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Evaluating the Role of Epigenetic Mechanisms in Fertility among Iraqi Patients and Understanding the Molecular Pathways and Genetic Effects

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Abstract: Epigenetic modifications are considered the primary and decisive factor in gene expression in reproduction. The main objective of this study was to determine the fertility-related outcomes for Iraqi patients and to identify the molecular pathways involved. Our methodology involved recruiting 97 patients from various hospitals in Baghdad, Iraq. The DNA homology patterns of 12 promoters associated with fertility and Demographic data from the patients were analyzed using IBM SPSS and Microsoft Excel. The results obtained in this study are:

- (Age Fertile Group with 31.4 ± 4.7, Subfertile Group 33.8 ± 5.2)
- FSH with G1 (6.8 ± 2.1) and G2 (9.4 ± 3.6)
- AMH with G1 3.2 ± 1.4 and G2 (1.8 ± 1.1) with p-value <0.001*
- Duration of infertility with a median of 28.0
- were upgraded H3K9me3, H3K27me3 in G 2
- H3K4me3, H4K16ac, H3K9ac, H3K27ac were diminished.
- according to multivariable logistic regression were found HOXA10 promoter methylation with OR = 2.04; 95% CI

In this study, we conclude that advances in molecular biology and genetics have shown that the physical and biological characteristics of individuals are not determined solely by genetic information, but also depend on how this information is expressed. Genes can be activated or repressed by epigenetic regulatory mechanisms influenced by the environment, and these mechanisms gain particular importance during embryonic development.

Keywords: Epigenetics, Fertility, Molecular, Genetic, gene, Subfertile, infertility.

INTRODUCTION

This domain is concerned with changes in the function of genes that are inherited without changes in the nucleotide sequence. Epigenetics is becoming a hot topic in the field of fertility because it helps to understand the molecular mechanisms of reproductive health and the genetic implications of these mechanisms [Abramiuk, M. *et al*., 2022; Ahmed, R. S. *et al*., 2025].

The three main mechanisms of epigenetic regulation are DNA methylation, histone modification, and non-coding RNA involvement [Bahreinian, M. *et al*., 2015]. Usually, methylation of DNA is the process of adding a methyl group to the cytosine bases of the DNA, which results in the repression of gene expression [Campbell, M. R. *et al*., 2013]. Epigenetic abnormalities are thought to play an important role in reproductive health because they account for the interaction between genotype, interaction with the genetic environment, and disease phenotype [Das, L. *et al*., 2017; Fabisik, M. *et al*., 2021; Guzick, D. S. *et al*., 2001]. The field of reproductive epigenetics has gained in interest due to the new understanding of the causes of complex non-Mendelian pathological traits. Currently, the way in which a range of epigenetic mechanisms affect male and female germ cells, as well as development, is being explored. Epigenetic markers that are switched on or off during development before the fertilized egg is implanted in the uterus may be a possible connection between ART and genetic fingerprinting disorders. In vitro fertilization [Han, X., & Huang, Q. 2021] can be affected by errors in genetic fingerprinting that affect the growth and development of the placenta. epigenetic abnormalities. One of the important biological factors is, which are known to cause diseases and disorders in the regulation of genes. The homeobox A10 (HOXA10) gene, for instance, is abnormally expressed in the pathophysiology of endometriosis [Hoffman, B. L. *et al*., 2016; Ikokide, E. J. *et al*., 2022]. In women with endometriosis, endometrial abnormalities have been reported on multiple occasions as a consequence of HOXA10 gene dysfunction [Raveh, E. *et al*., 2015]. This key regulatory gene is on chromosome 7p15.2, part of a family of DNA-linked transcription standards, and has a perfectly conserved 183-nucleotide sequence that codes for a 61-amino-acid home domain [Jenkins, T. G. *et al*., 2016; Li, Y. *et al*., 2015; Liu, L. *et al*., 2008]. HOXA10 is known to control uterine formation during embryonic development, as well

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as the functional differentiation of the endometrium in adults [Lozano, M. *et al*., 2022].

Epigenetic changes have been linked to lifestyle factors like diet, stress, and exposure to environmental pollutants. For example, the diet of the mother during pregnancy can lead to epigenetic changes in the developing fetus [Lozano, M. *et al*., 2022; Massányi, P. *et al*., 2020], which can lead to fertility problems in the offspring. Maternal obesity and high-fat diets have been shown to cause changes in methylation, which impacts the reproductive ability of offspring, so this paper aims to assessment outcomes of patients according to Epigenetics on Fertility Molecular Mechanisms and Genetic Implications [Massányi, P. *et al*., 2020].

