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Original Article

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Maternal serum vasohibin-1 and vasohibin-2 concentrations in pregnant women diagnosed with late fetal growth restriction or small for gestational age fetus

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ABSTRACT

Aims: Vasohibin-1, a member of the vasohibin family, is an inhibitor of angiogenesis, while vasohibin-2 stimulates angiogenesis. Placental expressions of vasohibins and their relationship with preeclampsia have been investigated, but their effects on intrauterine fetal growth are unknown. In this context, we aimed to investigate the concentrations of vasohibin-1 and 2 in the serum of pregnant women diagnosed with late fetal growth restriction (FGR) or small for gestational age (SGA) in the third trimester.

Methods: This prospective non-interventional cohort study was conducted on 81 pregnant women, 26 of whom were diagnosed with late FGR, 28 were diagnosed with SGA, and 27 were healthy controls. The groups were compared in terms of serum vasohibin-1 and 2 concentrations in the third trimester.

Results: The groups were similar in terms of demographic characteristics and gestational age at blood sampling for vasohibin 1 and 2 ($p<0.05$). The median vasohibin 1 concentration was determined to be 1227.41 ng/mL in the late FGR group, 1311.15 ng/mL in the SGA group, and 1391.38 ng/mL in the control group ($p=0.139$). The median vasohibin 2 concentration was determined to be 11.24 ng/mL in the late FGR group, 11.86 ng/mL in the SGA group, and 14.34 ng/mL in the control group ($p=0.198$).

Conclusion: Serum vasohibin-1 and 2 concentrations were found to be similar in pregnant women diagnosed with late FGR and SGA and in pregnant women with appropriate-for-gestational-age (AGA) fetuses. Vasohibin-1 and 2 are involved in the regulation of placental angiogenesis, but their roles in intrauterine fetal growth remain unclear.

Keywords: Fetal growth restriction, pregnancy, small for gestational age, vasohibin-1, vasohibin-2

INTRODUCTION

Fetal growth depends on many factors, including the genetic background of the fetus, maternal characteristics, the structure of the placenta, and nutrient supply.[1] In some pregnancies, due to maternal and fetal diseases or placental disorders, the fetus cannot reach its potential growth curve and falls further behind in gestational age. A fetus that is smaller than the gestational age calculated from the last menstrual date confirmed by crown rump length (CRL) measurement in the first trimester is either a fetus with fetal growth restriction (FGR) or a fetus that is small for gestational age (SGA). Although differential diagnosis is not always possible with a single examination, it is important to distinguish FGR from SGA fetuses for clinical management, as fetuses with FGR are at high risk for adverse perinatal outcomes.[2]

FGR is divided into two groups according to the initial gestational week. If FGR started before the 32nd week of gestation in the absence of any fetal congenital anomaly, it is called early FGR; if it started on the 32nd week of gestation or later, it is called late FGR.[3] For the diagnosis of early FGR, three solitary parameters have been defined: fetal abdominal circumference (AC)<3rd , estimated fetal weight (EFW)<3rd percentile, and absent end-diastolic flow in the umbilical artery. In addition, four contributory parameters have been defined: AC or EFW<10th percentile and a pulsatility index (PI)>95th percentile in either the umbilical or uterine artery. For the diagnosis of late FGR, AC or EFW<3rd percentile have been defined as solitary parameters, while the following contributory parameters have been defined: EFW or AC<10th percentile, AC or EFW crossing centiles by >two quartiles on growth charts, and cerebroplacental ratio <5th percentile or umbilical artery PI>95th percentile.[3]

If the fetal AC or EFW measurement is between the 3rd and 10th percentiles but has normal uteroplacental and

fetoplacental circulation, the fetus is considered SGA. SGA involves structurally small, mostly healthy fetuses, who are at lower risk of adverse perinatal outcomes.[4]

Vasohibin-1 and vasohibin-2, two members of the vasohibin family, are the proteins responsible for the regulation of angiogenesis.[5] The human vasohibin-1 gene is located on chromosome 14q24.3, and its 44 kDa protein is post-translationally processed into vasohibin-1A and vasohibin-1 B isoforms.[6] The gene for human vasohibin-2 is located on chromosome 1q32.3, and its protein is composed of 355 amino acid residues.[7] It has been determined that vasohibin-1 and 2 are highly conserved among different species.[8]

Vasohibin-1 is dominantly expressed in endothelial cells in vitro, and its mRNA expression is induced by stimulations with certain angiogenic factors, such as the VEGF/VEGFR2 pathway, and FGF-2 via PKC-d pathway activation.[9] Vasohibin-1 has been found to inhibit the migration and proliferation of endothelial cells in cultures and exhibits feedback anti-angiogenic activity in vivo.[5] The endogenous expressions of vasohibin-2 in endothelial cells have been observed to be very low and independent of VEGF induction. However, vasohibin-2 is mainly expressed in mononuclear cells mobilized from bone marrow to stimulate angiogenesis.[10] Both vasohibin-1 and 2 proteins have been detected in the endothelial cells of developing organs of embryos and have been observed to be widely expressed in endothelial cells of embryonic organs in mid-gestation. It has been shown that from late pregnancy until birth, the expression of these proteins continues to a certain degree to meet the increased angiogenesis demand.[10]

In a study published in 2014, the role of the vasohibin family on angiogenesis in the placenta was evaluated. Wild-type, vasohibin-1$^{(-/-)}$, and vasohibin-2$^{(-/-)}$ mice models were used in the study to explore the function of vasohibins. They showed that the fetal vascular area was higher in the vasohibin-1$^{(-/-)}$ mice and lower in the vasohibin-2$^{(-/-)}$ mice relative to the wild-type mice.[11]

In light of all the above information, we aimed to investigate maternal serum vasohibin-1 and 2 concentrations in pregnant women diagnosed with FGR and SGA in the third trimester. We hypothesized that the concentration of vasohibin-1, an angiogenesis inhibitor, would be higher and that the concentration of vasohibin-2, which stimulates angiogenesis, would be lower in the FGR group compared to the SGA and control groups.

METHODS

The Local Ethics Committee of Ümraniye Training and Research Hospital, İstanbul, Turkiye, approved this study (Date: 16/03/2023, Decision No: 80). The study protocol followed the guidelines set by the Declaration of Helsinki, and informed written consent was obtained from all the participants. This prospective non-interventional cohort study included 81 pregnant women aged between 18 and 45 years who applied to the Gynecology and Obstetrics Clinic of Ümraniye Training and Research Hospital, İstanbul, Turkiye, between April 2022 and June 2022 and were followed up and delivered in our hospital. In the pregnancy follow-ups, 26 pregnant women were diagnosed with late FGR after 32 weeks of gestation and included in the late FGR group, 28 pregnant women were diagnosed with SGA and included in the SGA group, and 27 healthy pregnant women had AGA fetuses in the third trimester and formed the control group. The three groups were formed by matching maternal age, BMI, and gestational week at blood sampling.

Gestational age was calculated according to the last menstrual period and confirmed by fetal CRL measured in the first trimester. Serial fetal biometric measurements and percentiles of the participants were recorded during antenatal follow-ups until birth. Late FGR and SGA groups were created using the Delphi procedure reported in 2016 and the criteria reported in the ISUOG Application Guide published in 2020. Accordingly, pregnant women who did not have congenital anomalies and whose fetal EC or EFW values were below the 3rd percentile at or after the 32nd week of gestation were diagnosed with late FGR. Pregnant women whose fetal AC or EFW values were between the 3rd and 10th percentiles according to gestational age but whose umbilical artery Doppler values were normal were diagnosed with SGA.[3,12]

Multiple pregnancies, those who conceived via in vitro fertilization, and those with any pregestational disease were not included in the study. Pregnant women who had congenital uterine anomalies, were using any anticoagulant drugs, or were smokers were not included in the study. Pregnant women with known chromosomal or structural abnormalities in themselves, their partners, or their fetuses were not included in the study. Pregnant women who were categorized into the high-risk group in fetal chromosomal anomaly screening tests were not included in the study. In addition, those who were diagnosed with FGR and additionally developed gestational hypertension or preeclampsia were not included in the study.

Participants' age, BMI, and obstetric histories were recorded. Fetal biometric and umbilical artery Doppler velocimetry measurements were performed by the same obstetrician on the same ultrasound device (Hitachi Aloka F37 Ultrasound Device).

