Journal of Nutrition and Food Security
Shahid Sadoughi University of Medical Sciences
School of Public Health
Department of Nutrition

eISSN: 2476-7425 pISSN: 2476-7417 JNFS 2026; 11(2): 205-213 Website: jnfs.ssu.ac.ir

17-Beta Estradiol Levels, Dietary Intake, Anthropometric Indices, and Determination of the Q36R Polymorphism in the Kiss1 Gene in Infertile Women: A Case-Control Study

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ARTICLE INFO

ORIGINAL ARTICLE

Article history:
Received: 24 Sep 2025
Revised: 21 Dec 2025
Accepted: 28 Dec 2025

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Keywords:
Infertility; KISS1; anthropometry; Dietary intake;17 beta-estradiol.

ABSTRACT

Background: This study compares serum 17-beta-estradiol (E2), dietary intake, anthropometric indices, and the Kiss1 gene Q36R polymorphism between infertile women and a healthy control group in Zahedan, Southeast Iran. **Methods:** In a case-control study, forty-five infertile women (cases) and 45 healthy women (controls) were assessed for anthropometric indices (weight, height, waist circumference, and body mass index). Food intake was then evaluated using a food frequency questionnaire (FFQ). Serum 17-beta-estradiol levels were measured via ELISA, and PCR determined the Kiss1 gene Q36R polymorphism. Finally, data were analyzed using the t-test, the Mann-Whitney U test, Fisher's exact test, and the chi-square test. **Results:** Mean serum E2 levels were significantly lower in the case group (61.40±128.15 ng/ml) compared to the control group (117.24±84.26 ng/ml) (P<0.001). Anthropometric variables did not differ significantly between groups. However, t-tests and Mann-Whitney tests revealed significant differences in most nutritional factors between cases and controls. The allelic distribution of the Kiss1 Q36R polymorphism was not significant between the two groups. **Conclusion:** The case group exhibited significantly lower mean serum E2 levels compared to controls, but the Kiss1 Q36R polymorphism's allelic distribution was similar in both groups. Further research should investigate the roles of Kiss1 polymorphisms and dietary factors in infertility.

Introduction

Infertility is a disease defined by the inability to achieve a pregnancy after 12 months of regular, unprotected sexual intercourse, or due to impaired reproductive capacity in an individual, either alone or with a partner, as per the most recent international glossary on infertility and fertility care. Regular sexual intercourse is essential for pregnancy. Infertility, according to World Health Organization (WHO) guidelines, is a disability resulting from functional impairment. Primary infertility is diagnosed when a woman meeting infertility criteria has never previously been

This paper should be cited as: Soltan Mohammad M, Kalili T, Ghasemi M, Mortezayi Z. ***17-Beta Estradiol Levels, Dietary Intake, Anthropometric Indices, and Determination of the Q36R Polymorphism in the Kiss1 Gene in Infertile Women: A Case-Control Study.*** *Journal of Nutrition and Food Security (JNFS)*, 2026; 11(2): 205-213.

[DOI: 10.18502/jnfs.v11i2.21430]

diagnosed with the condition. In contrast, secondary infertility is the inability to become pregnant after previously having had a successful pregnancy (Zegers-Hochschild *et al.*, 2017). Infertility affects approximately 1 in 7 couples in the Western world and 1 in 4 in developing countries. Rates can exceed 30% in regions such as South Asia, Sub-Saharan Africa, the Middle East and North Africa, Central and Eastern Europe, and Central Asia (Mascarenhas *et al.*, 2012). Lifestyle factors significantly impact fertility and the likelihood of pregnancy and delivery. Furthermore, lifestyle choices impact reproductive health, influencing both infertile couples and the general population (Youness, 2018). Physical activity, as a lifestyle factor, impacts female reproductive function. However, studies examining the relationship between physical activity and infertility have yielded inconclusive and controversial results (Vaziri *et al.*, 2017).

Nutritional patterns significantly influence fertility in women of reproductive age. Deficiencies or imbalances can cause endocrine disorders, impairing follicular development and ovulation (Vaziri *et al.*, 2017).