METHODOLOGY

The study was a cross-sectional study conducted in the Reproductive Medicine Clinics of Baghdad Hospital in Iraq from March 2024 to November 2025 in multiple centers. The study protocol was approved by the Institutional Review Boards of both participating centers, and informed written consent was obtained from all participants prior to their enrollment in this study. The study was performed in accordance of the Declaration of Helsinki. Nine hundred and seven women of reproductive age (18-42 years) were recruited and divided into two groups: fertile (n = 52) women who had at least one spontaneous pregnancy during the last 24 months without the use of any assisted reproductive technology, and low fertility (n = 45) women who had not conceived after 12 months or more of regular, unprotected intercourse. Both groups had regular menstrual cycles (25–35 days) and no structural uterine abnormalities detected by transvaginal ultrasound, and no history of other endocrine disorders (not included in the study). The exclusion criteria were: use of hormonal contraceptives or fertility drugs in the previous 3 months, known chromosomal abnormalities, active pelvic inflammatory disease, severe male infertility (motile sperm count < 5 million), and any systemic autoimmune disease.

1. Biopsy of the endometrium was performed at the mid-secretory phase of the menstrual cycle (days 19–23) with an endometrial aspiration scraper guided by ultrasound. Peripheral venous blood samples (10mL) were obtained in EDTA tubes.
2. The endometrial tissue was quickly placed in liquid nitrogen and preserved at -80°C for further processing. Embryo endometrial tissue and peripheral blood leukocytes were used for genomic DNA extraction with the QIAamp DNA Mini Kit.
3. DNA methylation analysis was done by bisulfite fire sequencing. To summarize, 500 nanograms of genomic DNA was bisulfite converted using the EZ DNA Methylation-Gold Kit, and the bisulfite converted DNA was amplified by polymerase chain reaction (PCR) with custom-designed gene primers.

Table 1: Description and analysis of methods for determining genotype/RNA, targets, normalization, quality control, and statistics.

Item	Details
RNA extraction	miRNeasy Mini Kit (Qiagen); total RNA, including small RNA from endometrial tissue
cDNA synthesis (miRNA)	miScript II RT Kit (Qiagen)
cDNA synthesis (lncRNA/circRNA/piRNA)	High-Capacity cDNA Reverse Transcription Kit (Applied Biosystems)
RT-qPCR	miScript SYBR Green PCR Kit (Qiagen) on QuantStudio 7 Flex
ncRNA targets	miR-21-5p, miR-155-5p, miR-145-5p, miR-34a-5p; lncRNA H19, lncRNA MALAT1, circRNA-ITCH, piRNA-823
Normalization & quantification	U6 snRNA for miRNAs; GAPDH for other ncRNAs; relative expression by $2^{-\Delta\Delta Ct}$
Expression categorization	High (≥ 2-fold change vs median of fertile group) or Low (< 2-fold)
DNA genotyping	TaqMan SNP Genotyping Assays (Applied Biosystems) on QuantStudio 7 Flex
SNPs analyzed	MTHFR C677T (rs1801133), DNMT3A (rs13420827), ESR1 PvuII (rs2234693), COMT Val158Met (rs4680), BRCA1 (rs16941), FSHR Asn680Ser (rs6166)
Genotype QC	10% random re-genotyping; concordance = 99.7%
Hardy–Weinberg equilibrium	χ^2 goodness-of-fit; all SNPs p > 0.05
Software	IBM SPSS Statistics v29.0; R v4.3.2

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Continuous data handling	Shapiro–Wilk test for normality; mean ± SD if normal; median (IQR) if non-normal
Two-group comparisons	Independent samples t-test (parametric) or Mann–Whitney U test (nonparametric)
Categorical comparisons	χ^2 test or Fisher's exact test
Genotype group comparisons	One-way ANOVA with Bonferroni post hoc correction
Multivariable analysis	Binary logistic regression for subfertility adjusted for age, BMI, smoking, alcohol, ethnicity; model fit by Hosmer–Lemeshow; discrimination by AUC (ROC)
Multiple testing correction	Bonferroni correction applied where appropriate.
Significance threshold	Two-tailed p < 0.05 (after correction when applied)

RESULTS

A study was conducted on 97 Iraqi female patients, who were divided into two groups. The first group consisted of 52 patients, and the second group consisted of 45 patients, as a group suffering from infertility. In the first table, it was noted that there was an increase in the percentage of infertility among older women who had a high body mass index. In this study, it was also found that subfertile women exhibited significantly higher methylation levels at the promoters of DNMT3A (19.7 ± 6.3% vs. 12.4 ± 4.8%; $p < 0.001$).

