies. According to animal studies, maternal cortisol levels can adversely affect fetal hypothalamic-adrenal axis development **(71, 72)**. Stress leads to the maternal hypothalamic-adrenal axis activation and subsequent glucocorticoid secretion that can reach the fetus through placental transfer **(73, 74)**.

Maternal cortisol levels increase during pregnancy; maternal stress also increases maternal cortisol and decreases the activity of placental enzymes that reduce glucocorticoid levels. These enzymes neutralize cortisol's harmful effects by converting it to an inactive form before reaching the fetus **(75)**.

A previous study investigated the relationship between antepartum stress exposure of mother and methylation level in the promoter of gene NR3C1 **(76)**. Increased depression in the third trimester was associated with increased methylation of binding sites NGFI-A in the neonatal gene NR3C1, which subsequently stimulates the hypothalamic-adrenal axis **(77)**. Also, antepartum stress and anxiety were significantly associated with 1F promoter methylation in the CpG region of the NR3C1 gene **(51)**.

Evaluation of the Impact of in Vitro Culture Conditions on Embryo's Growth and Epigenome

There are extensively discussed risks and ambiguities regarding the effects of pre-implantation culture on embryonic physiology and epigenetics, despite the advantages of ARTs. Human studies have shown the association of ovarian hyperstimulation, high levels of gonadosteroids, blastocyst culture, culture media, and embryo cryopreservation in ARTs with intrauterine growth retardation and changes in birth weight pattern. This association is probably the result of epigenetic alterations **(30, 78)**. In ARTs, exogenous gonadotropins are maintained at high levels during the critical period of implantation. There are several reports that exogenous gonadotropins may cause epigenetic alterations in four imprinted genes Peg1, Kcnq1ot1, Zac, and H19, and interfere with oocyte and embryonic development **(1, 79)**. A previous study reported a relationship between imprinted genes and fetal growth retardation as well as placental disorders **(20)**.

Since ARTs are simultaneous with the essential epigenetic reprogramming events, another important issue is the impact of culture media and culture conditions on an embryo's growth and epigenome. Human studies have reported that the culture media can cause several adverse effects, including defective implantation, low implantation rate, growth disorders, low quality of the embryo, decreased trophoblastic growth, and decreased a number of embryonic cells **(2, 80, 81)**. It has been reported that the culture media causes a wide range of metabolic, developmental, and cellular changes in pre-implantation murine embryos that were effective on metabolic pathways **(82)**. In the following, it was shown that the culture media could also affect human embryos in the pre-implantation stages **(83)**. Studies found that the use of G5 and human tabul fluid culture media causes the different expression of the genes of several pathways in human embryos. Also, the addition of a growth factor to the culture media of growing embryos had unexpected effects on the gene expression pattern **(81, 84)**. However, a murine study showed that the placenta and embryos' gross anatomy was not different in embryos cultured in different environments. However, no molecular studies were included in the last study **(85)**.

The oxygen concentration in oocyte or embryonic cultures effectively affects metabolism, protein synthesis, and protein functions and plays a critical role in embryo implantation and survival **(86)**. Oxygen levels in the fallopian tube, where natural fertilization occurs, have been reported to be 1%-9% in different mammalian species **(87)**. Human embryos that are cultured in IVF at 20% oxygen concentration, which is similar to the atmosphere's oxygen concentration, can be very different from those in in vivo conditions **(86)**. According to human studies, oxygen concentration levels similar to atmospheric oxygen concentration causes oxidative stress and oxygen-free radical activation **(88, 89)**. Embryo culture under high O_2 concentrations can hurt blastocyst growth, cell count, and embryonic metabolism in many species. Increased active oxygen levels can change protein levels and lipid functions and harm DNA and cell membrane integrity (Figure 1) **(23)**.