Approximately 5 mL of blood samples were drawn at any time of the day during the third trimester to investigate serum vasohibin-1 and 2 concentrations in the participants. Blood samples were placed in biochemistry tubes and kept at room temperature for about 20 minutes before centrifugation at 3000 rpm for 10 minutes. After centrifugation, the supernatant was separated and stored at –80 degrees. Serum vasohibin-1 concentrations were measured with the Human Vasohibin-1 ELISA Kit (Bioassay Technology Laboratory, 202 5/F 2 Bldg, 501 Changsheng S Rd, Nanhu Dist, Jiaxing, Zhejiang, China, Catalog No: E6395Hu) using the enzyme-linked immunosorbent assay method.

Serum vasohibin-2 concentrations were measured with the Human Tubulinyl-Tyr carboxypeptidase 2 ELISA Kit (Bioassay Technology Laboratory, 202 5/F 2 Bldg, 501 Changsheng S Rd, Nanhu Dist, Jiaxing, Zhejiang, China, Catalog No: E7212Hu) using the enzyme-linked immunosorbent assay method. For the vasohibin-1 ELISA kit used in the study, the inter-measurement value was 20–7000 ng/L, and the sensitivity was determined to

The late FGR, SGA, and control groups were compared in terms of maternal serum vasohibin-1 and 2 concentrations as the primary outcome of the study.

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 25.0 (IBM Corp., Chicago, IL, USA). The Kolmogorov–Smirnov test was used to check whether the distribution of the data was normally distributed. Descriptive statistical methods (mean, standard deviation, median, IQR, frequency, ratio) were used when evaluating the study data. An independent t-test was used to compare pairs of groups with parametric distribution, while one-way ANOVA was used for comparisons of more than two groups. The Mann–Whitney U test was used to compare pairs of groups with non-parametric distribution, while the Kruskal–Wallis test was used for comparisons of more than two groups. Significant differences resulting from more than two group comparisons were examined using the Tamhane and Tukey tests. Statistical significance was evaluated at $p<0.05$ for all values.

RESULTS

When the late FGR, SGA, and control groups were compared in terms of demographic characteristics, the groups were similar in terms of age, BMI, and parity (p=0.397, p=0.899, p=0.158, respectively). While the gestational week at which ultrasonographic examination was performed was similar in the three groups, fetal biparietal diameter, abdominal circumference, femur length measurement and estimated fetal weight were significantly lower in the late FGR group compared to the other two groups (p=0.981, p=0.005, p=0.001, p=0.009, p=0.001, respectively) (Table 1).

Table 1. Comparison of groups in terms of demographic ve ultrasonographic features

		LateFGR group =26	SGA group n=28	Control group n=27	p-value
Age (Years) Median (IQR)		29.5 (7)	30.5 (11)	29 (9)	0.397*
BMI (kg/m²) Median (IQR)		30.2 (4)	30.4 (3.2)	30.8 (2.2)	0.899*
Parity	Nulliparous n (%)	15 (57.7)	9 (32.1)	11 (40.7)	0.158**
	Multiparous n (%)	11 (42.3)	19 (67.9)	16 (59.3)	
Gestational week at which ultrasonographic evaluation was performed		34.5 (5)	35 (5.5)	35 (5)	0.981*
Biparietal diameter (mm) Median (IQR)		76.5 (14)	82.5 (9.5)	85 (11)	0.005*
Abdominal circumference (mm)Median (IQR)		268 (52)	294.5 (36)	310 (46)	0.001*
Femur length (mm) Median (IQR)		61 (12)	65.5 (9)	67 (9)	0.009*
EstimatedFetal Weight (g) Median (IQR)		1719 (945)	2243 (763.5)	2539 (1029)	0.001*

* Kuruskal Wallis test, ** chi-square test, FGR: fetal growth restriction, SGA: small for gestational age

When the three groups were evaluated in terms of perinatal outcomes, the gestational age at birth was significantly lower in the FGR group than in the other groups, while the number of participants who gave birth by cesarean section was higher (p=0.000, p=0.025, respectively). Newborn weight and height and first- and fifth-minute Apgar scores were significantly lower in the late FGR group, and admission to the neonatal intensive care unit was significantly higher than in the other two groups (p=0.000, for all) (Table 2).

Table 2. Comparison of the groups in terms of perinatal outcomes

		Late FGR group n=26	SGA group n=28	Control group n=27	p-value
		Mean± SD	Mean± SD	Mean± SD	
Gestational age at birth (week) Median (IQR)		37 (3)	39 (2.5)	38 (3)	0.000*
Mode of delivery	Vaginal Birth n (%)	5 (19.2)	14 (50)	14 (51.9)	0.025**
	Cesarean Section n (%)	21 (80.8)	14 (50)	13 (48.1)	
Birth weight (g) mean± SD		2039 ± 575	2664 ± 474	3286 ± 370	0.000***
Birth height (cm) Median (IQR)		45 (3)	48 (3.7)	50 (3)	0.000*
1st minute apgar score Median (IQR)		8 (1)	8 (1)	9 (1)	0.000*
5th minute apgar score Median (IQR)		9 (0)	(1)[9]	10 (0)	0.000*
NICU admission n (%)		14 (53.8)	4 (14.3)	1(3.7)	0.000**

Kuruskal Wallis test, **chi-square test, *** One-way ANOVA test, FGR: fetal growth restriction, SGA: small for gestational age, NICU: neonatal intensive care unit

The three groups were similar in terms of gestational age at which blood was drawn (p=0.981). The three groups were also similar in terms of maternal serum vasohibin-1 and 2 concentrations (p=0.139, p=0.198, respectively). The highest serum vasohibin 1 concentration was detected in the control group, followed by the SGA and late FGR groups (1391.38 ng/mL, 1311.15 ng/mL, 1227.41 ng/mL, respectively) (Figure 1). The highest serum vasohibin 2 concentration was detected in the control group, followed by the SGA and late FGR groups (14.34 ng/mL, 11.86 ng/mL, 11.24 ng/mL, respectively) (Figure 2) (Table 3).

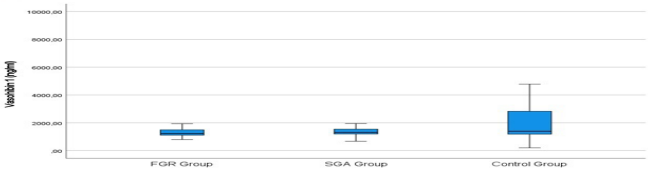

Figure 1. Box plot of serum vasohibin 1 concentrations of FGR, SGA, and control groups

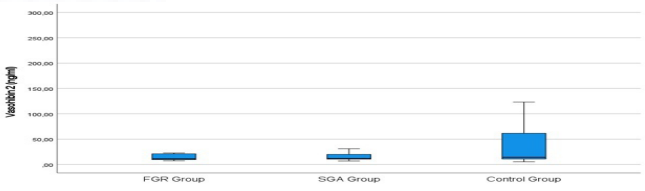

Figure 2. Box plot of serum vasohibin 2 concentrations of FGR, SGA, and control groups

Table 3. Comparison of the groups in terms of maternal serum vasohibin-1 and vasohibin-2 concentrations

	Late FGR Group n=26	SGA Group n=28	Control Group n=27	p-value
Gestational age at blood sampling (weeks) Median (IQR)	34.5 (5)	35 (5.5)	35 (5)	0.981
Vasohibin-1 concentration (ng/mL) Median (IQR)	1227.41 (386.29)	1311.15 (354.03)	1391.38 (2235.63)	0.139
Vasohibin-2 concentration (ng/mL) Median (IQR)	11.24 (11.59)	11.86 (9.39)W	14.34 (52.73)	0.198

Kruskal Wallis Test, FGR: fetal growth restriction, SGA: small for gestational age

DISCUSSION

In this study, the relationships between fetal growth and maternal serum vasohibin-1 and 2 concentrations taken in the third trimester were investigated. Serum vasohibin 1 and 2 concentrations were found to be similar in pregnant women whose pregnancies were complicated by late FGR, pregnant women diagnosed with SGA, and pregnant women with AGA fetuses.