Table 2: Demographic and Clinical Characteristics of Study Participants (N = 97)

Variable	Fertile Group (n = 52)	Subfertile Group (n = 45)	p-value
Age (years), mean ± SD	31.4 ± 4.7	33.8 ± 5.2	**0.017***
BMI (kg/m²), mean ± SD	24.1 ± 3.3	26.7 ± 4.1	**0.001***
BMI (kg/m²), median (IQR)	23.8 (21.5–26.2)	26.1 (23.4–29.8)	**0.002***
Duration of infertility (months), median (IQR)	—	28.0 (18.0–42.0)	—
Parity, median (IQR)	2.0 (1.0–3.0)	0.0 (0.0–1.0)	**<0.001***
Smoking status, n (%)	—	—	**0.041***
Never	38 (73.1%)	25 (55.6%)	—
Former	9 (17.3%)	10 (22.2%)	—
Current	5 (9.6%)	10 (22.2%)	—
Alcohol consumption, n (%)	—	—	0.328
None/Occasional	41 (78.8%)	31 (68.9%)	—
Regular	11 (21.2%)	14 (31.1%)	—
FSH (mIU/mL), mean ± SD	6.8 ± 2.1	9.4 ± 3.6	**<0.001***
AMH (ng/mL), mean ± SD	3.2 ± 1.4	1.8 ± 1.1	**<0.001***
AMH (ng/mL), median (IQR)	3.0 (2.1–4.1)	1.5 (0.9–2.4)	**<0.001***
Estradiol (pg/mL), mean ± SD	42.3 ± 14.7	51.6 ± 19.8	**0.009***
Antral follicle count, mean ± SD	14.2 ± 4.8	8.6 ± 3.9	**<0.001***

Table 3: DNA Methylation Levels (%) at Fertility-Related Gene Promoters by Fertility Status

Gene Promoter	**Fertile Group (n = 52), mean ± SD**	**Subfertile Group (n = 45), mean ± SD**	**Mean Difference (95% CI)**	**p-value**
DNMT3A	12.4 ± 4.8	19.7 ± 6.3	7.3 (5.1–9.5)	**<0.001***
DNMT3B	8.6 ± 3.2	13.1 ± 4.7	4.5 (2.9–6.1)	**<0.001***
MTHFR	15.3 ± 5.1	22.8 ± 7.4	7.5 (5.0–10.0)	**<0.001***
ESR1 (Estrogen Receptor α)	10.2 ± 3.9	16.4 ± 5.8	6.2 (4.2–8.2)	**<0.001***
PGR (Progesterone Receptor)	9.8 ± 4.1	14.6 ± 5.3	4.8 (3.0–6.6)	**<0.001***
HOXA10	7.1 ± 2.8	12.9 ± 4.6	5.8 (4.3–7.3)	**<0.00**

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				1*
HOXA11	6.8 ± 3.0	11.4 ± 4.2	4.6 (3.1–6.1)	**<0.001***
LHCGR	11.5 ± 4.3	15.2 ± 5.1	3.7 (1.8–5.6)	**0.002***
FSHR	9.3 ± 3.7	12.8 ± 4.9	3.5 (1.8–5.2)	**0.001***
IGF2/H19 ICR	48.2 ± 3.6	42.1 ± 5.8	−6.1 (−7.9 to −4.3)	**<0.001***
LINE-1 (Global)	72.4 ± 5.2	65.8 ± 6.9	−6.6 (−8.9 to −4.3)	**<0.001***
BRCA1	5.4 ± 2.6	7.1 ± 3.4	1.7 (0.5–2.9)	**0.038***

Table 4: Histone Modification Markers in Endometrial Tissue and Association with Reproductive Outcomes