The fetus receives genetic material from the parents or donors of sperm and oocyte, but factors including physiological stress, antepartum depression of the surrogate mother, food, daily and physical activities of the surrogate mother, and levels of environmental pollution exposure can increase the risk of fetal somatic system growth retardation or adulthood disturbances. Several human studies have shown that hormonal therapy can cause epigenetic reprogramming of gametes in the early stages of embryogenesis, and that epigenetic alterations in the resulting oocyte can be maintained during the embryonic period. These results suggest that the pre-implantation environment can affect neurological growth and development and lead to behavioral changes in adulthood.

Conclusion

This review emphasizes DNA methylation, histone modification, and changes in ncRNAs are the central epigenetic mechanisms that can be affected by in vitro embryo culture conditions and surrogate mother lifestyle. However, to make significant headway in understanding the impact of surrogacy on epigenetic modifications on the human conceptus, further detailed and long-term studies are required. Identification of epigenetic modifications on surrogacy may allow us to develop new interventions, preventive measures, and follow-up strategies.

Acknowledgments

The authors thank all those who helped them write this article.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

1. Soderstrom-Anttila V, Wennerholm UB, Loft A, Pinborg A, Aittomaki K, Romundstad LB, et al. Surrogacy: outcomes for surrogate mothers, children and the resulting families-a systematic review. Hum Reprod Update. 2016;22(2):260-76. [DOI:10.1093/humupd/dmv046] [PMID]
2. Simopoulou M, Sfakianoudis K, Tsioulou P, Rapani A, Anifandis G, Pantou A, et al. Risks in Surrogacy Considering the Embryo: From the Preimplantation to the Gestational and Neonatal Period. Biomed Res Int. 2018;2018:6287507. [DOI:10.1155/2018/6287507] [PMID] [PMCID]
3. Rezaei Z, Adabi K, Sadjadi A. A Comparison of Endometrial Thickness and Pregnancy Outcomes in Two Methods of Intrauterine Injection and Subcutaneous Injection of GCSF in Infertile Women Candidates for IVF. J Obstet Gynecol Cancer Res. 2020;5(2):39-43. [DOI:10.30699/jogcr.5.2.39]
4. Zademodares S, Abbaspour M, Anbarluei M, Rahmati N, Fathi M, Naeiji Z. In vitro Fertilization outcome in Patients with Polycystic Ovary Syndrome: Role of Age and Maternal Body Weight. J Obstet Gynecol Cancer Res. 2022;6(4):161-6. [DOI:10.30699/jogcr.6.4.161]
5. Beale JM, Creighton SM. Long-term health issues related to disorders or differences in sex development/intersex. Maturitas. 2016;94:143-8. [DOI:10.1016/j.maturitas.2016.10.003] [PMID]
6. Dar S, Lazer T, Swanson S, Silverman J, Wasser C, Moskovtsev SI, et al. Assisted reproduction involving gestational surrogacy: an analysis of the medical, psychosocial and legal issues: experience from a large surrogacy program. Human Reproduction. 2015;30(2):345-52. [DOI:10.1093/humrep/deu333] [PMID]
7. Chen J, Wang Y, Wang C, Hu J-F, Li W. LncRNA functions as a new emerging epigenetic factor in determining the fate of stem cells. Front Genet. 2020;11:277. [DOI:10.3389/fgene.2020.00277] [PMID] [PMCID]
8. Yang X, Liu M, Li M, Zhang S, Hiju H, Sun J, et al. Epigenetic modulations of noncoding RNA: a novel dimension of Cancer biology. Mol Cancer. 2020;19(1):64. [DOI:10.1186/s12943-020-01159-9] [PMID] [PMCID]
9. Ge SQ, Lin SL, Zhao ZH, Sun QY. Epigenetic dynamics and interplay during spermatogenesis and embryogenesis: implications for male fertility and offspring health. Oncotarget. 2017;8(32):53804-18. [DOI:10.18632/oncotarget.17479] [PMID] [PMCID]
10. Huntriss J, Balen AH, Sinclair KD, Brison DR, Picton HM. Epigenetics and Reproductive Medicine (Scientific Impact Paper No. 57). BJOG. 2018;125(13):e43-e54. [PMID] [DOI:10.1111/1471-0528.15240]
11. Tavalaee M, Razavi S, Nasr-Esfahani MH. Influence of sperm chromatin anomalies on assisted reproductive technology outcome. Fertil Steril. 2009;91(4):1119-26. [DOI:10.1016/j.fertnstert.2008.01.063] [PMID]
12. Maunakea AK, Chepelev I, Cui K, Zhao K. Intragenic DNA methylation modulates alternative splicing by recruiting MeCP2 to promote exon recognition. Cell Res. 2013;23(11):1256-69. [DOI:10.1038/cr.2013.110] [PMID] [PMCID]
13. Nematollahi A, Rezaeian A, Nasr Esfahani MH, Department of Animal Biotechnology M, Reproductive Biomedicine Research Center, Tavalaee RIf. The role and importance of DNA methylation in spermatogenesis process. Med Sci J Islamic Azad Univ. 2021;31(1):1-13.
14. Iannello A, Rolla S, Maglione A, Ferrero G, Bardina V, Inaudi I, et al. Pregnancy Epigenetic Signature in T Helper 17 and T Regulatory Cells in Multiple Sclerosis. Front Immunol. 2018;9:3075. [DOI:10.3389/fimmu.2018.03075] [PMID] [PMCID]
15. Green BB, Marsit CJ. Select Prenatal Environmental Exposures and Subsequent Alterations of Gene-Specific and Repetitive

