Journal of Experimental and Basic Medical Sciences 2025;6(1):21-27

Review

Epigenetic Impacts of Exercise During Pregnancy

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ABSTRACT

Pregnancy represents a distinct period in a woman's life characterized by significant physiological, psychological, and hormonal alterations, wherein the adoption of healthy lifestyle habits is critically important for both maternal and fetal well-being. Exercise offers multifaceted benefits during gestation, including the alleviation of pregnancy-related discomforts, facilitation of the birthing process, weight management, enhancement of psychological well-being, and improvement in overall quality of life. Epigenetic mechanisms, which encompass the heritable effects of environmental factors on gene expression, highlight the substantial influence of maternal nutrition and behaviors on fetal development. It is hypothesized that exercise during pregnancy can positively modulate fetal metabolic and neurodevelopmental processes through epigenetic pathways such as deoxyribonucleic acid methylation and histone modification. This review examines the epigenetic and physiological effects of exercise on both the mother and the fetus during pregnancy. Furthermore, the beneficial effects of exercise on cardiovascular health, as well as its regulatory role on neurodevelopmental processes such as synaptic plasticity and neurotransmitter synthesis, have been emphasized.

Keywords: Epigenetics, exercise, fetal health, healthy pregnancy, maternal health, pregnancy.

Pregnancy constitutes a unique physiological state in women's lives, marked by significant physical, psychological, and hormonal transformations. Consequently, adopting health-promoting lifestyle habits during pregnancy is of paramount importance for both maternal and fetal well-being. Engagement in exercise or sport not only alleviates certain pregnancy-related discomforts but also confers numerous benefits, including the facilitation of the labor and delivery process, maintenance of weight control, promotion of positive psychological states, and enhancement of overall quality of life.[1-4]

Several studies indicate that the rate of exercise or sports participation during pregnancy tends to be low.[3,4] Although risk factors may vary based on physiological and anatomical differences, exercise during pregnancy is generally beneficial for most women. In the absence of contraindications, pregnant individuals should be encouraged to engage in exercise or light sports activities. It is imperative that these exercises are carefully planned by qualified professionals, taking into consideration potential obstetric risks.[1-3] Furthermore, expectant mothers should be informed about conditions necessitating the cessation or interruption of exercise. Absolute contraindications to exercise during pregnancy include a history of preterm birth in previous pregnancies or the presence of preterm birth risk in the current pregnancy, intrauterine growth restriction, placenta previa, cervical insufficiency, premature rupture of membranes, ongoing second and third-trimester bleeding, pregnancy-induced hypertension or preeclampsia, and severe cardiovascular or respiratory diseases.[3]

Epigenetics

First proposed in the 1950s, the term epigenetics refers to reversible alterations in deoxyribonucleic acid (DNA) and histone proteins that cannot be explained by changes in the DNA sequence. These

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Cite this article as: Geçit SZ, Avcı Ş, Erbaş O. Epigenetic Impacts of Exercise During Pregnancy. JEB Med Sci 2025;6(1):21-27.

doi: 10.5606/jebms.2025.1106

Received : February 20, 2025
Accepted : March 10, 2025
Published online : July 9, 2025

modifications provide a better understanding of the discordance between genotype and phenotype, resulting from changes in gene function. Defined as 'heritable changes in gene function that can be transmitted through mitosis and/or meiosis,' epigenetics plays a particularly significant role in the dynamic process of development from embryo to adult organism, especially in the modulation of gene expression during cellular differentiation.[5-7]

Consequently, environmental factors such as nutritional patterns and maternal behaviors can readily influence the epigenetic processes of the fetus.[7,8] Epigenetic processes elucidate how two individuals with identical genetic makeup, raised in the same environment, can exhibit distinct characteristics.[9] Furthermore, it has been proposed that epigenetic variations in sister chromatids may lead to alterations in gene expression levels.[10]

DNA Methylation

Deoxyribonucleic acid methylation, the first discovered and most extensively studied epigenetic modification, plays a critical role in the regulation of gene expression. This process, typically occurring at CpG islands and the 5th carbon of cytosine and mediated by DNA methyltransferase (DNMT) enzymes, leads to gene silencing. While hypomethylation in promoter regions is associated with active gene expression, hypermethylation can result in the inactivation of tumor suppressor genes, potentially contributing to cancer development.[7-9]