Fetal growth during pregnancy is a dynamic process that is dependent on multiple factors.[13] It has been established that some disorders in the early stages of placental development are associated with adverse pregnancy outcomes, such as fetal growth retardation or preeclampsia.[14,15] In addition to known classical theories such as inappropriate trophoblast migration or insufficient remodeling in the spiral arteries, many molecules that may be related to fetal growth restriction have been investigated in recent years.[16]

The placenta is a multifaceted, transient organ with a very high rate of angiogenesis, organized in a way that allows nutrient intake, waste removal, and gas exchange for the fetus.[17] Placental angiogenesis is regulated by many factors, including the vascular endothelial growth factor (VEGF)/ VEGF receptor system, angiopoietin/TIE receptor system, platelet-derived growth factor (PDGF)/PDGF receptor system, and transforming growth factor ß (TGF- ß)/ TGF- ß receptor system.[18] Among them, the VEGF family is considered the most important factor for promoting angiogenesis in the placenta.[19]

Vasohibin-1 was isolated as a negative feedback regulator of angiogenesis induced in endothelial cells by angiogenesis stimulators, such as VEGF and fibroblast growth factor 2 (FGF-2).[20] Subsequently, a gene homologous to vasohibin-1 was identified and named vasohibin-2.[21] Studies have shown that vasohibin-1, expressed in the termination zone of endothelial cells, inhibits angiogenesis, while vasohibin-2, secreted predominantly from mononuclear cells, promotes angiogenesis at the sprouting front.[10]

Suenaga et al.[11] used a mouse model to demonstrate the role of vasohibins in the placenta. They showed that the placental vascular area in mice with vasohibin-1 gene knockdown was increased compared to the wild type. On the contrary, it was shown that in mice with vasohibin-2 gene knockdown, the vascular area was decreased compared to the wild type. Moreover, vasohibin-2 also plays a role in regulating cell fusion for syncytiotrophoblast formation. In this study, researchers also performed immunohistochemical analysis to determine the localization of vasohibin proteins in the term human placenta. It has been shown that the vasohibin-1 protein is highly expressed in endothelial cells of the villous body, while the vasohibin-2 protein is selectively expressed only in trophoblasts.

Farina et al.[22] investigated various gene expressions in chorionic villus samples taken for fetal karyotype at the 11th week of gestation from pregnant women who developed preeclampsia in the advanced gestational week. It was shown that vasohibin-1 gene expression increased 2.3 times in the group that developed preeclampsia compared to the normal healthy group that did not develop preeclampsia.In 2021, Liang et al.[23] investigated the relationship between preeclampsia and vasohibin-1. In this study, vasohibin-1 expression in placental tissue and vasohibin-1 concentration in the serum of pregnant women who developed preeclampsia during pregnancy were evaluated and compared with normotensive healthy controls. Both serum vasohibin-1 concentration and expression of vasohibin-1 in placental tissue were found to be significantly higher in preeclamptic pregnant women than in normotensive controls. The authors suggested that vasohibin-1 could be used as a biomarker for preeclampsia.

At the beginning of our study, we assumed that the vasohibin 1 concentration in the late FGR group would be higher than in the SGA and control groups, similar to what was observed in preeclamptic pregnant women in Liang et al.'s[23] study. In contrast, we found the lowest serum vasohibin 1 concentration in the late FGR group. Additionally, at the beginning of our study, we expected vasohibin-2 concentration to be lower in the late FGR group than in the SGA and control groups. Consistent with this, we detected the lowest vasohibin-2 concentration in the late FGR group, although the finding was not statistically significant.

To the best of our knowledge, this is the first study to examine maternal serum vasohibin-1 and 2 concentrations in the third trimester in pregnant women diagnosed with late FGR and SGA.

Limitations

The small number of participants and the fact that serum vasohibin-1 and 2 concentrations were evaluated only once in the third trimester are important limitations of this single-center study.

CONCLUSION

In this study, it was determined that serum vasohibin-1 and 2 concentrations were similar in the third trimester in pregnant women diagnosed with late FGR and SGA and in pregnant women with AGA fetuses. Vasohibin-1 and 2 are involved in the regulation of placental angiogenesis, but their roles in intrauterine fetal growth remain unclear. This preliminary study provides a foundation for future studies aimed at examining the roles of vasohibin-1 and 2 molecules in intrauterine fetal growth.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Ümraniye Training and Research Hospital Clinical Researches Ethics Committee (Date: 16.03.2022, Decision No: 80).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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The consequence of 12 weeks of pilates exercise on the quality of sleep and life of pregnant women

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ABSTRACT

Aims: As one of the most critical periods in women's lives, pregnancy affects their physical, mental, and functional conditions. These changes can affect the quality of life and sleep of pregnant women. The main purpose of this study is to investigate the effect of pilates exercises on 150 young pregnant women between the ages of 20-40.

Methods: This randomized double-blind clinical trial study was done between September 2023 and March 2024, including 60 pregnant women in case group and 90 control subjects of similar age and body mass index (BMI). This study investigated the effect of 12 weeks of pilates exercises on the quality of women's sleep and life. Quality of life was measured by the short-form 36 (SF-36) and quality of sleep by the Pittsburgh Sleep Quality Index (PSQI). People were randomly divided into intervention and control groups. Pregnant women in the intervention group were required to participate in two pilates sessions per week for 12 weeks from the 20th week of pregnancy.

Results: Our results found that quality of life levels were statistically significant higher than case group after intervention compared to control group (p<0.05; 67.19 vs. 54.94). Also, a statistically significant association between the case and control regarding quality of sleep (p<0.05; 5.41 vs. 6.77).

Conclusion: It is concluded that performing moderate-intensity pilates exercises for 12 weeks in the last months of pregnancy can increase sleep quality and life.

Keywords: Pregnant women, pilates, sleep quality, quality of life, women's life

INTRODUCTION

Pregnancy is one of the most essential stages of a women's life and is associated with fundamental lifestyle change.[1] Physiological, anatomical, and biochemical changes in pregnant women cause stress and decrease their quality of life (QoL).[2] According to studies, discomfort and problems during pregnancy reduce a woman's ability to perform daily roles in life and cause many changes in people's physical, mental, and social issues, all of which can disrupt the QoL of pregnant women.[1]

The quality of sleep has a significant impact on the QoL and is one of the main foundations of health.[3] Sleep in pregnant women is generally disrupted as a consequence of numerous factors.[4] Sleep problems is one of the most prevalent complaints during pregnancy.[5] The most common type of sleep disorder in pregnancy is insomnia. Most sleep disorders during pregnancy are experienced by expectant mothers in the third trimester and closer to the end of pregnancy. Insomnia, with changes in a women's immune system, such as changes in the level of C-reactive protein and cytokines, can have adverse consequences such as premature birth, reduced pain tolerance, blood pressure disorders, mental health problems, low birth weight, glucose tolerance disorders and depression during pregnancy and postpartum are related.[6,7]

Despite the apparent reduction of sleep quality in pregnancy, the mechanisms and solutions to this problem are still unknown. Sleeping pills are the first recommended treatment for chronic insomnia, which has severe side effects for pregnant women. Therefore, complementary and alternative therapies such as acupressure, acupuncture, aromatherapy, reflexology, and exercise have been followed in many studies.[8]

QoL includes different aspects of health and physical, mental, and social comfort of people. Each dimension of quality of life has two subjective and objective elements that can be measured. Moderate physical activity can improve a person's QoL by affecting physical and mental health. Regarding the necessity of physical activity in women with uncomplicated pregnancies, the American College of Obstetricians and Gynecologists (ACOG) recommends exercising at moderate intensity for 20-30 minutes a day during pregnancy on most or all days of the week.[9] Pilates exercise is a prevalent physical activity preferred by pregnant women.[10] ACOG recommends modified pilates during pregnancy.[11] By saving and increasing the energy level, pilates improves the body's strength, stability, and flexibility and is beneficial in musculoskeletal pain, stress and fatigue reduction, creating relaxation, and curing sleep health.[12,13]

Despite the many advantages of pilates and suggestions for doing this exercise during pregnancy, its benefits are still debated, and more relevant research is needed. Considering the existing uncertainties about the effect of pilates on the quality of sleep and life of pregnant women, the present study was conducted to investigate the effect of pilates on the outcomes expressed in pregnant women.

METHODS

This randomized double-blind clinical trial was conducted on patients between September 2023 and March 2024. Local ethics committee approval was obtained from İstanbul Medipol University Non-invasive Clinical Researches Ethics Committee (Date: 12.10.2023 Decision No: 839). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study did not include women with a ban on exercise during pregnancy. Women who had chronic diseases, multiple pregnancies and were not between 20-40 years old were also excluded from the study.