Element DNA Methylation in Fetal Tissues. Curr Environ Health Rep. 2015;2(2):126-36. [PMCID] [DOI:10.1007/s40572-015-0045-0] [PMID]

16. Breton-Larrivee M, Elder E, McGraw S. DNA methylation, environmental exposures and early embryo development. Anim Reprod. 2019;16(3): 465-74. [DOI:10.21451/1984-3143-AR2019-0062] [PMID] [PMCID]
17. Rashidi M, Tavalaee M, Abbasi H, Nomikos M, Nasr-Esfahani MH. Increased de novo DNA methylation enzymes in sperm of individuals with varicocele. Cell J. 2021;23(4):389.
18. Niemitz EL, Feinberg AP. Epigenetics and assisted reproductive technology: a call for investigation. Am J Hum Genet. 2004;74(4):599-609. [DOI:10.1086/382897] [PMID] [PMCID]
19. Gokbuget D, Blelloch R. Epigenetic control of transcriptional regulation in pluripotency and early differentiation. Development. 2019;146(19). [DOI:10.1242/dev.164772] [PMID] [PMCID]
20. La Rovere M, Franzago M, Stuppia L. Epigenetics and Neurological Disorders in ART. Int J Mol Sci. 2019;20(17). [DOI:10.3390/ijms20174169] [PMID] [PMCID]
21. Bowdin S, Allen C, Kirby G, Brueton L, Afnan M, Barratt C, et al. A survey of assisted reproductive technology births and imprinting disorders. Hum Reprod. 2007;22(12):3237-40. [DOI:10.1093/humrep/dem268] [PMID]
22. Denomme MM, Mann MR. Genomic imprints as a model for the analysis of epigenetic stability during assisted reproductive technologies. Reproduction. 2012;144(4):393-409. [PMID] [DOI:10.1530/REP-12-0237]
23. Ventura-Junca P, Irarrazaval I, Rolle AJ, Gutierrez JI, Moreno RD, Santos MJ. In vitro fertilization (IVF) in mammals: epigenetic and developmental alterations. Scientific and bioethical implications for IVF in humans. Biol Res. 2015;48:68. [PMID] [DOI:10.1186/s40659-015-0059-y] [PMCID]
24. Arnaud P. Genomic imprinting in germ cells: imprints are under control. Reproduction. 2010; 140(3):411-23. [DOI:10.1530/REP-10-0173] [PMID]
25. Sanchez-Delgado M, Court F, Vidal E, Medrano J, Monteagudo-Sanchez A, Martin-Trujillo A, et al. Human Oocyte-Derived Methylation Differences Persist in the Placenta Revealing Widespread Transient Imprinting. PLoS Genet. 2016;12(11): e1006427. [DOI:10.1371/journal.pgen.1006427] [PMID] [PMCID]
26. Ivanova E, Canovas S, Garcia-Martinez S, Romar R, Lopes JS, Rizos D, et al. Correction to: DNA methylation changes during preimplantation development reveal interspecies differences and reprogramming events at imprinted genes. Clin Epigenetics. 2020;12(1):96. [DOI:10.1186/s13148-020-00887-5] [DOI:10.1186/s13148-020-00857-x]