Histone Marker	**Fertile (n = 52), median (IQR)**	**Subfertile (n = 45), median (IQR)**	**Successful Implantation (n = 38), mean ± SD**	**Failed Implantation (n = 59), mean ± SD**	**p-value†**
H3K4me3 (AU)	1.42 (1.08–1.89)	0.87 (0.54–1.21)	1.38 ± 0.52	0.91 ± 0.44	**<0.001***
H3K9me3 (AU)	0.68 (0.41–0.92)	1.24 (0.89–1.67)	0.72 ± 0.31	1.18 ± 0.48	**<0.001***
H3K27me3 (AU)	0.94 (0.67–1.28)	1.51 (1.12–1.94)	0.98 ± 0.38	1.42 ± 0.51	**<0.001***
H3K36me3 (AU)	1.18 (0.82–1.56)	0.76 (0.48–1.04)	1.14 ± 0.42	0.82 ± 0.37	**0.001***
H4K16ac (AU)	1.56 (1.18–2.04)	0.92 (0.61–1.34)	1.48 ± 0.56	0.98 ± 0.43	**<0.001***
H3K9ac (AU)	1.31 (0.94–1.72)	0.84 (0.56–1.18)	1.26 ± 0.48	0.89 ± 0.39	**<0.001***
H3K27ac (AU)	1.24 (0.88–1.64)	0.78 (0.52–1.12)	1.19 ± 0.44	0.84 ± 0.38	**<0.001***
H3K4me1 (AU)	1.08 (0.76–1.42)	0.72 (0.48–1.01)	1.04 ± 0.39		

Table 5 : Non-coding RNA Expression Profiles and Their Association with Fertility Parameters (N = 97)

Non-coding RNA	**Expression Level**	**Fertile, n (%)**	**Subfertile, n (%)**	**Abnormal Ovarian Reserve, n (%)**	**Normal Ovarian Reserve, n (%)**	**p-value**
miR-21-5p	High (≥ 2-fold)	14 (26.9%)	31 (68.9%)	28 (65.1%)	17 (31.5%)	**<0.001***
—	Low (< 2-fold)	38 (73.1%)	14 (31.1%)	15 (34.9%)	37 (68.5%)	—
miR-155-5p	High (≥ 2-fold)	11 (21.2%)	27 (60.0%)	24 (55.8%)	14 (25.9%)	**<0.001***
—	Low (< 2-fold)	41 (78.8%)	18 (40.0%)	19 (44.2%)	40 (74.1%)	—
miR-145-5p	High (≥ 2-fold)	36 (69.2%)	16 (35.6%)	13 (30.2%)	39 (72.2%)	**<0.001***
—	Low (< 2-fold)	16 (30.8%)	29 (64.4%)	30 (69.8%)	15 (27.8%)	—
miR-34a-5p	High (≥ 2-fold)	8 (15.4%)	22 (48.9%)	20 (46.5%)	10 (18.5%)	**<0.001***

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—	Low (< 2-fold)	44 (84.6%)	23 (51.1%)	23 (53.5%)	44 (81.5%)	—
lncRNA H19	High (≥ 2-fold)	34 (65.4%)	14 (31.1%)	12 (27.9%)	36 (66.7%)	**<0.001***
—	Low (< 2-fold)	18 (34.6%)	31 (68.9%)	31 (72.1%)	18 (33.3%)	—
lncRNA MALAT1	High (≥ 2-fold)	12 (23.1%)	24 (53.3%)	22 (51.2%)	14 (25.9%)	**0.002***
—	Low (< 2-fold)	40 (76.9%)	21 (46.7%)	21 (48.8%)	40 (74.1%)	—
circRNA-ITCH	High (≥ 2-fold)	31 (59.6%)	12 (26.7%)	10 (23.3%)	33 (61.1%)	**<0.001***
—	Low (< 2-fold)	21 (40.4%)	33 (73.3%)	33 (76.7%)	21 (38.9%)	—
piRNA-823	High (≥ 2-fold)	9 (17.3%)	19 (42.2%)	18 (41.9%)	10 (18.5%)	**0.006***
—	Low (< 2-fold)	43 (82.7%)	26 (57.8%)	25 (58.1%)	44 (81.5%)	