Pilates exercises for the case group started from the 20th week of pregnancy. At the beginning of the research gestational age was determined through ultrasound. Exercises were performed in the gym under the supervision of a certified pilates instructor and based on safe pilates exercises (modified plank, banana leg, and modified roll-up) during pregnancy. The intervention was conducted with moderate intensity for 12 weeks and twice a week. Each pilates training session, including 8-10 strength exercises, was done for 30 minutes. The trainer controlled the research participants' attendance list to ensure the exercises' regularity. The women of the case group were followed up regularly through phone calls every week. Women in the control group also received usual care.

This study's data collection tools included a demographic profile questionnaire, the Pittsburgh Sleep Quality Index (PSQI), and short-form 36 (SF-36) questionnaire.[14,15] To investigate the effect of pilates exercise, sleep quality and life quality questionnaires were completed by women in both case and control groups. PSQI is an international standard instrument validated in several studies. The reliability and validity of the Turkish version of this questionnaire were checked and confirmed.[16] The total score of this index is between 0-21, and the total score is greater than 6, showing the inappropriateness of sleep quality.

The quality of life index SF-36 is also an international standard instrument whose Turkish version validated in previous study.[17] This questionnaire consists of 8 sections, which include physical function (10 items), physical pain (2 items), social function (2 items), mental health (5 items), general health (5 items), vitality (4 items), physical problems (4 items) and mental problems (3 items) and includes 36 questions in total. Therefore, the mentioned questionnaire tries to express a comprehensive assessment of the individual's current health status to the researcher by examining the individual's health status in 8 dimensions. The total score of this index is between 0-100.

Statistical Analysis

The study used mean (M) and standard deviation (SD) to report the descriptive statistics of data. The categorical variables described by number and percent and analyzing by Chi-Squared test. To compare the data between groups, the Independent t-test was employed, which is appropriate for normal distributions. SPSS software (version 21.0, SSPS Inc., Chicago, IL, USA) was employed for statistical analysis. The threshold for statistical significance was set at a p-value of less than 0.05.

RESULTS

This study included one hundred fifty age-matched (25.11±4.24) and body mass index (BMI) matched (26.21±3.42) women. Table 1 shows a comparison of demographic parameters between case and control groups. Demographic characteristics including age, BMI, women's occupation, use of pregnancy supplements, history of previous pregnancy and history of regular exercise were compared.

Table 1. A comparison of demographic parameters between case and control groups (n=150)

Demographic parameters	Case (n=60) M±SD n(%)		Control (n=90) M±SD n(%)	p-value
Age	25.36±4.94		24.90±4.11	0.814
BMI	26.45±3.87		26.01±3.45	0.645
Women's occupation	Housewife	39 (65)	50 (62.5)	0.971
	Employee	12 (20)	17 (21.1)	
	Student	9 (15)	13 (16.25)	
BMI	Underweight (<18)	7 (11.7)	10 (12.5)	0.940
	Healthy weight (18-25)	20 (33.3)	25 (31.25)	
	Over weight (25-30)	21 (35)	27 (33.75)	
	Obesity (>30)	12 (20)	17 (21.25)	
Use of pregnancy supplements	Yes	51 (85)	72 (90)	0.094
	No	9 (15)	8 (10)	
History of previous pregnancy	Yes	27 (45)	34 (42.5)	0.146
	No	33 (55)	46 (57.5)	
History of regular exercise	Yes	22 (36.7)	32 (40)	0.104
	No	38 (63.3)	38 (60)	

BMI: Body mass index

There was not a statistically significant between the case and control regarding women's occupation (p>0.05). There was not a statistically significant between the case and control regarding use of pregnancy supplements, history of previous pregnancy, and history of regular exercise (p>0.05).

Table 2 shows comparison PSQI and SF-36 scores between case and control groups in detail. As stated in the table above, an Independent t-test did not find a statistically significant association between case and control in terms of PSQI score in pre-intervention (p>0.05). The PSQI score was similar for case and control groups (6.21 vs. 6.38). There was a statistically significant association was observed between the case and control regarding PSQI score in post-intervention (p<0.05). Women after pilates exercise had significantly higher sleep quality than controls (5.41 vs. 6.77). In Table 2, the comparison and examination of the sleep quality score separately before and after the intervention in each case and control group shows that the average sleep quality score before the intervention was insignificant between the control and intervention groups. However, after the intervention, the average sleep quality score of the case group was significantly lower than the score of the control group, and considering that in the PSQI, the total score is greater than six and shows the inappropriateness of the sleep quality, so it concluded that the case group experienced better sleep quality than the control group.

As stated in Table 2, a statistically significant association was observed between the case and control regarding the SF-36 score in post-intervention (p<0.05). The case group had significantly higher quality of life score than controls after the pilates exercise (67.19 vs. 54.94). There was not a statistically significant association was observed between the case and control regarding SF-36 score in pre-intervention (p<0.05). Figure shows a comparison of PSQI and SF-36 scores between case and control groups.

Table 2. A comparison PSQI and SF-36 scores between case and control groups (n=150)

Comparison criteria		Case (n=60) M±SD	Control (n=90) M±SD	p-value
PSQI	Pre-intervention	6.21±0.94	6.38±21.35	0.68
	Post-intervention	5.41±1.14	6.77±1.09	0.005
SF-36	Pre-intervention	54.94±4.11	55.65±5.93	0.7
	Post-intervention	67.19±5.15	54.94±7.45	<0.001

PSQI: Pittsburgh Sleep Quality Index, SF-36: short-form-36

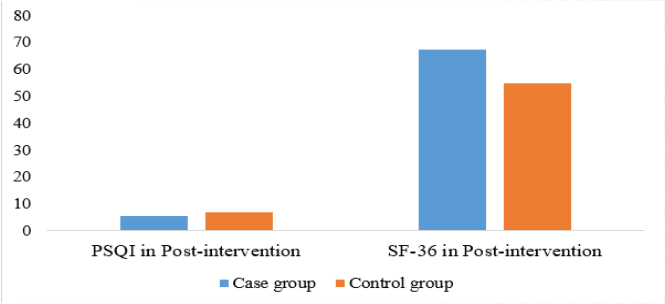

Figure. A comparison of PSQI and SF-36 scores between case and control groups

DISCUSSION

The present study, conducted to measure Pilates' effect on the quality of sleep and life of pregnant women between the ages of 18-30, showed that regular Pilates exercise during the last months of pregnancy increases the quality of sleep and life in pregnant women. Meanwhile, in the present study, sleep quality decreased with the progress of pregnancy in the control group, and the quality of life remained unchanged.

Scholars have recently highlighted the significance of exercise for pregnant women.[18] Our results were comparable to those of prior investigations that reported the positive impact of physical activities on pregnant women's QoL and mental health.[19,20] The details of physical activities and their positive impact are still essential and debatable topics among researchers. Liu et al.[21] showed that group-based aerobic or resistance exercises increase the positive effects of these exercises on pregnant women's QoL.

Ferraz et al.[22] in a systematic review and meta-analysis, reviewed articles to evaluate the effect of pilates on the QoL of pregnant women. Based on the findings of this study, pilates exercises increase the QoL in pregnant women by reducing low-back pain. Mazzarino et al.[23] reported regular pilates exercises to increase the QoL of low-risk pregnant women. They showed that this type of exercise is feasible for pregnant women and have small benefits for QoL, pain, and mobility. The results were consistent with the present study. Contrary to the results of the present study, Gustafsson et al.[24] showed that performing sports exercises for 24 sessions at home did not improve pregnant women's QoL. In this study, unlike the current study, sports training did not improve the quality of life. The lack of alignment in the results of these studies can be due to the difference in sports training, intervention time, and lifestyle of the investigated community.

Azward et al.[25] indicated the positive effect of yoga on improving sleep quality in the third trimester in pregnant women. Kocsis et al.[26] showed the positive effect of gymnastics on the sleep quality of pregnant women during a designed 10-week exercise program. McCarthy et al.[27] in a systematic review and meta-analysis, showed that different types of exercise during pregnancy improve sleep quality during pregnancy. Although the exercise type differed in these studies, the results were consistent with the present study. Hyun et al.[28] reported that eight weeks of home-based tele-pilates exercise (50 min/day and twice a week) relieves pelvic and back pain and increases sleep quality during pregnancy. et al.[29] suggested clinical Pilates exercises, including 18 positions, as a safe and effective method for reducing pain, disability and sleep problems in pregnant women. Insomnia in pregnant women is annoying, especially in the final months, and because the exact cause is unknown, regular Pilates exercises can be used for its treatment.