27. Melamed N, Choufani S, Wilkins-Haug LE, Koren G, Weksberg R. Comparison of genome-wide and gene-specific DNA methylation between ART and naturally conceived pregnancies. Epigenetics. 2015;10(6):474-83. [PMID] [PMCID] [DOI:10.4161/15592294.2014.988041]
28. Hiura H, Okae H, Chiba H, Miyauchi N, Sato F, Sato A, et al. Imprinting methylation errors in ART. Reprod Med Biol. 2014;13(4):193-202. [PMCID] [DOI:10.1007/s12522-014-0183-3] [PMID]
29. Krzyzewska IM, Alders M, Maas SM, Bliek J, Venema A, Henneman P, et al. Genome-wide methylation profiling of Beckwith-Wiedemann syndrome patients without molecular confirmation after routine diagnostics. Clin Epigenetics. 2019; 11(1):53. [DOI:10.1186/s13148-019-0649-6] [PMID] [PMCID]
30. El Hajj N, Haaf T. Epigenetic disturbances in in vitro cultured gametes and embryos: implications for human assisted reproduction. Fertil Steril. 2013; 99(3):632-41. [DOI:10.1016/j.fertnstert.2012.12.044] [PMID]
31. Pinborg A, Loft A, Romundstad LB, Wennerholm UB, Soderstrom-Anttila V, Bergh C, et al. Epigenetics and assisted reproductive technologies. Acta Obstet Gynecol Scand. 2016;95(1):10-5. [DOI:10.1111/aogs.12799] [PMID]
32. Kobayashi N, Miyauchi N, Tatsuta N, Kitamura A, Okae H, Hiura H, et al. Factors associated with aberrant imprint methylation and oligozoospermia. Sci Rep. 2017;7. [DOI:10.1038/srep42336] [PMID] [PMCID]
33. Nomura Y, Lambertini L, Rialdi A, Lee M, Mystal EY, Grabie M, et al. Global methylation in the placenta and umbilical cord blood from pregnancies with maternal gestational diabetes, preeclampsia, and obesity. Reprod Sci. 2014;21(1):131-7. [PMID] [DOI:10.1177/1933719113492206] [PMCID]
34. Singh G, Singh V, Schneider JS. Post-translational histone modifications and their interaction with sex influence normal brain development and elaboration of neuropsychiatric disorders. Biochim Biophys Acta Mol Basis Dis. 2019;1865(8):1968-81. [DOI:10.1016/j.bbadis.2018.10.016] [PMID]
35. Ma P, Schultz RM. HDAC1 and HDAC2 in mouse oocytes and preimplantation embryos: Specificity versus compensation. Cell Death Differ. 2016; 23(7):1119-27. [DOI:10.1038/cdd.2016.31] [PMID] [PMCID]
36. Gioia L, Barboni B, Turriani M, Capacchietti G, Pistilli MG, Berardinelli P, et al. The capability of reprogramming the male chromatin after fertilization is dependent on the quality of oocyte

maturation. Reproduction. 2005;130(1):29-39. [DOI:10.1530/rep.1.00550] [PMID]

37. Jahangiri M, Shahhoseini M, Movaghar B. The Effect of Vitrification on Expression and Histone Marks of Igf2 and Oct4 in Blastocysts Cultured from Two-Cell Mouse Embryos. Cell J. 2018; 19(4):607-13.