Mutations in DNMT genes have been linked to certain cancer types, and inhibitors of these genes, along with other epigenetic therapies, represent promising approaches in cancer treatment. Furthermore, it is hypothesized that abnormalities in DNA methylation may be associated with aging and other diseases. DNA methylation and histone modification constitute significant mechanisms involved in the regulation of gene expression. The DNMT1 plays a crucial role in establishing and maintaining *de novo* methylation patterns by catalyzing methylation at hemi-methylated DNA sites, while DNMT3a and DNMT3b are also involved in *de novo* methylation. The DNMT2 lacks a regulatory domain, and DNMT3L lacks a catalytic domain, rendering them enzymatically inactive. Certain proteins that bind to methylated CpG regions contribute to gene silencing through histone modifications. These epigenetic regulations provide a fundamental mechanism for controlling gene expression in different tissues and during developmental processes.[6]

Histone Methylation and Modification

Histones, the fundamental structural units of chromatin, undergo a variety of post-translational modifications, including acetylation, methylation, and phosphorylation. These modifications play regulatory roles in processes such as gene transcription, DNA repair, and recombination.[11]

Unlike acetylation, histone methylation does not alter the electrical charge of histone proteins but is associated with either gene activation or inactivation. The specific histone residue at which methylation occurs determines the direction of this effect. Histone methyltransferases (HMTs) and histone demethylases (HDMs) regulate this dynamic process. The enhancer of zeste homolog 2, an HMT enzyme, is overexpressed in various cancer types and is considered to possess oncogenic potential. Conversely, HDM enzymes such as lysine-specific demethylase 1 have been implicated in neurological disorders as well as cancer. Histone modifications, working in concert with DNA methylation, are key epigenetic regulators that determine cell fate.[6]

MicroRNAs

Microribonucleic acids (miRNAs), small RNA molecules ranging from 20 to 24 nucleotides in length, play a significant role in the post-transcriptional regulation of gene expression. Synthesized in the nucleus and subsequently transported to the cytoplasm, miRNAs assemble into the RNA-induced silencing complex and bind to target messenger RNAs (mRNAs), leading to the repression of gene expression or the degradation of the mRNA transcript. Alterations in miRNA profiles have been observed in various cancers, including breast cancer, and these changes have been linked to epigenetic mechanisms. Consequently, the suppression of oncogenic miRNAs or the upregulation of tumor-suppressing miRNAs is considered a promising therapeutic strategy in cancer treatment.[7,12]

Endocrine System

The endocrine system comprises a network of endocrine glands situated throughout the body that synthesize and secrete hormones. These chemical messengers play crucial roles in regulating growth, development, metabolism, energy homeostasis, and reproduction.[8,13]

Key endocrine glands include the hypothalamus, pituitary gland, pineal gland (epiphysis), thyroid gland, adrenal glands, pancreas, ovaries (in females), and testes (in males).[13]

Exercise, Epigenetics, and Hormones

Research indicates that genetic factors influence predisposition to sports performance. While approximately 66% of this predisposition is attributed to genetic factors, non-genetic elements such as training, nutrition, motivation, and sleep also play a significant role. Furthermore, genetic polymorphisms can be indicative of an athlete's aptitude for specific sports disciplines, as genes and gene families associated with endurance (e.g., erythropoietin gene), speed (e.g., alpha-actinin), and strength (e.g., myostatin gene) have been identified. Certain experimental studies have observed that alterations in skeletal muscle fiber composition can lead to increased endurance. Moreover, given the reversible nature of epigenetic modifications, individuals can potentially develop a more athletic physique through specific sports training, irrespective of their baseline genetic predispositions.[14,15]

It is well-established that engaging in exercise yields positive physiological and psychological effects on the body. However, the application of strenuous exercise may induce physiological stress, potentially leading to organ damage. While exercise can elevate hormone release during activity, it may reduce hormone secretion during periods of rest. The precise impact of exercise on hormonal regulation remains a significant area of ongoing research.[16]