Obesity is often associated with metabolic abnormalities and related complications. Research increasingly focuses on obesity as a key factor in female infertility. However, Individuals with the same BMI can have varying fat distributions. The role of central obesity in reproductive health is of growing interest (Vaziri *et al.*, 2017).

Kisspeptin (KP), encoded by KISS1, is a peptide hormone crucial for fertility and neuroendocrine modulation of the hypothalamic-pituitary-gonadal (HPG) axis (Vaziri *et al.*, 2017). Loss of gene function or the presence of single-nucleotide polymorphisms (SNPs) in KISS1 and KISS1R are risk factors for sexual immaturity and infertility in humans (Shen *et al.*, 2010). KP binding to its receptor, KISS1R, is essential for puberty onset and hormone release from the reproductive axis. KISS1R gene mutations can cause KISS1R to lose function, resulting in the downregulation of GnRH pulsatile secretion and infertility (Luan *et al.*, 2007). KP plays a role in the feedback regulation of GnRH production, and consequently, the release of gonadal hormones essential for normal reproductive function (Irwig *et al.*, 2004) Investigations have confirmed the importance of KP in the reproductive axis, its role in unexplained infertility, and its potential as a therapeutic agent to enhance oocyte maturation and ovulation (Mumtaz *et al.*, 2017). Although mutations that decrease KISS1 gene expression and receptor activation can cause infertility, data on KISS1 gene mutations and polymorphisms are limited (Abbara *et al.*, 2014). A study in northern Iran found no association between the Q36R (rs35431622) variant of the KISS1 gene and female infertility, suggesting that inconsistent results across studies may stem from geographic genetic variations (Vaziri *et al.*, 2017).

Serum 17-beta estradiol (E2) supports oocyte/follicular maturation and uterine preparation for implantation. E2 also modulates GnRH neurosecretory activity, which is critical for reproductive feedback regulation (Jacobi *et al.*, 2007). In addition to reproduction, E2 participates in diverse metabolic processes, such as regulating feeding behavior and body weight, through feedback mechanisms. Specifically, E2 modulates hypothalamic control of metabolism, decreasing food intake while increasing energy expenditure and activity, particularly via actions in the Mediobasal hypothalamus (Irwig *et al.*, 2004)

The authors hypothesized a relationship between fertility, lifestyle, E2 serum levels, and Kiss1 polymorphism. Given the limitations of existing research, this study aims to evaluate E2 levels, dietary status, anthropometric indices, and the Kiss1 gene Q36R polymorphism in infertile women.

Materials and Methods

Design and participants

In a case-control study, forty-five women under 40 with infertility, referred to the Molood Infertility Center in Zahedan, Southeast Iran; they were eligible for the study and were screened and recruited into the case group. The control group consisted of 45 healthy women under 40 from Zahedan Imam Ali Hospital.

[DOI: 10.18502/jnfs.v11i2.21430]

Based on similar studies (Vaziri *et al.*, 2017), this study would achieve 95% confidence interval and 90% test power, with a sample size of 33 participants per group. To enhance the accuracy and validity of the study, the authors included 45 infertile women in the case group and 45 healthy women in the control group.

Inclusion and exclusion criteria

The study included women with unexplained infertility of at least one year's duration, excluding those with PCOS, who had regular menstrual cycles, patent fallopian tubes, and normal uterine cavities on hysterosalpingography, and those whose partners had normal spermograms. The control group included healthy women with at least one healthy child (over 2 years old and after breastfeeding) and no history of cardiovascular, brain, hypertensive, diabetic, thromboembolic, or other systemic diseases. Exclusion criteria include gynecological disorders (leiomyomas, endometriosis, uterine polyps, and PCOS), acute or chronic infections, abnormal uterine imaging, irregular menstrual cycles, recurrent miscarriage, smoking, ovarian masses, an age over 40, an abnormal hormonal profile, and hormonal drug use within the past 2 months. Women who declined participation were excluded.