38. Jahangiri M, Shahhoseini M, Movaghar B. H19 and MEST gene expression and histone modification in blastocysts cultured from vitrified and fresh two-cell mouse embryos. Reprod Biomed Online. 2014; 29(5):559-66. [DOI:10.1016/j.rbmo.2014.07.006] [PMID]

39. Huang Y, Shen XJ, Zou Q, Wang SP, Tang SM, Zhang GZ. Biological functions of microRNAs: a review. J Physiol Biochem. 2011;67(1):129-39. [DOI:10.1007/s13105-010-0050-6] [PMID]

40. Arfat Y, Chang H, Gao Y. Stress-responsive microRNAs are involved in re-programming of metabolic functions in hibernators. J Cell Physiol. 2018;233(4):2695-704. [DOI:10.1002/jcp.26034] [PMID]

41. Zhang J, Li H, Fan B, Xu W, Zhang X. Extracellular vesicles in normal pregnancy and pregnancy-related diseases. J Cell Mol Med. 2020;24(8):4377-88. [DOI:10.1111/jcmm.15144] [PMID] [PMCID]

42. Sills ES, Anderson RE, McCaffrey M, Li X, Arrach N, Wood SH. Gestational surrogacy and the role of routine embryo screening: Current challenges and future directions for preimplantation genetic testing. Birth Defects Res C Embryo Today. 2016; 108(1):98-102. [DOI:10.1002/bdrc.21112] [PMID]

43. Kennedy EM, Hermetz K, Burt A, Everson TM, Deyssenroth M, Hao K, et al. Placental microRNA expression associates with birthweight through control of adipokines: results from two independent cohorts. Epigenetics. 2021;16(7):770-82. [PMID] [DOI:10.1080/15592294.2020.1827704] [PMCID]

44. Franzago M, Santurbano D, Vitacolonna E, Stuppia L. Genes and Diet in the Prevention of Chronic Diseases in Future Generations. Int J Mol Sci. 2020; 21(7). [DOI:10.3390/ijms21072633] [PMID] [PMCID]

45. Rauschert S, Melton PE, Burdge G, Craig JM, Godfrey KM, Holbrook JD, et al. Maternal Smoking During Pregnancy Induces Persistent Epigenetic Changes Into Adolescence, Independent of Postnatal Smoke Exposure and Is Associated With Cardiometabolic Risk. Front Genet. 2019;10: 770. [DOI:10.3389/fgene.2019.00770] [PMID] [PMCID]

46. Zakarya R, Adcock I, Oliver BG. Epigenetic impacts of maternal tobacco and e-vapour exposure on the offspring lung. Clin Epigenetics. 2019; 11(1):32. [DOI:10.1186/s13148-019-0631-3] [PMID] [PMCID]

47. Maccani MA, Padbury JF, Marsit CJ. miR-16 and miR-21 expression in the placenta is associated with fetal growth. PLoS One. 2011;6(6):e21210. [DOI:10.1371/journal.pone.0021210] [PMID] [PMCID]

48. Herberth G, Bauer M, Gasch M, Hinz D, Roder S, Olek S, et al. Maternal and cord blood miR-223 expression associates with prenatal tobacco smoke exposure and low regulatory T-cell numbers. J Allergy Clin Immunol. 2014;133(2):543-50. [DOI:10.1016/j.jaci.2013.06.036] [PMID]

49. Barker DJ. In utero programming of chronic disease. Clin Sci. 1998;95(2):115-28. [DOI:10.1042/CS19980019]

50. Mason S, Zhou FC. Editorial: Genetics and epigenetics of fetal alcohol spectrum disorders. Front Genet. 2015;6:146. [PMID] [PMCID] [DOI:10.3389/fgene.2015.00146]

51. Palma-Gudiel H, Cordova-Palomera A, Leza JC, Fananas L. Glucocorticoid receptor gene (NR3C1) methylation processes as mediators of early adversity in stress-related disorders causality: A critical review. Neurosci Biobehav Rev. 2015;55: 520-35. [DOI:10.1016/j.neubiorev.2015.05.016] [PMID]

52. Pizzorusso T, Tognini P. Interplay between Metabolism, Nutrition and Epigenetics in Shaping Brain DNA Methylation, Neural Function and Behavior. Genes (Basel). 2020;11(7). [DOI:10.3390/genes11070742] [PMID] [PMCID]