THE PHYSIOLOGICAL AND PSYCHOLOGICAL EFFECTS OF EXERCISE

In the United States, the annual mortality rate for women due to cardiac disease is approximately 25%. In contrast, coronary heart disease is the primary cause of mortality among women in Türkiye. Key contributing factors include diabetes, smoking, stress, and physical inactivity. Exercise promotes the development of cardiac muscle and reduces the risk of myocardial infarction.[4]

Engaging in exercise during pregnancy has demonstrated positive effects such as a reduction in cardiovascular risks, maintenance of weight, and improved management of diabetes.[17] Furthermore, it corrects postural imbalances and reduces the risk of miscarriage. Exercise has been observed to optimize blood glucose levels in individuals with diabetes. During pregnancy, exercise provides support to the muscular and skeletal systems, thereby mitigating potential complications during childbirth and increasing the likelihood of a vaginal delivery.[3,18]

Consequently, physical activity facilitates a less complicated delivery. However, the oxygen demand increases by approximately 20% during pregnancy. Strenuous exercise regimens can elevate oxygen consumption, potentially posing risks during gestation. Moreover, the increased hormonal activity and weight gain associated with pregnancy exert pressure on the skeletal and muscular systems, necessitating the preference for light exercises that do not strain the expectant mother.[1]

Increased stress during pregnancy is a hormone that can influence childbirth. It elevates the secretion of oxytocin and prostaglandin hormones while simultaneously reducing the release of beta-endorphin and progesterone. These hormonal fluctuations can potentially lead to adverse birth outcomes.[19]

However, one study involving pregnant women aged 18-35 years found that daily activity levels in the exercise intervention group had a positive impact on cardiovascular and metabolic functions, and that prenatal exercise was associated with an increased likelihood of vaginal delivery.[20]

Another study observed that pregnant women who participated in exercise experienced greater benefits in terms of their cardiovascular system and demonstrated an increase in psychological self-confidence.[21]

EPIGENETIC INFLUENCE

Epigenetics is defined as heritable changes in gene expression that occur without any alteration in the DNA sequence, often influenced by nutritional patterns and/or environmental factors.[22]

Furthermore, epigenetic modifications occurring during gestation have an impact on the fetus.[23]

The placenta, during gestation, serves as the organ responsible for providing the fetus with nutrients and gases, as well as facilitating the removal of waste products. For instance, DNA methylation can alter gene expression, thereby influencing placental function. Such epigenetic modifications may lead to changes in nutrient and gas transport within the placenta.[24]

Epigenetic mechanisms, which also play a significant role in hormonal regulation, influence both the mother and the fetus during pregnancy. While DNA methylation can assist in pregnancy by regulating hormone activity, epigenetic alterations may also negatively impact fetal development.

Notably, oxytocin and thyroid hormones are crucial during gestation. For instance, disruption of thyroid hormone function can have adverse effects on the neurological development of the fetus.[25,26]

Factors such as maternal age, weight, nutritional status, and detrimental habits significantly influence these alterations in gene expression. All aspects of an expectant mother's regimen during pregnancy, including medication use, must be managed under strict supervision. Similarly, experiencing trauma during pregnancy can lead to certain heritable outcomes in the fetus.[27]

The Epigenetic Impact of Exercise

Changes in gene expression occurring during pregnancy influence DNA methylation. These alterations also affect hormone release and, consequently, histone modification.[6,11]

Alterations in DNA methylation can affect genes associated with metabolism, potentially reducing the future risk of diabetes in the offspring.[28]

Certain animal studies have observed improved insulin sensitivity in the offspring of mothers who exercised during pregnancy compared to the offspring of sedentary mothers.[29] Alternatively, alterations in histone modification, influenced by hormones released by the mother during exercise and growth factors, can support fetal development. This may involve the regulation of metabolic activities and the promotion of placental development. Furthermore, transport processes within the placenta can facilitate fetal growth and support neurodevelopment.[30]

Although research on placental effects is limited, existing studies suggest that exercise interventions influence placental growth and functional capacity. While the precise underlying mechanisms remain unclear, fluctuations in oxygen and substrate delivery during exercise are hypothesized to contribute to these effects. Regular exercise modulates the levels of growth factors, thereby impacting overall growth and development. Furthermore, the type and duration of exercise can modify these outcomes.[31]