Anthropometric measurements

Participants underwent standard anthropometric measurements, and weight was measured to the nearest 100 grams using a Seca scale (Hamburg, Germany) with minimal clothing and no shoes. Height was measured to the nearest 0.1 cm using a standard gauge, with participants barefoot and aligned against the gauge at the back of the legs, buttocks, shoulders, and back. Body mass index (BMI) was also calculated as weight (kg) divided by height (m^2). Abdominal obesity was defined as a waist circumference (WC) $\geq$ 88 cm, measured at the end of a normal exhalation midway between the last rib and the iliac crest.

Dietary intake

Dietary intake of women in case and control groups were assessed using a 147-item food frequency questionnaire (Ghorabi *et al.*, 2019). An experienced nutritionist administered the questionnaire using a standard protocol, giving each participant at least 30 minutes of individual attention. Participants reported the frequency of their food intake (daily, weekly, or monthly), and their nutritional status was assessed using NUT4 software.

Physical activity

Physical activity, categorized as mild, moderate, or high, was assessed using the International Physical Activity Questionnaire (IPAQ) to determine activity levels over the past week.

17-beta estradiol measurement and KISS1 gene polymorphism determination

Following informed consent, blood samples were collected from women in both case and control groups to measure E2 and Q36R. DNA was initially extracted from samples using the salting-out method, and the polymerase chain reaction (PCR) was used to identify the rs35431622 (Q36R) polymorphism of the KISS1 gene for molecular polymorphism experiments.

KISS1-specific primers were designed based on scientific literature (Vaziri *et al.*, 2017) and slightly modified and BLASTed in the NCBI database (National Center for Biotechnology Information). Following preparation of the PCR kit and primers, the reaction mixture was prepared, and the reaction program was run in the thermal cycler. Genotyping was then performed using the NaeI restriction enzyme. The genotype was determined based on the electrophoresis pattern of the enzyme-digested PCR product. To resolve existing issues and the lack of timely access to restriction enzymes, ARMS-PCR was used. This method employs genotype-specific primers designed at the 3' end, with separate PCR reactions performed in individual mycotubes for each genotype.

Ethical concentrations

The Ethics Committee on Human Experimentation at Zahedan University of Medical Sciences, Iran, approved the study protocol. Participants received information about the study's goals and procedures via a leaflet. All participants

[DOI: 10.18502/jnfs.v11i2.21430]

were informed that studies involving human participants adhered to the ethical standards of the Institutional Research Committee and the Declaration of Helsinki of 1975, as revised in 2000 (available at http://www.wma.net/e/policy/17-c_e.html). Study participants signed the informed consent statement before participating. Zahedan University of Medical Sciences Ethics Committee approved the study protocol with the Ethical Code, IR.ZAUMS.REC.1400.103 and the Thesis code 10264.

Data analysis

Data were analyzed using SPSS version 22.0 (IBM Corp., New York, USA). Normality was assessed via the Kolmogorov–Smirnov test. Statistical tests were then selected based on data distribution and included the independent t-test, Mann–Whitney U, Fisher's exact test, and Chi-square tests. Statistical significance was set at P-value<0.05.

Results

This study compared women with infertility (case group) to healthy controls. The mean age was the not significant between the case (27.40±2.45) and control (27.84±2.88) groups (*P*=0.43). BMI (*P*=0.007) and WC (*P*=0.03) were significantly different between the groups (**Table 1**).

Comparison of physical activity levels in case and control groups

While both the case and control groups predominantly engaged in moderate physical activity (**Table 1**), the case group had a higher proportion of individuals with low physical activity. However, this difference was not statistically significant (*P*=0.66)

Comparison of mean E2 serum levels between case and control groups

Mann-Whitney testing revealed a significant difference between case and control groups (*P*<0.001), with the case group exhibiting a significantly lower mean serum level of E2 (61.40±128.15 ng/ml) compared to the control group (117.24±84.26 ng/ml).

Table 1. Demographic and anthropometric characteristics of case and control groups.