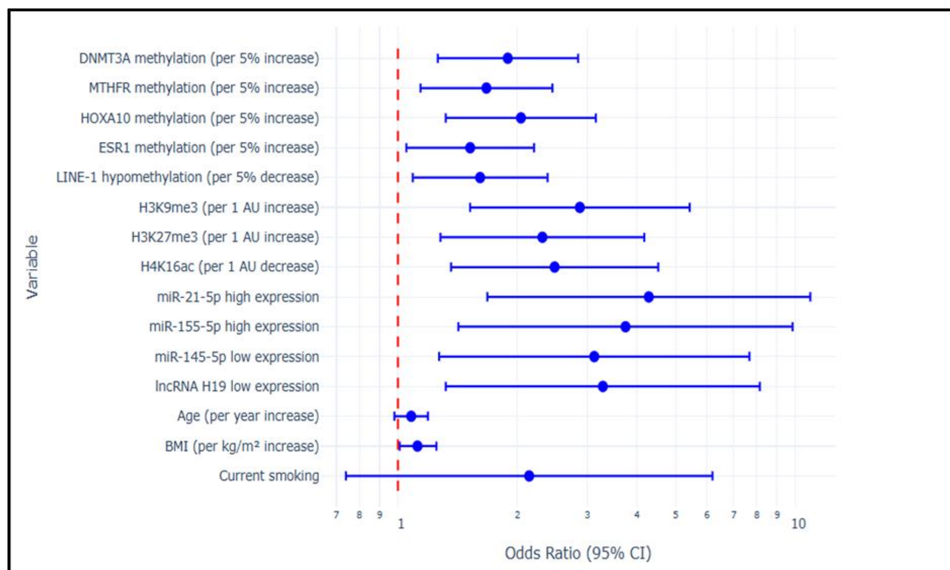

Figure 1: Assessment findings of the study according to Multivariable Logistic Regression Analysis of Epigenetic Factors Predicting Subfertility

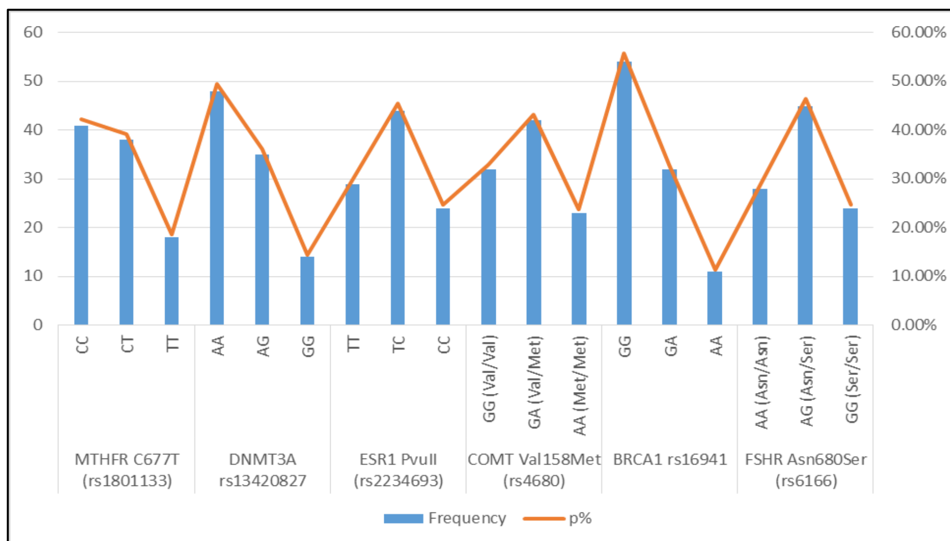

Figure 2: Association between Genetic Polymorphisms and Epigenetic Marker Levels in the Study Cohort

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DISCUSSION

There were significant differences in chromatin changes in endometrial cells from fertile and subfertile women (Table 3) detected by histone modification analysis. A number of repressive histone marks were significantly increased in subfertile women, whereas activating marks, including H3K4me3, H4K16ac, H3K9ac, and H3K27ac, were significantly decreased. The connection between histone marks and implanting outcomes was especially interesting, with the best outcomes having more activating marks and fewer repressive marks [Okpashi, V. E., & Ebunta, A. F. 2021].

There were clear differences between fertile and subfertile women in the expression of non-coding RNA, and the proportion of women with high miR-21-5p expression was significantly greater in the subfertile group (68.9% vs. 26.9%; $p < 0.001$), as was high miR-155-5p expression (60.0% vs. 21.2%; $p < 0.001$). In contrast, fertile women had higher expression of the tumor-suppressive miR-145-5p (69.2% vs. 35.6%, $p < 0.001$). For long non-coding RNA, the expression of low lncRNA H19 was significantly associated with subfertility (68.9% vs. 34.6%, $p < 0.001$) and abnormal ovarian reserve (72.1% vs. 33.3%).