The main contribution of this study is to increase the quality of sleep and life in pregnant women. Reducing the quality of sleep and life is one of the most common problems in this period. The importance of physical activity during pregnancy is clear, but the details related to the number of exercises and their intensity should be considered more in research. This study investigated the effect of regular pilates exercises on pregnant women and reported its effects.

The size of the present study could be larger, and it is recommended to repeat the present study with a more significant number of participants in future studies.

There are few studies on regular pilates practice to improve quality of life and treat insomnia. In the discussion section, the results of the present study were compared with a limited number of related studies. It is recommended to conduct more research on specific groups of pregnant women in future studies to examine the pilates exercises. Researching the effect of regular pilates exercises on women with older age and higher BMI can reveal the possible risks of these exercises on women.

CONCLUSION

In view of the fact that the positive effects of Pilates exercises on the QoL and sleep reported in this study, it is possible to suggest pilates during pregnancy to pregnant women. Insomnia and reduced quality of life in pregnant women profoundly affect them, and providing solutions without negative effects can be helpful. There is a need for more research on the subject with larger sample size.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by İstanbul Medipol University Non-invasive Clinical Researches Ethics Committee (Date: 12.10.2023 Decision No: 839).

Informed Consent

All patients signed the free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Review

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Male infertility: an overview of etiology, diagnosis and management

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ABSTRACT

Male infertility, a multifaceted condition characterized by the inability to achieve pregnancy within a partner after a year of unprotected intercourse, affects approximately 7% of men globally. The etiology of male infertility is diverse, including genetic abnormalities, hormonal imbalances, physical obstructions, and lifestyle factors. This review synthesizes current knowledge on the causes, diagnostic methods, and therapeutic interventions for male infertility, with an emphasis on recent advances in genetic and assisted reproductive technologies (ART). The diagnostic approach to male infertility involves a comprehensive evaluation, including semen analysis, hormonal profiling, genetic testing, and imaging techniques, to identify underlying causes. Management strategies range from lifestyle modifications and pharmacological treatments to surgical interventions and ART, such as in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI). Emerging technologies, including the use of artificial intelligence in semen analysis and the development of novel sperm retrieval techniques, promise to enhance diagnostic accuracy and treatment outcomes. Despite significant progress, challenges remain in improving access to care and addressing ethical considerations in the use of ART. This review highlights the importance of a multidisciplinary approach to the management of male infertility, integrating advances in medical science with considerations of patient well-being and ethical standards. Future research directions include elucidating the genetic basis of idiopathic male infertility, optimizing ART outcomes, and developing personalized treatment strategies. The ultimate goal is to improve the reproductive health and quality of life for affected individuals and couples.

Keywords: Male infertility, semen analysis, assisted reproductive technology, genetic abnormalities, hormonal imbalances, lifestyle factors

INTRODUCTION

Infertility, defined as the inability to achieve pregnancy after 12 months of regular, unprotected sexual intercourse, affects millions of couples worldwide. Within this context, male infertility contributes to approximately 50% of all infertility cases, either as a sole factor or in conjunction with female factors.[1] Despite its high prevalence, male infertility often remains overshadowed by female infertility in both research and public discourse, leading to a lack of awareness and understanding about its significant impact on affected individuals and couples.[2]

The study of male infertility encompasses a wide range of disciplines, including endocrinology, genetics, urology, and reproductive medicine, reflecting the complexity of its causes and the multifaceted approaches required for its diagnosis and treatment.[3] Advances in medical science over the past decades have significantly improved our understanding of male reproductive health, yet many aspects of male infertility remain poorly understood, underscoring the need for continued research and education.[4]

Male infertility can result from a variety of factors, including genetic abnormalities, hormonal imbalances, physical obstructions in the reproductive tract, lifestyle influences, and environmental exposures.[5] These factors can affect spermatogenesis, the process of sperm production, and/or the sperm's ability to fertilize an egg, thereby impairing male fertility.[6] The consequences of infertility extend beyond the biological inability to conceive, impacting psychological well-being, relationships, and quality of life for many men and their partners.[7]

This review aims to provide a comprehensive overview of the current state of knowledge on male infertility, including its causes, diagnostic approaches, and treatment options.

By synthesizing recent advances in the field, we seek to highlight the importance of a multidisciplinary approach to the management of male infertility, which not only addresses the biological aspects of the condition but also considers the psychological and social implications for affected individuals.[8] Furthermore, we discuss emerging technologies and future research directions that hold promise for improving diagnostic accuracy and treatment outcomes for men with infertility, ultimately contributing to the broader goals of reproductive health and family planning.[9]

The understanding and management of male infertility are evolving fields, reflecting ongoing research and advances in medical science. As such, this review underscores the dynamic nature of the topic and the continuous need for up-to-date knowledge to inform clinical practice and support those affected by male infertility.[10]

Etiology of Male Infertility

Genetic factors: Genetic abnormalities are a significant cause of male infertility, accounting for up to 15% of cases.[11] Chromosomal anomalies like Klinefelter syndrome, Y chromosome microdeletions, and mutations in specific genes related to spermatogenesis can severely impact sperm production and function. Genetic screening has become an essential component of the infertility evaluation, allowing for targeted interventions and informed decision-making regarding assisted reproductive technologies (ART).[12]

Hormonal disturbances: Hormones play a crucial role in regulating spermatogenesis and male reproductive function. Disorders affecting the hypothalamic-pituitary-gonadal axis can lead to insufficient production of testosterone and other key hormones, resulting in reduced sperm production and infertility.[13] Conditions such as hyperprolactinemia, thyroid disorders, and adrenal disorders can also impact fertility through hormonal imbalances. Treatment of these underlying hormonal issues can often restore fertility or improve outcomes with ART.[14]

Anatomical and physical obstructions: Obstructions in the male reproductive tract, such as those caused by congenital absence of the vas deferens, epididymal blockages, or scarring from infections or surgeries, can prevent the normal transport of sperm from the testes to the ejaculate.[15] Such conditions can often be corrected surgically, thereby improving the chances of natural conception or facilitating sperm retrieval for use in ART.[16]

Lifestyle and environmental factors: Lifestyle choices and environmental exposures have been increasingly recognized for their impact on male fertility. Factors such as smoking, excessive alcohol consumption, illicit drug use, obesity, and exposure to environmental toxins (e.g., pesticides, heavy metals) have been linked to reduced sperm quality and quantity.[17] Additionally, occupational hazards and exposure to heat can also adversely affect spermatogenesis. Modifying these lifestyle factors can improve sperm parameters and overall fertility prospects.[18]

Understanding the etiology of male infertility is crucial for the development of effective treatment strategies. By addressing the underlying causes, whether genetic, hormonal, anatomical, or lifestyle-related, clinicians can offer more targeted and successful interventions for couples struggling with infertility.

DIAGNOSTIC EVALUATION

Semen Analysis, Parameters and Interpretation

Semen analysis remains the cornerstone of male infertility evaluation, providing essential information on sperm count, motility, and morphology.[19] Parameters such as semen volume, sperm concentration, total sperm count, vitality, and morphology are assessed according to the World Health Organization (WHO) criteria. Abnormal results may indicate issues with spermatogenesis, obstruction, or ejaculation and require further investigation.[20]

Hormonal Assessment

Hormonal profiling is crucial for identifying disorders of the hypothalamic-pituitary-gonadal axis that could affect spermatogenesis and overall reproductive health. Measurements typically include follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone, and prolactin levels. Abnormal levels may suggest hypogonadism, hyperprolactinemia, or other endocrine disorders requiring targeted treatment.[21]

Genetic Testing in Infertility

For men with severe sperm production issues or specific clinical presentations (such as azoospermia), genetic testing can identify chromosomal anomalies, Y chromosome microdeletions, and mutations in genes affecting fertility. Such tests help in counseling couples about their reproductive options, including the use of donor sperm or the risks of transmitting genetic conditions to offspring.[22]

Imaging Modalities (Ultrasound, Magnetic Resonance Imaging (MRI))

Imaging techniques play a role in diagnosing anatomical causes of infertility, such as varicoceles, obstructive azoospermia, and congenital anomalies. Scrotal ultrasound is the most commonly used imaging tool for evaluating the testicles and surrounding structures. MRI may be employed for more detailed assessment of complex cases or when ultrasound findings are inconclusive.[23]

The comprehensive diagnostic evaluation of male infertility involves a multimodal approach, incorporating semen analysis, hormonal profiling, genetic testing, and imaging to identify the underlying causes of infertility. This enables the formulation of a targeted treatment plan to address specific issues and improve the chances of successful conception.