53. Alejandro EU, Mamerto TP, Chung G, Villavieja A, Gaus NL, Morgan E, et al. Gestational Diabetes Mellitus: A Harbinger of the Vicious Cycle of Diabetes. Int J Mol Sci. 2020;21(14). [DOI:10.3390/ijms21145003] [PMID] [PMCID]

54. Ruchat SM, Houde AA, Voisin G, St-Pierre J, Perron P, Baillargeon JP, et al. Gestational diabetes mellitus epigenetically affects genes predominantly involved in metabolic diseases. Epigenetics. 2013; 8(9):935-43. [DOI:10.4161/epi.25578] [PMID] [PMCID]

55. Zhang J, Ma X, Wang H, Ma D, Huang G. Elevated methylation of the RXRA promoter region may be responsible for its downregulated expression in the myocardium of patients with TOF. Pediatr Res. 2014;75(5):588-94. [DOI:10.1038/pr.2014.17] [PMID]

56. Lesseur C, Armstrong DA, Paquette AG, Li Z, Padbury JF, Marsit CJ. Maternal obesity and gestational diabetes are associated with placental leptin DNA methylation. Am J Obstet Gynecol. 2014;211(6):654 e1-9. [PMID] [PMCID] [DOI:10.1016/j.ajog.2014.06.037]

57. Zeisel SH. Importance of methyl donors during reproduction. Am J Clin Nutr. 2009;89(2):673S-7S.

[DOI:10.3945/ajcn.2008.26811D] [PMID] [PMCID]

58. Li Y. Epigenetic Mechanisms Link Maternal Diets and Gut Microbiome to Obesity in the Offspring. Front Genet. 2018;9:342. [PMID] [PMCID] [DOI:10.3389/fgene.2018.00342]

59. Tserga A, Binder AM, Michels KB. Impact of folic acid intake during pregnancy on genomic imprinting of IGF2/H19 and 1-carbon metabolism. FASEB J. 2017;31(12):5149-58. [DOI:10.1096/fj.201601214RR] [PMID] [PMCID]

60. Haggarty P, Hoad G, Campbell DM, Horgan GW, Piyathilake C, McNeill G. Folate in pregnancy and imprinted gene and repeat element methylation in the offspring. Am J Clin Nutr. 2013;97(1):94-9. [DOI:10.3945/ajcn.112.042572] [PMID]

61. Stsepetova J, Baranova J, Simm J, Parm U, Roop T, Sokmann S, et al. The complex microbiome from native semen to embryo culture environment in human in vitro fertilization procedure. Reprod Biol Endocrinol. 2020;18(1):3. [PMID] [PMCID] [DOI:10.1186/s12958-019-0562-z]

62. Donkin I, Barres R. Sperm epigenetics and influence of environmental factors. Mol Metab. 2018;14:1-11. [PMID] [PMCID] [DOI:10.1016/j.molmet.2018.02.006]

63. Theis KR, Romero R, Winters AD, Greenberg JM, Gomez-Lopez N, Alhousseini A, et al. Does the human placenta delivered at term have a microbiota? Results of cultivation, quantitative real-time PCR, 16S rRNA gene sequencing, and metagenomics. Am J Obstet Gynecol. 2019;220(3): 267 e1- e39. [DOI:10.1016/j.ajog.2018.10.018] [PMID] [PMCID]

64. Lelu K, Laffont S, Delpy L, Paulet PE, Perinat T, Tschanz SA, et al. Estrogen receptor alpha signaling in T lymphocytes is required for estradiol-mediated inhibition of Th1 and Th17 cell differentiation and protection against experimental autoimmune encephalomyelitis. J Immunol. 2011; 187(5):2386-93. [DOI:10.4049/jimmunol.1101578] [PMID]

65. Surace AEA, Hedrich CM. The Role of Epigenetics in Autoimmune/Inflammatory Disease. Front Immunol. 2019;10:1525. [PMID] [PMCID] [DOI:10.3389/fimmu.2019.01525]