Variables	Case (n = 45)	Control (n = 45)	P-value
Education			
Illiterate	19 (42.2)[a]	14 (31.1)	0.10
Diploma	15 (33.3)	13 (28.9)	
BSc	7 (15.6)	9 (20.0)	
MSc	3 (6.7)	6 (13.3)	
PhD	1 (2.2)	3 (6.7)	
Job			
Housewife	32 (71.1)	30 (66.7)	0.82
Employee	13 (28.9)	15 (33.3)	
Ethnicity			
Balouch	28 (62.2)	27 (60.0)	0.50
Fars	17 (37.8)	18 (40.0)	
Physical activity			
Mild	18 (40.0)	14 (31.1)	0.66
Moderate	24 (53.3)	27 (60.0)	
High	3 (6.7)	4 (8.9)	
Height (m)	1.62±0.04[b]	1.62±0.50	0.97
Weight (kg)	72.78±12.89	66.28±9.31	0.007
BMI (kg/m^2)	27.29±4.06	24.92±3.11	0.007
WC (cm)	91.97±5.73	89.37±5.00	0.03
Age (year)	27.40±2.45	27.84±2.88	0.43

BMI: Body mass index; ***WC***: *Waist circumference;* ***BSc***: *Bachelor' degree;* ***MSc***: *Master degree;* ***PhD***: *Professor degree;* [a]: *n (%);* [b]: *Mean±SD.*

Comparison of mean serum E2 levels based on Q36R allele frequency in case-control groups

As shown in **Table 2**, Mann-Whitney tests indicated significant differences in mean serum E2 levels between case and control groups for both the AA (*P*<0.001) and AG (*P*=0.02) genes.

Table 2. Mean serum E2 levels by Q36R allele frequency in case and control groups.

Alleles	Case (n = 45)	Control (n = 45)	P-value[a]
AA (ng/ml)	59.77±141.93	1.10±8.46	< 0.0001
AG (ng/ml)	67.10±64.34	1.39±8.34	0.02

[a]: *Based on the Mann-Whitney test*

Comparison of anthropometric indices in case-control groups based on Q36R

Table 3 shows a significant difference in mean WC and BMI between case and control groups for the AA polymorphism (*P*=0.04 and *P*=0.005,

[DOI: 10.18502/jnfs.v11i2.21430]

respectively). No significant differences were observed for the AG polymorphism in either WC (*P*=0.56) or BMI (*P*=0.45).

Table 3 Comparison of anthropometric indices based on q36r in case - control groups

Variable	Case (n = 45)	Control (n = 45)	P-value[b]
BMI (kg/m^2)			0.005
AA	27.49 ± 4.09[a]	24.80 ± 2.48	
AG	26.56 ± 4.11	25.36 ± 4.07	0.45
P-value[c]	0.43	0.79	
WC (cm)			0.04
AA	92.20 ± 5.92	88.97 ± 4.16	
AG	91.20 ± 5.22	90.80 ± 7.36	0.56
P-value	0.62	0.86	

***BMI:** Body mass index; **WC:** Waist circumference; [a]: Mean±SD ; [b]: Student t-test ; [c]: Mann-Whitney test .*

Dietary intake

Table 4 shows significant differences in nutrient levels between case and control groups using both t-tests and Mann-Whitney tests. Carbohydrate intake was significantly higher in the case group (285.79±39.84 g) compared to the control group (243.63±15.18 g). The control group had a significantly higher mean intake of vitamins A, D, E, K, and C, as well as MUFA and PUFA, compared to the infertile women. The differences were statistically significant (*P*<0.05).

Discussion

This case-control study found that the case group had significantly lower mean serum E2 levels compared to the control group. Estrogens, produced by the ovaries, are essential for female reproductive regulation (Cornil *et al.*, 2015). The major estrogens - estrone (E1), 17-beta-estradiol (E2), and estriol (E3) - are synthesized during steroidogenesis (Bondesson *et al.*, 2015). Estrogens mediate physiological effects by binding to estrogen receptors. Research has shown that in ovariectomized rodents, estrogen therapy combined with endurance exercise results in weight loss, reduced visceral fat, and lower LDL cholesterol levels (Choi *et al.*, 2005, Gollisch *et al.*, 2009). A two-week swimming training program in healthy, non-anorectic mice (Saadat *et al.*, 2016) reduced serum estradiol and FSH levels. The study also found decreased alpha estrogen receptor expression in uterine tissue and reduced beta estrogen receptor expression in ovarian tissue following exercise. Uterine and ovarian apoptosis, however, remained consistent across all groups.