Management and Treatment

Lifestyle modifications: Addressing modifiable lifestyle factors is a cornerstone in the management of male infertility. Changes such as reducing alcohol and tobacco use, achieving a healthy weight, and avoiding exposure to environmental toxins have been shown to significantly improve sperm quality and fertility outcomes.[24] Dietary modifications, including increased intake of antioxidants, have also been associated with enhanced sperm parameters.[25]

Pharmacological treatment: For cases of male infertility stemming from hormonal imbalances or specific medical conditions, pharmacological treatments can be effective. Gonadotropins, anti-estrogens (such as clomiphene citrate),

and aromatase inhibitors are among the medications used to improve spermatogenesis by correcting hormonal levels.[26] Additionally, the use of antioxidants has gained attention for its potential to reduce oxidative stress, a known cause of sperm DNA damage.[27]

Surgical interventions: Surgical options for the treatment of male infertility include varicocelectomy for varicocele, transurethral resection of ejaculatory ducts for obstructions, and microsurgical repair of vas deferens or epididymal blockages.[28] For azoospermic men, techniques such as microdissection testicular sperm extractin(micro-TESE)are employed to retrieve sperm directly from the testes for use in ART.[29]

ART:ART, such as in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI), has revolutionized the treatment of male infertility, offering hope to couples where other treatments have failed. ICSI, in particular, involves the direct injection of a single sperm into an egg, and is especially beneficial for cases of severe male factor infertility.[30] The success of ART procedures depends on various factors, including the underlying cause of infertility, the age of the female partner, and the quality of the sperm and egg.[31]

The management and treatment of male infertility require a personalized approach, taking into consideration the specific causes and circumstances of each case. Through a combination of lifestyle modifications, pharmacological treatments, surgical interventions, and the use of ART, many couples affected by male infertility can achieve their dream of parenthood.

Emerging Technologies and Future Directions

The role of artificial intelligence (AI) in diagnosis: AI and machine learning are revolutionizing the field of male infertility diagnosis by enabling more accurate and efficient analysis of semen parameters. AI algorithms can analyze vast datasets from semen analysis to identify patterns and predict fertility outcomes with higher precision than traditional methods.[32] Furthermore, AI can assist in the morphological assessment of sperm, identifying subtle anomalies that may not be visible to the human eye, thus improving the selection process for ART.[33]

Advances in sperm retrieval techniques: Recent innovations in sperm retrieval techniques have significantly improved the prospects for men with azoospermia to father biological children. Techniques such as (micro-TESE) have been refined to increase the yield of viable sperm while minimizing tissue damage.[34] Additionally, the development of non-invasive methods for sperm retrieval and the use of stem cell technology to generate sperm from somatic cells are areas of ongoing research with the potential to transform the treatment of male infertility.[29]

Ethical considerations in ART: As ART, including IVF and ICSI, becomes increasingly sophisticated, ethical considerations become more complex. Issues such as the disposition of unused embryos, genetic testing and selection of embryos, and the use of donor gametes raise important questions about consent, privacy, and the welfare of potential offspring.[25] The advent of gene editing technologies, such as CRISPR-Cas9, for correcting genetic defects in embryos further complicates the ethical landscape, necessitating careful consideration of the long-term implications for individuals and society.[18]

The integration of emerging technologies into the diagnosis and treatment of male infertility holds promise for improving outcomes for affected individuals and couples. However, these advancements also require careful consideration of ethical implications and the establishment of guidelines to ensure that these technologies are used responsibly and equitably. As the field continues to evolve, ongoing dialogue among clinicians, researchers, ethicists, and patients will be essential to navigate the challenges and opportunities presented by these innovations.

CONCLUSION

The management of male infertility encompasses a complex interplay of diagnostic evaluations, therapeutic interventions, and, increasingly, the application of advanced technologies and ethical considerations. The key points addressed in this review highlight the multifaceted nature of male infertility, underscoring the importance of a comprehensive approach to diagnosis, which includes semen analysis, hormonal assessment, genetic testing, and imaging modalities. Treatment strategies, ranging from lifestyle modifications and pharmacological treatments to surgical interventions and assisted reproductive technologies like IVF and ICSI, have been discussed to illustrate the diverse options available to couples facing this challenge.[33]

The importance of a multidisciplinary approach in the management of male infertility cannot be overstated. Collaboration among specialists in urology, endocrinology, genetics, psychology, and reproductive medicine is crucial to address the wide array of factors that can contribute to male infertility. This team-based approach ensures that patients receive holistic care that addresses not only the physical aspects of infertility but also the psychological and emotional impacts, enhancing the overall likelihood of successful treatment outcomes.[30]

Future research directions in the field of male infertility are poised to further elucidate the underlying mechanisms of male reproductive dysfunction, improve diagnostic accuracy, and develop more effective treatments. Emerging technologies, such as artificial intelligence in diagnosis and advances in sperm retrieval techniques, offer promising avenues for enhancing the precision and efficacy of infertility treatments. Additionally, the ethical considerations surrounding assisted reproductive technologies call for ongoing research and dialogue to navigate the complex moral landscape of modern reproductive interventions. The continued exploration of these areas is essential to advance the science of reproductive medicine and improve the care and outcomes for individuals and couples affected by male infertility.[32]

In conclusion, male infertility is a complex condition requiring a nuanced and comprehensive approach to management. By embracing a multidisciplinary strategy and continuing to pursue research in emerging technologies and ethical considerations, the field can move forward in offering effective solutions and hope to those struggling with infertility.

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Review

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Nutritional support for immune health during infections

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ABSTRACT

Infectious diseases are common in underdeveloped and developing countries. Malnutrition plays an important role in disease etiology, remarkably increasing morbidity and mortality risks during the early stages of life, such as infancy and childhood. Nutrients such as glutamine, arginine, omega-3 and omega-6 fatty acids, zinc, selenium, iron, vitamins A, C, E, D and B6, components of breast milk, and adequate energy intake strengthen the immune system, reduce infection risk, and play a key role in combating diseases. This review highlights the importance of nutrition for the treatment of infectious diseases.

Keywords: Nutrition, immunity, infectious diseases

INTRODUCTION

Adequate nutrition is essential to prevent infections and reduce morbidity and mortality. Nutritional status influences the host's susceptibility to infections and its ability to fight them.[1] Malnutrition is the primary cause of immunodeficiency (Figure).[2]

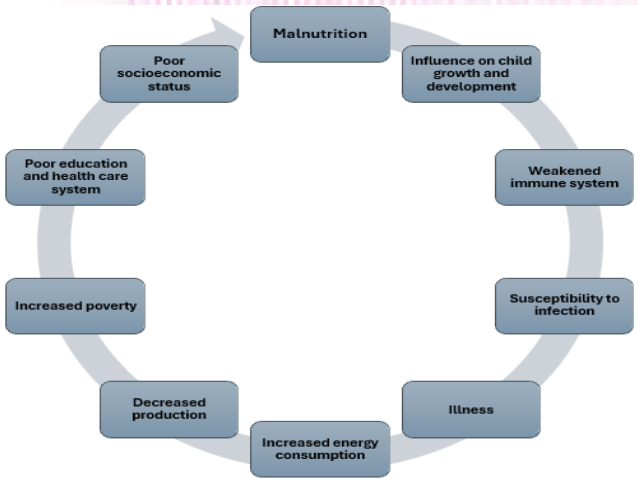

Figure. Cycle of the malnutrition and infection[7]

Owing to the deficiency of some micronutrients, the immune system is adversely affected, causing a weakening of the immune system and infection.[3,4] Therefore, adequate nutrition is critical during fetal development and infancy, when the immune system is not fully mature.[5]

Infectious diseases are differently affected by nutritional intake. Diseases such as pneumonia, infectious diarrhea, measles, and tuberculosis are highly affected by malnutrition, while infections such as influenza, viral encephalitis, and tetanus are moderately or minimally affected by malnutrition.[6]

EFFECTS OF NUTRIENTS ON INFECTIOUS DISEASES

Nutritional habits and food consumption directly impact the immune system. Nutrient deficiency, excessive consumption of sugary and allergenic foods, and high blood cholesterol levels suppress the immune system.[8] Proper nutrition also influences the immune system by affecting the composition of gut microbiota. Moreover, the microbiota produces metabolites such as short-chain fatty acids and ligands of the aryl hydrocarbon receptor that process food components and control the development and activity of certain immune cells, including regulatory T cells.[9] Glutamine, arginine, omega-3 and omega-6 fatty acids, zinc, selenium, iron, vitamins A, C, E, D, and breast milk components are the main nutrients that affect the immune system.[10-12] Deficiency of these nutrients in children may impair the immune system function in later periods.[13]

These nutrients have various functions in the human body.[14] We can list these as follows:

- It acts as fuel for the immune system's activity.
- It forms building blocks for the production of RNA and DNA, proteins (antibodies, cytokines, receptors, acute phase proteins, etc.), and new cells.