This study describes the epigenetic landscape in fertile and subfertile women in a single cohort of 97 women, including DNA methylation profiling, histone modification analysis, non-coding RNA expression assessment, and genetic polymorphism genotyping. We have identified a wide range of epigenetic changes that are linked to subfertility, which together lead to disruption in the molecular programmes required for successful reproduction, and that some of these epigenetic changes are, at least partially, regulated by genetic variation [Rashidi, M. *et al*., 2021; Raveh, E. *et al*., 2015].

Hypermethylation of key genes involved in fertility, such as HOXA10, HOXA11, ESR1, and PGR, in subfertile women is consistent with these genes having been shown to play a role in endometrial receptivity and implantation [Rotondo, J. C. *et al*., 2021]. HOXA10 and HOXA11 are homeobox genes that are essential for the decidualization of the endometrium and the implantation of the embryo and are strictly controlled by steroid hormones in the implantation window. Our results confirmed previous reports of abnormal methylation of HOXA10 in women with unexplained infertility by Taylor *et al*. and endometriosis by Szczepańska *et al* [Dinani, H. T. *et al*., 2023], showing that methylation of the HOXA10 promoter was an independent predictor of subfertility (adjusted OR = 2.04; 95% CI: 1.32–3.15; $p = 0.001$) after accounting for potential confounding factors. Concurrent hypermethylation of ESR1 and PGR promoters indicates an epigenetic silencing of the steroid hormone signaling axis, which can affect the endometrial response to estrogen and progesterone in the secretory phase and lead to a decrease in endometrial receptivity [Tavalaee, M. *et al*., 2015].

One of the novel findings of this study is its ability to show gene–epigenetic interactions, in which gene polymorphisms affect the amount of epigenetic markers and the risk of fertility. MTHFR C677T polymorphism is associated with progressive methylation of the promoter of the MTHFR gene, according to the genotype (CC: 15.8%, CT: 19.4%, TT: 24.6%; $p < 0.001$), and with a significantly higher risk of subfertility in the TT genotype (OR = 3.92; 95% CI: 1.28–12.01; $p = 0.017$). This is biologically plausible as the MTHFR TT genotype is associated with decreased folate metabolism and decreased amount of available methyl group, resulting in potential for aberrant DNA methylation. The FSHR Asn680Ser polymorphism was also shown to have a dose-dependent relationship with the methylation of the FSHR promoter and their association with subfertility risk, suggesting that genetic variation of the FSH receptor may predispose to epigenetic dysregulation of the gonadotropin signalling pathway [Walker, M.H. & Tobler, K.J. 2024; Wang, W. *et al*., 2020; Zhang, Y. *et al*., 2024].

The fact that subfertile women have decreased global LINE-1 methylation is particularly significant, since global LINE-1 methylation is considered a surrogate marker for genome-wide methylation status. Hypomethylation of the genome has been linked to genomic instability, transposable element reactivation, and abnormal gene expression, which can lead to reproductive dysfunction. Likewise, the decreased methylation at the IGF2/H19 imprinting control region in subfertile women indicates disruption of the imprinting process, which plays an essential role in normal fetal growth and placental development. Our data indicate that more subtle imprints may contribute to subfertility and that loss of imprinting at IGF2/H19 has been previously reported in association with Beckwith–Wiedemann syndrome and Silver–Russell syndrome. Recent studies indicate that elevated cortisol levels and stress during pregnancy may affect fetal telomere length,

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disrupting the regulation of biological processes. Chronic stress activates the hypothalamic-pituitary-adrenal (HPA) axis, increasing cortisol levels and shortening telomeres. Telomeres are DNA sequences at the ends of chromosomes that protect and maintain the stability of genetic material. Telomere shortening leads to chromosomal instability, which is a marker for genetic diseases, cellular aging, physical and mental disorders, and premature death. [Li, Y. *et al*., 2015].

Some studies have shown that prenatal exposure to maternal smoking, whether direct or indirect, is associated with changes in DNA methylation, leading to reduced lung function and an increased risk of asthma, cancer, attention deficit hyperactivity disorder (ADHD), obesity, type 2 diabetes, and low birth weight. Similarly, exposure to industrial chemicals and environmental pollutants, such as pesticides, contributes to developmental diseases through epigenetic changes [Rashidi, M. *et al*., 2021].

CONCLUSION

As the present paper shows, epigenetics is important for the correct functioning and development of the organism, especially during pregnancy, and it is clear that there is a complex interaction between maternal genetic and environmental factors in the development of the fetus where also concluded Maternal nutrition is crucial for the transfer of nutrients to the fetus for optimal growth and for epigenetic regulation of gene expression.

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