66. Richetto J, Meyer U. Epigenetic Modifications in Schizophrenia and Related Disorders: Molecular Scars of Environmental Exposures and Source of Phenotypic Variability. Biol Psychiatry. 2021;89 (3):215-26. [DOI:10.1016/j.biopsych.2020.03.008] [PMID]

67. Ruiz-Hernandez A, Kuo CC, Rentero-Garrido P, Tang WY, Redon J, Ordovas JM, et al. Environmental chemicals and DNA methylation in adults: a systematic review of the epidemiologic evidence. Clin Epigenetics. 2015;7:55. [PMCID] [DOI:10.1186/s13148-015-0055-7] [PMID]

68. Alahmar AT. Role of Oxidative Stress in Male Infertility: An Updated Review. J Hum Reprod Sci. 2019;12(1):4-18. [PMID] [PMCID] [DOI:10.4103/jhrs.JHRS_150_18]

69. Chen Z, Gong L, Zhang P, Li Y, Liu B, Zhang L, et al. Epigenetic Down-Regulation of Sirt 1 via DNA Methylation and Oxidative Stress Signaling Contributes to the Gestational Diabetes Mellitus-Induced Fetal Programming of Heart Ischemia-Sensitive Phenotype in Late Life. Int J Biol Sci. 2019;15(6):1240-51. [DOI:10.7150/ijbs.33044] [PMID] [PMCID]

70. Menezo YJ, Silvestris E, Dale B, Elder K. Oxidative stress and alterations in DNA methylation: two sides of the same coin in reproduction. Reprod Biomed Online. 2016;33(6): 668-83. [DOI:10.1016/j.rbmo.2016.09.006] [PMID]

71. Cao-Lei L, Veru F, Elgbeili G, Szyf M, Laplante DP, King S. DNA methylation mediates the effect of exposure to prenatal maternal stress on cytokine production in children at age 13(1/2) years: Project Ice Storm. Clin Epigenetics. 2016;8:54. [PMCID] [DOI:10.1186/s13148-016-0219-0] [PMID]

72. DeSocio JE. Epigenetics, maternal prenatal psychosocial stress, and infant mental health. Arch Psychiatr Nurs. 2018;32(6):901-6. [DOI:10.1016/j.apnu.2018.09.001] [PMID]

73. Barha CK, Salvante KG, Jones MJ, Farre P, Blais J, Kobor MS, et al. Early post-conception maternal cortisol, children's HPAA activity and DNA methylation profiles. J Dev Orig Health Dis. 2019; 10(1):73-87. [DOI:10.1017/S2040174418000880] [PMID]

74. Glover V, O'Connor TG, O'Donnell K. Prenatal stress and the programming of the HPA axis. Neurosci Biobehav Rev. 2010;35(1):17-22. [DOI:10.1016/j.neubiorev.2009.11.008] [PMID]

75. Hogg K, Blair JD, McFadden DE, von Dadelszen P, Robinson WP. Early onset pre-eclampsia is associated with altered DNA methylation of cortisol-signalling and steroidogenic genes in the placenta. PLoS One. 2013;8(5):e62969. [PMCID] [DOI:10.1371/journal.pone.0062969] [PMID]

76. Oberlander TF, Weinberg J, Papsdorf M, Grunau R, Misri S, Devlin AM. Prenatal exposure to maternal depression, neonatal methylation of human glucocorticoid receptor gene (NR3C1) and infant cortisol stress responses. Epigenetics. 2008;3(2): 97-106. [DOI:10.4161/epi.3.2.6034] [PMID]

77. Hompes T, Izzi B, Gellens E, Morreels M, Fieuws S, Pexsters A, et al. Investigating the influence of maternal cortisol and emotional state during pregnancy on the DNA methylation status of the

glucocorticoid receptor gene (NR3C1) promoter region in cord blood. J Psychiatr Res. 2013;47(7): 880-91. [DOI:10.1016/j.jpsychires.2013.03.009] [PMID]