- Forms specific substrates for the production of immune-active metabolites (e.g., arginine as a nitric oxide substrate).
- Regulators of immune cell metabolism (e.g., vitamin A, zinc)
- They have specific antibacterial or antiviral effects (e.g., vitamin D and zinc).
- They protect the host from oxidative and inflammatory stress (e.g., vitamin C, vitamin E, zinc, selenium, long-chain omega-3 fatty acids, and many plant polyphenols).
- They act as substrates for gut microbiota, thus modulating the immune system.
- The following are the nutrition and lifestyle recommendations for effective functioning of the immune system:[15]
- Unprocessed products such as vegetables, fruits, seeds, cereals, and legumes should be consumed.
- The consumption of fat and refined sugar should be limited.
- Drink at least 2 liters of water per day.
- Sleep for at least seven hours a day.

NUTRIENTS

Vitamin A

Vitamin A and its derivatives retinoids, are critical for immune functions, including innate immunity, cell-mediated immunity, and humoral antibody immunity.[16] Vitamin A plays an important role in maintaining the integrity and secretion of the epithelial and mucosal surfaces. These systems form a primary nonspecific host defense mechanism. Studies have demonstrated that vitamin A stimulates and strengthens numerous immune processes, including the following:[17]

- Cell-mediated cytotoxicity stimulation against tumors.
- Natural killer cell activity
- Lymphocyte blastogenesis
- Mononuclear phagocytosis
- Antibody response.

Vitamin A supplementation significantly reduces morbidity during the acute and recovery phases of measles infection; increases the total number of lymphocytes in peripheral blood, and measles IgG antibody concentration in these patients.[18]

Vitamin C

Vitamin C plays a critical role in maintaining immune system function and contributes to both innate and acquired immunity, particularly immune cell function (epithelial barrier integrity, chemotaxis, antimicrobial activity of phagocytes, natural killer cell activity, and the immune system), as well as lymphocyte proliferation and differentiation.[19,20] It has been shown that taking 1-3 grams/day of vitamin C for three days a week increases T cell proliferation in the long term.[21]

Vitamin E

Free radicals damage the membrane of immune cells, reducing their response to pathogenic challenges, leading to impaired immune and inflammatory responses, and consequently, the development of inflammatory diseases.[22] Vitamin E is an important antioxidant that cleans free radicals from the body.[23] It protects against oxidative stress, increases the activity of natural killer cells, and contributes to antibody formation.[24] Vitamin E deficiency weakens the immune system, whereas adequate intake supports both innate and acquired immunity.[25] Vitamin E is closely associated with crucial immune cell functions such as macrophages, dendritic cells, B cells, and natural killer cells. Vitamin E supports the interaction between dendritic cells and T cells, especially Th1 cells, and stimulates IL-2 production.14 It has been shown that supplementation with 100 mg/day of vitamin E for eight weeks regulate the development of natural killer cells.[26] Vitamin E supplementation positively affects respiratory tract infections in newborn babies.[27]

Vitamin B6

Vitamin B6 serves as a coenzyme in synthesizing proteins that make up antibodies and cytokines.[28] Vitamin B6 plays an essential role in the production of interleukins and T lymphocytes, and its deficiency results in decreased IL-2 production and increased IL-4 production.[29] In the presence of chronic inflammation, there is an inverse relationship between vitamin B6, IL-6, and TNF-α levels.[30] The liver, kidney, meat, and green leafy vegetables contain high amounts of vitamin B6 (Table 1).[27]

Table 1. Vitamin B6 values in 100 grams of some foods

Food	Amounts of vitamin B6 (mg per 100 grams)
Breast milk	5-22
Cow's milk	50-70
Meat	300-400
Liver	700-800
Kidney	400-1000
Rice flour	30-50
Green leafy vegetables	250-300
Fresh fruits	50-60

The human body cannot synthesize vitamin B6. It can be found in food or in microorganisms in the digestive system, such as Helicobacter pylori, Bifidobacterium longum, Bacteroides fragilis, Collinsella aerofaciens, and Prevotella copri, which make pathways for B6 vitamin synthesis.[30]

Vitamin D

Vitamin D affects both innate and acquired immunity.[31] Vitamin D increases chemotaxis, phagocytosis, and the production of antimicrobial proteins.[32] Vitamin D protects against bacterial or viral upper respiratory tract infections.[33] It has been shown that individuals with vitamin D deficiency have an increased risk of contracting tuberculosis.[34] Furthermore, the treatment of T cells with calcitriol or its analogs, especially vitamin D, inhibits the secretion of pro-inflammatory Th1 (IL2, interferon-γ, tumor necrosis factor α), Th9 (IL9), and Th22 (IL22) cytokines while supporting the production of anti-inflammatory Th2 cytokines (IL3, IL4, IL5, IL10).[35,36]

Vitamin D also has an impact on autoimmune diseases. Vitamin D deficiency is associated with type 1 diabetes (T1D), multiple sclerosis (MS), systemic lupus erythematosus, rheumatoid arthritis, and irritable bowel syndrome.[37]

Vitamin D supplementation has been shown to reduce pain in patients with rheumatoid arthritis, and improvements in mental health have been observed in individuals with MS.[38,39]

Zinc

Zinc is a catalytic component of over 300 enzymes that regulates cell communication, proliferation, differentiation, and survival. It is also an effective mineral for innate and acquired immunity.[40] Zn increases the number of natural killer cells and reduces their cytotoxicity. It decreases the number of T cells, Th1/Th2 ratio, and IL-2 production.[41] Zinc also regulates B lymphocytes and cytokine synthesis.[42]

However, excess zinc can also negatively affect the immune system, leading to zinc deficiency.[41] Zinc prevents the entry of viruses into the body and inhibits their replication.[43,44] Zinc also enables the intestinal microbiota to be modulated.[45]

Iron

Iron is effective in innate immunity because it controls the production of antimicrobial factors such as nitric oxide and hydroxyl radicals. Acquired immunity is effective in increasing lymphocytes.[46] Pathogenic microorganisms and viruses need nutrients in the blood, such as free-floating iron, to sustain their activities. However, the host must have sufficient iron concentration to induce an immune response.[47] Natural killer cells require iron for proliferation and differentiation.[48] Iron is also required for T-cell proliferation. It plays a role in DNA synthesis, especially in Th1 cells.[49]

Iron deficiency decreases the cell-mediated immunity, activity of myeloperoxidase enzyme, and activity of neutrophil and natural killer cells.[50,51]

Glutamine

Glutamine is the most abundant amino acid in the human body.[52] Due to its ability to increase lymphocyte function and IL-6 levels in macrophage cells, glutamine is effective in the immune system.[53,54] A previous study showed that, glutamine supplementation increased the effectiveness of neutrophils against Staphylococcus aureus.[55] Furthermore, glutamine plays a role in cellular protection against oxidative stress by serving as the main substrate for producing the antioxidant glutathione.[56]

When an infection starts in the body, immune cells consume more glutamine than carbohydrates. In mammals, glutamine is produced, stored, and secreted by the skeletal muscles.[57] Increased glutamine consumption by tissues such as the liver and immune cells can lead to glutamine deficiency.[58] A decrease in plasma glutamine levels leads to impaired immune system function. Decreased glutamine levels reduce cytokine production and lymphocyte proliferation, leading to apoptosis in these cells.[59]

Breast Milk

Breast milk plays an active role in the immune system, with its bioactive components, such as immunoglobulins, cytokines, chemokines, and growth factors.[60] Quantitative immunoglobulins are found in breast milk:IgM, IgG, IgD, and IgA (**Table 2**).