The current study found significant differences in mean E2 serum levels based on physical activity between groups. However, in highly active individuals, there was no significant difference in mean 17-beta-estradiol serum levels between the two groups (*P*=0.07). Additionally, the study groups exhibited significant differences in dietary intake. While mean energy intake did not show significant differences, the case group had significantly higher carbohydrate and saturated fatty acid intake. Conversely, the control group consumed more monounsaturated fatty acids, polyunsaturated fatty acids, fat-soluble vitamins, and vitamin C. It seems that the control group had a higher intake of antioxidant-rich foods and nutrients affecting fertility compared to the case group. Dietary intakes largely aligned with Ji et al.'s study (Saadat *et al.*, 2016). Moreover, Bravo et al. found an association between coffee consumption, inactivity, and lower estradiol levels in a cross-sectional study (Huitrón-Bravo *et al.*, 2016). Endocrine responses are also influenced by factors such as nutritional status, training history, age, sex, interactions with other sports interventions, and exercise program type (Kraemer and Ratamess, 2005).

[DOI: 10.18502/jnfs.v11i2.21430]

Table 4. Daily dietary intake in case and control groups.

Dietary intake	Case (n = 45)	Control (n = 45)	P-value
Energy (kcal)	2923.29 ± 366.37[a]	2992.65 ± 165.38	0.45
Protein (g)	131.16 ± 18.10	133.25 ± 6.47	0.47
Carb (g)	285.79 ± 39.84	243.63 ± 15.18	< 0.001
TC (g)	490.48 ± 98.65	602.18 ± 56.99	< 0.001
SFA (g)	38.28 ± 5.13	42.51 ± 4.69	< 0.001
MUFA (g)	53.74 ± 14.63	64.91 ± 5.09	< 0.001
PUFA (g)	28.20 ± 9.33	33.72 ± 4.41	0.48
Total fiber (g)	42.54 ± 8.28	38.91 ± 4.37	0.01
Vitamins			
A (RAE)	1081.80 ± 191.58	1270.21 ± 103.83	< 0.001
D (ug)	1.62 ± 0.32	1.89 ± 0.22	< 0.001
E (mg)	13.30 ± 5.12	16.83 ± 2.89	0.01
K (mg)	137.07 ± 21.25	200.66 ± 59.20	< 0.001
C (mg)	94.19 ± 16.66	119.93 ± 20.78	< 0.001
B1 (mg)	1.74 ± 0.28	1.62 ± 0.13	0.01
B2 (mg)	2.58 ± 0.37	2.64 ± 0.18	0.41
B3 (mg)	29.83 ± 3.77	27.89 ± 1.09	0.002
B5 (mg)	5.82 ± 0.98	5.93 ± 0.31	0.48
B6 (mg)	2.24 ± 0.28	2.48 ± 0.16	< 0.001
B9 (mg)	426.80 ± 61.95	440.00 ± 23.79	0.18
B12 (mg)	14.11 ± 2.49	15.20 ± 0.95	0.42
Minerals			
Zinc (mg)	21.85 ± 2.97	20.91 ± 1.30	0.05
Calcium (mg)	928.66 ± 122.05	865.83 ± 134.09	0.02
Iron (mg)	26.23 ± 2.88	28.02 ± 4.79	0.47
Magnesium (mg)	453.24 ± 74.61	450.62 ± 38.79	0.83
Phosphorus(mg)	1721.14 ± 247.37	1707.99 ± 90.30	0.73
Potassium (mg)	3817.12 ± 627.16	4099.11 ± 263.17	0.05
Selenium(mg)	143.25 ± 21.07	122.20 ± 11.29	< 0.001
Copper (mg)	2.79 ± 0.52	3.14 ± 0.25	0.001
Manganese(mg)	5.55 ± 0.99	5.68 ± 0.89	0.52
Chrome (mg)	0.08 ± 0.02	0.04 ± 0.01	< 0.001