Moreover, epigenetics plays a role in improving cardiovascular health through physical activity. Although the precise mechanism remains to be fully elucidated, exercise has been shown to potentially prevent symptoms of cardiometabolic diseases such as hypertension, hyperlipidemia, and vascular disorders. Another study observed that exercise exerts effects on leukocytes, leading to alterations in genes and miRNAs associated with cardiac conditions.[32]

Exercise can modulate synaptic plasticity, neurotransmitter synthesis, and the expression of neurodevelopmental genes.[31] By upregulating the expression of genes crucial for brain development and nourishment, exercise can promote the structural development and functional enhancement of the fetal brain. Furthermore, the reduction in maternal stress levels associated with physical activity can induce alterations in methylation patterns, thereby shaping the fetus's stress response mechanisms.[33]

Such positive effects on brain development may result in observable improvements in cognitive behaviors postnatally.[34]

Recommendations and Clinical Guidance

Pregnancy is a process that induces biopsychosocial changes in a woman's body and life. Initiated by the fertilization of a mature ovum by a sperm and subsequent implantation in the uterus, this process typically spans approximately 280 days.[18] The alterations observed in a woman's metabolism and bodily functions during this period are termed the body's adaptation to pregnancy. These changes serve three primary objectives: to prepare the mother for labor and delivery, to induce physiological modifications in the mother to meet the needs of the developing fetus, and to nourish, house, and protect the fetus until birth.[35] In addition to these physiological adaptations, pregnancy is also associated with changes in weight, appetite, mood, and activity experiences.[36]

In recent years, the increasing interest of women in exercise programs has led to a growing desire to continue engaging in physical activity during pregnancy.[36] There is substantial historical evidence suggesting that physically active women experience an easier childbirth. Aristotle initiated this line of thought by noting that difficult labors were associated with a sedentary lifestyle. Examples from this period include Lamaze's psychoprophylactic childbirth methods, which emphasized controlled breathing and relaxation techniques, and squatting exercises aimed at strengthening the perineal muscles to facilitate labor.[37]

Controlled physical activities undertaken during pregnancy maintain overall health, prevent many chronic diseases, and contribute to the preservation and improvement of mental well-being. Guidelines recommend that pregnant individuals engage in appropriately intense prenatal exercises for approximately 30 minutes daily, seven days a week, under the guidance of qualified professionals who

possess sufficient knowledge to ensure the correct execution of movements without complications. Despite these significant recommendations, it is estimated that only about 20% of pregnant individuals currently adhere to these exercise guidelines.[18]

During pregnancy, exercises that minimize the risk of balance loss and fetal trauma, while involving rhythmic movement of large muscle groups and active engagement of the abdominal and hip muscles, are recommended. Examples of suitable exercises during pregnancy include low-impact aerobics, swimming, water exercises, stationary cycling, treadmill walking, Pilates exercises, and yoga exercises.[35]

Pilates

Pilates is an exercise modality suitable for pregnant women as it strengthens the muscles responsible for lumbopelvic stabilization, improves postural alignment and respiratory patterns, and activates muscles involved in daily life activities, thereby promoting a sense of mental and social well-being.[35,36]

Pilates during pregnancy is a highly beneficial exercise modality that aids in spinal stabilization, pelvic floor control, and the improvement of breathing and posture. Clinical Pilates exercises are particularly effective in treating pelvic floor dysfunction. By strengthening the abdominal muscles, Pilates promotes spinal elongation, thereby alleviating lower back pain. It also enhances coordination, balance, and muscle tone, leading to increased activity levels. Furthermore, Pilates provides expectant mothers with increased flexibility and strength while promoting relaxation and calmness, making it a seemingly advantageous form of exercise for both maternal and fetal well-being.[37]

By promoting spinal elongation and strengthening the abdominal muscles, Pilates provides ample space for the fetus, facilitating comfortable movement.[35]

The breathing exercises incorporated in Pilates enhance the mother's lung capacity, easing respiration and improving oxygen flow to the baby. Strong abdominal muscles offer support to the fetus during labor and significantly reduce the risk of issues such as diastasis recti. The calming effect of Pilates lowers the mother's stress levels, creating a tranquil environment for the baby. Considering these benefits, Pilates emerges as a safe and healthy exercise modality that plays a crucial role in ensuring a positive pregnancy experience for both mother and child.[36]