Table 2. Concentrations of essential soluble immune factors in human milk under physiological conditions.[60]

Immune factors	Type	Concentrations
IgA (mg/L)	Mature breast milk	160-2435
	Colostrum	1428-8700
	Preterm breast milk	260-3181
IgG (mg/L)	Mature breast milk	14-230
	Colostrum	40-150
	Pretersm breast milk	70-90
IgM (mg/L)	Mature breast milk	7.5-170
	Colostrum	160-660
	Preterm breast milk	380-440
TGF-β2 (mg/L)	Mature breast milk	0.26-99
	Colostrum	1.8-336
	Preterm breast milk	7.5-15.5
EGF (mg/L)	Mature breast milk	2.2-10.8
	Preterm breast milk	0.7-1.9
IL-7 (ng/L)	Mature breast milk	17.2-131.5
	Colostrum / preterm breast milk	75-1088
IL-8 (ng/L)	Mature breast milk	2.3-1704
	Preterm breast milk	309-2542
GRO-α (mg/L)	Mature breast milk	0.05-15
MIP-1β (ng/L)	Mature breast milk	2.7-76

IgA is the most abundant, accounting for 95%, and its levels decrease gradually after birth. IgA protects against enteric and respiratory antigens.[61] Therefore, breastfed infants are more resistant to respiratory tract infections.[62]

Lactoferrin, one of the most abundant proteins found in breast milk, prevents infection, plays a role in iron metabolism, and has important functions in the immune system, owing to its anti-inflammatory and antioxidant properties. It exerts bacteriostatic effects by binding and transporting iron into the body.[63] Lactoferrin enhances the activity of natural killer cells. In addition, it prevents viral accumulation in cells and entry of the virus into the host through the angiotensin-converting enzyme-2 receptor pathway.[64] Lactoferrin mediates changes in the expression of signaling molecules, which control the balance between molecules that cause inflammation and molecules that stop it.[65] The expression of anti-inflammatory cytokines, such as IL-4 and IL-10, and pro-inflammatory cytokines, such as tumor necrosis factor-alpha, IL-1, IL-6, IL-12, and chemokines, such as IL-8, is controlled by lactoferrin.[66] Breast milk contains bioactive growth factors. These bioactive components play an important role in the development of healthy infants because they contribute to the production of red blood cells and exhibit anti-inflammatory and antioxidant properties.[63]

The oligosaccharides found in breast milk prevent respiratory pathogens such as Streptococcus pneumoniae from binding to the respiratory epithelium. Additionally, milk glycoproteins prevent colonization by intestinal pathogens such as Vibrio cholera and Escherichia coli.[67]

Breast milk interacts directly with glycan-binding proteins

expressed in epithelial cells and innate immune system cells.[68] One of the components found in breast milk is long-chain polyunsaturated fatty acids. Omega-3 and omega-6 fatty acids improve Th1 and Th2 immune cell responses.[69] Additionally, although docosahexaenoic acid (DHA) and arachidonic acid make up a relatively small portion of the total fatty acids in human breast milk, they play a role in the development of immunity.[70] If infant formulas are supplemented with these fatty acids for infants who are not breastfed, the number of lymphocytes and cytokines will be similar to those in breastfed infants.[70] Additionally, breast milk contains lactic acid bacteria such as Lactobacillus, Lactococcus, and Leuconostoc as well as bacterial species such as Bifidobacterium, Streptococcus, Enterococcus, and Staphylococcus.[71,72] Breast milk containing more than 820 species of bacteria enhances the development of the infant's early immune system, maintains tolerance to commensal microbial members, and enhances intestinal host defense against pathogens.[73]

Proteins

Some proteins such as lectin, lactoferrin, and whey proteins stimulate immune responses. Lectin and lactoferrin can recognize viruses by binding to their glycoproteins. Whey proteins, however, enhance immunity and reduce certain cancer risks.[74] A protein intake of 3-4 g/kg/day is recommended for infants, while for older children, a protein intake of 1.5-2 g/kg/day is recommended.27

Protein deficiency causes dysfunction in epithelial and physiological barriers, and impairs macrophage, neutrophil, and natural killer cell functions [75] Additionally, protein deficiency in the diet leads to atrophy of lymphoid organs and a deficiency of T lymphocytes, which increases susceptibility to viral and bacterial pathogens, as well as opportunistic infections.[76]

Fats

Fatty acids play a role in regulating many responses, including inflammation and immune function.70 Omega-3 polyunsaturated fatty acids (PUFAs), in particular, play an important role in regulating the immune system due to their antioxidant properties.[77] Omega-3 PUFAs are important fatty acids that strengthen anti-inflammatory responses, block hyperinflammatory reactions, and reduce the incidence of systemic inflammatory response syndrome and infectious complications.[78,79] Furthermore, omega-3 fatty acids regulate the activation of macrophages, neutrophils, basophils and lymphocytes.[80]

CONCLUSION

Nutrition plays an important role in the development of the immune system and the fight against infectious diseases. Malnutrition and obesity, which result from inadequate and unbalanced nutrition, weaken the immune system and reduce the effectiveness of fighting diseases. However, adequate and balanced nutrition, which provides energy and essential nutrients, enhances the development and effectiveness of innate and acquired immunity, making the emergence of infectious diseases less likely and improving the ability to fight disease. Therefore, outbreaks of diseases are increasing, especially in the 21st century, and ensuring that children have adequate and balanced nutrition is crucial to avoiding infectious diseases.

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Letter to the Editor

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Integrating vitamin D supplementation into IVF protocols: A comprehensive strategy for Improving reproductive success and psychological well-being

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Dear Editor,

In response to the article "An investigation into the relationship between serum vitamin D levels and the success rate of pregnancy in a cycle of in vitro fertilization" by Nurgül Ulusoy and Ayşe Şeyma Küçükakça, published in the January 2024 issue, I commend the authors for illuminating a vital aspect of reproductive medicine. This study not only highlights the significance of serum vitamin D levels in enhancing IVF success rates but also prompts a broader discussion on the integration of nutritional and environmental interventions in infertility treatments.

The research underlines the potential benefits of vitamin D supplementation, suggesting a simple yet impactful approach to improving clinical outcomes in IVF protocols. This insight, supported by both Lerchbaum and Obermayer-Pietsch[1], and further evidenced by Anifandis et al.[2] through the prognostic value of follicular fluid 25-OH vitamin D levels, emphasizes the necessity of incorporating vitamin D screening and supplementation into standard infertility treatment protocols.

To extend the utility of these findings, I propose the following considerations for future research:

1. **Exploring Mechanisms:** Delving into how vitamin D influences embryo implantation and early fetal development could unveil new fertility treatment targets, building on the foundational work by Rudick et al.[3]
2. **Longitudinal Impacts:** Research into the long-term health implications of maternal vitamin D status on offspring can deepen our understanding of pre-conception care's broader effects.
3. **Personalization of Care:** Investigating individual differences in vitamin D metabolism may lead to more tailored and effective supplementation strategies, optimizing IVF outcomes.
4. **Beyond Vitamin D:** A holistic approach should also consider other nutritional and environmental factors that could synergistically enhance fertility.[4]
5. **Psychological Aspects:** Understanding the psychological impact of infertility and the role of vitamin D in modulating stress and emotional well-being during IVF treatments warrants exploration.[5]

By advocating for a multifaceted research agenda encompassing these areas, we can validate and expand upon Ulusoy and Küçükakça's findings, offering more nuanced and effective interventions for couples facing infertility. This approach promises not only to amplify the clinical efficacy of IVF treatments but also to contribute to the holistic health and emotional resilience of individuals undergoing these procedures.

In conclusion, the study by Ulusoy and Küçükakça opens promising pathways for integrating vitamin D optimization into infertility treatments. I am eager to see how these insights will shape future practices and research in reproductive medicine, leading to improved outcomes for patients worldwide.

Thank you for your commitment to advancing the field of reproductive health.

Sincerely.

Keywords: Vitamin D supplementation,IVF success rates,nutritional interventions, reproductive medicene, personalized care, psychological well-being

ETHICAL DECLARATIONS

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The authors have no conflicts of interest to declare.

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All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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