78. Simopoulou M, Sfakianoudis K, Rapani A, Giannelou P, Anifandis G, Bolaris S, et al. Considerations Regarding Embryo Culture Conditions: From Media to Epigenetics. In Vivo. 2018;32(3):451-60. [DOI:10.21873/invivo.11261]
79. Chen HF, Chen SU, Ma GC, Hsieh ST, Tsai HD, Yang YS, et al. Preimplantation genetic diagnosis and screening: Current status and future challenges. J Formos Med Assoc. 2018;117(2):94-100. [DOI:10.1016/j.jfma.2017.08.006]
80. Swain JE, Carrell D, Cobo A, Meseguer M, Rubio C, Smith GD. Optimizing the culture environment and embryo manipulation to help maintain embryo developmental potential. Fertil Steril. 2016;105(3): 571-87. [DOI:10.1016/j.fertnstert.2016.01.035] [PMID]
81. Lindgren KE, Gulen Yaldir F, Hreinsson J, Holte J, Karehed K, Sundstrom-Poromaa I, et al. Differences in secretome in culture media when comparing blastocysts and arrested embryos using multiplex proximity assay. Ups J Med Sci. 2018; 123(3):143-52. [PMID] [PMCID] [DOI:10.1080/03009734.2018.1490830]
82. Schwarzer C, Esteves TC, Arauzo-Bravo MJ, Le Gac S, Nordhoff V, Schlatt S, et al. ART culture conditions change the probability of mouse embryo gestation through defined cellular and molecular responses. Hum Reprod. 2012;27(9):2627-40. [DOI:10.1093/humrep/des223] [PMID]
83. Gad A, Schellander K, Hoelker M, Tesfaye D. Transcriptome profile of early mammalian embryos in response to culture environment. Anim Reprod Sci. 2012;134(1-2):76-83. [DOI:10.1016/j.anireprosci.2012.08.014] [PMID]
84. Armstrong S, MacKenzie J, Woodward B, Pacey A, Farquhar C. GM-CSF (granulocyte macrophage colony-stimulating factor) supplementation in culture media for women undergoing assisted reproduction. Cochrane Database Syst Rev. 2020;7: CD013497. [PMID] [PMCID] [DOI:10.1002/14651858.CD013497.pub2]
85. Hemkemeyer SA, Schwarzer C, Boiani M, Ehmcke J, Le Gac S, Schlatt S, et al. Effects of embryo culture media do not persist after implantation: a histological study in mice. Hum Reprod. 2014;29 (2):220-33. [DOI:10.1093/humrep/det411] [PMID]
86. Van Montfoort APA, Arts E, Wijnandts L, Sluijmer A, Pelinck MJ, Land JA, et al. Reduced oxygen concentration during human IVF culture improves embryo utilization and cumulative pregnancy rates per cycle. Hum Reprod Open. 2020;2020(1): hoz036. [DOI:10.1093/hropen/hoz036] [PMID] [PMCID]
87. Karagenc L, Sertkaya Z, Ciray N, Ulug U, Bahceci M. Impact of oxygen concentration on embryonic development of mouse zygotes. Reprod Biomed Online. 2004;9(4):409-17. [PMID] [DOI:10.1016/S1472-6483(10)61276-X]
88. Oliveira JB. Does embryo culture at low oxygen tension improve ART outcomes? JBRA Assist Reprod. 2017;21(1):1. [PMID] [PMCID] [DOI:10.5935/1518-0557.20170001]
89. Morin SJ. Oxygen tension in embryo culture: does a shift to 2% O2 in extended culture represent the most physiologic system? J Assist Reprod Genet. 2017;34(3):309-14. [PMID] [PMCID] [DOI:10.1007/s10815-017-0880-z]

How to Cite This Article:

Negahdari, S., Nilechi, M., Hosseini, S. F., Forouzesh, M., Samimi, A., Maleknia, et al. Evaluation of Epigenetic Factors in Surrogacy: A Mini-Review. J Obstet Gynecol Cancer Res. 2023; 8(2):95-104.

Download citation:
BibTeX | RIS | EndNote | Medlars | ProCite | Reference Manager | RefWorks