Yoga

Yoga is a significant exercise modality for women during the preconception, prenatal, labor, and postpartum periods; however, its practice during pregnancy is not an ancient tradition. Initially regarded as a male-specific practice in India, yoga began to gain recognition with the advancement of health practices in the 1920s and became more popular among women in the late 1930s. The widespread adoption of yoga practices during pregnancy began in the 1980s, coinciding with the understanding that physical activity during gestation is beneficial for labor and the postpartum period.[38]

During pregnancy, natural physiological adaptations occur, such as an increase in heart rate and plasma volume. Pranayamic breathing, a fundamental technique in yoga practice involving deep and rhythmic inhalation and exhalation, activates the parasympathetic nervous system, leading to a reduction in heart rate, blood pressure, metabolic rate, and oxygen consumption. Studies have demonstrated that yoga has positive effects during pregnancy, including alleviating discomfort, promoting a greater sense of physical well-being, and regulating sleep disturbances.[38,39]

Parental yoga has been indicated to positively enhance maternal outcomes. Studies have reported that pregnant women who practice yoga three times a week between the 12th and 28th weeks of gestation experience a lower incidence of complications such as gestational hypertension, gestational diabetes, preeclampsia, and intrauterine growth restriction. Furthermore, it has been observed that pregnant individuals who practice yoga have shorter second and third stages of labor and a lower rate of cesarean sections. Additionally, the intensity of pain experienced during 3-4 cm cervical dilation in labor has been found to be less severe in pregnant women who practice yoga compared to those who do not.[40]

Aerobic exercises

Aerobic exercise is a dynamic form of physical activity that targets large muscle groups and enhances cardiovascular fitness. The intensity, frequency, duration, mode, and progression of aerobic exercise should be appropriately tailored to the individual's pregnancy stage and adjusted to avoid complications.[36,37]

These exercises improve cardiovascular health, thereby reducing the risk of cardiovascular diseases.[36]

Exercise intensity

During pregnancy, exercise can be performed at a light-to-moderate intensity, such as brisk walking at 3-4 metabolic equivalent of tasks. When determining exercise intensity, calculating the target heart rate using the heart rate reserve method offers more suitable conditions for both mother and baby. However, considering the natural increase in heart rate during pregnancy, the rate of perceived exertion (RPE) or the talk test can also be used to gauge exercise intensity. An RPE range of 12-14 is generally recommended, while the talk test assesses appropriate intensity based on the individual's ability to comfortably hold a conversation. These methods enhance the safety of exercise, making it easier to maintain a healthy level of physical activity throughout pregnancy.[1]

Exercise duration

It is considered appropriate for expectant mothers to commence exercise with 15-minute sessions three times per week, gradually progressing to 30-minute programs four times per week. Intermittent exercise regimens are preferable to continuous exercise, with activity periods of 15 minutes interspersed with 5-10 minute warm-up and cool-down phases at the beginning and end of each session. Exercise should be interrupted upon the onset of fatigue, and the session should conclude or rest periods adjusted according to the degree of perceived exertion. Furthermore, to mitigate potential risks for both the mother and the fetus, exercise duration should not exceed 45 minutes.[41,42]

In conclusion, engaging in exercise throughout pregnancy holds significant importance for the well-being of both the mother and the developing baby. Implementing these exercises in a controlled manner can facilitate the labor and delivery process, alleviate common pregnancy-related discomforts, and yield positive effects on overall health. Low-impact exercise modalities such as Pilates and yoga are particularly beneficial for both the mother and the fetus, as they strengthen the body while also providing relaxing effects for the expectant mother. Ensuring that exercises are performed at the appropriate intensity and duration enhances the safety of both the mother and the baby. Controlled aerobic exercises performed in the later stages of pregnancy can enhance cardiovascular health and contribute to positive outcomes during labor and delivery. However, it is crucial to emphasize that these exercises must be conducted under the guidance and supervision of qualified professionals, tailored to the individual condition of the expectant mother. Considering the benefits of exercise during pregnancy, a gradual increase in physical activity for expectant mothers, guided by expert recommendations and tailored to the baby's developmental stage, will contribute to a healthy pregnancy for both mother and child.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

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