***Carb**: Carbohydrate, **TC**: Total cholesterol, **MUFA**: Monounsaturated fatty acids, **PUFA**: Polyunsaturated fatty acids; [a]: Mean±SD..*

In the current study, the Q36R polymorphism had equal allelic distribution in both case and control groups. However, mean serum E2 levels differed significantly between case and control groups, based on AA and AG polymorphisms. Kisspeptins, encoded by the Kiss1 gene, are now recognized as key upstream regulators of GnRH, influencing puberty onset, gonadotropin secretion, ovulation, and metabolic fertility regulation (Oakley *et al.*, 2009). Gonadotropins positively regulate the expression of Kiss1 system elements (Navarro and Tena-Sempere, 2012). This study found no significant differences in mean age or Kiss1 Q36R allelic distribution between case and control groups, consistent with some studies but inconsistent with others, such as Vaziri *et al.*'s , which found no association between this polymorphism and infertility in women from northern Iran (Vaziri *et al.*, 2017). A study of 272 Chinese women revealed a new link between the Kiss1 gene and infertility. Tenenbaum et al. found that infertile individuals have significantly lower serum kisspeptin levels than fertile individuals (Tenenbaum-Rakover *et al.*, 2007). While KISS1's role in metastasis is established, recent studies also demonstrate its importance in puberty, ovulation, and fertility. Nimri et al. suggest that homozygous Pro/Pro and Arg/Arg genotypes at codon 31 of KISS1 may be linked to infertility (Nimri *et al.*, 2011). Mutations in the KISS1R gene have been

[DOI: 10.18502/jnfs.v11i2.21430]

linked to reproductive issues, including infertility (Poursharif *et al.*, 2017). A study by Pandey and Bhattacharya found that the response rate to infertility therapies decreased in patients with significant menstrual issues, such as irregular menstruation, oligomenorrhea, and ovarian dysfunction (Pandey and Bhattacharya, 2010).

The findings revealed that the frequency of the rs35431622 polymorphism in the Kiss1 gene differed significantly across BMI categories in women, for both case and control groups. In the control group, mean serum 17-beta-estradiol levels were higher than in the normal BMI range. However, in obese women, mean serum 17-beta-estradiol levels were higher in the case group than in the control group. As with other studies (Poursharif *et al.*, 2017), this one suggests a positive association between BMI and infertility. Obesity has been linked to reduced fertility, though the exact mechanisms are still unclear. Obese women, particularly those with central obesity, have lower conception rates per cycle and are more likely to experience hypothalamus-pituitary-ovary axis dysfunction, menstrual irregularities, and oligo/anovulation. Reducing abdominal fat can restore ovulation, since central adiposity is associated with menstrual disorders and infertility (Poursharif *et al.*, 2017).

Despite its valuable insights, the study is limited by its small sample size. Future research should include larger cohorts and broader hormonal assessments to better understand the relationship between serum E2 levels and infertility. These findings enhance our understanding of reproductive endocrinology and underscore the importance of personalized infertility approaches for women.

Conclusion

In the present study, lower estradiol levels in the case group compared to the control group suggest a link between estrogen and infertility. This significant difference underscores E2's importance in female reproductive health, impacting ovulation and menstrual regulation. The findings also suggest that physical activity and dietary factors may influence E2 levels, as variations were seen between active and inactive individuals. Healthy lifestyle habits, including nutritious eating and physical activity, may improve fertility and fetal-maternal health. The study also examined the effect of Kiss1 Q36R polymorphism on E2 levels, finding significant allelic differences. This indicates that genetic factors may contribute to estrogen level variations and potentially influence fertility.

Acknowledgments

This article was adapted from a master's thesis in nutrition. The authors would like to thank the Deputy of Research and Technology at Zahedan University of Medical Sciences for their support and the participating women for their cooperation.

Authors' contributions

Mortazavi Z supervised the study. Soltan-Mohammadi M and Ghasemi M contributed to data collection; Khalili T conducted experimental procedures; Zarei F performed data analyses. Soltan-Mohammadi M and Mortazavi Z contributed to study design and concept, data interpretation, and manuscript drafting, while Mortazavi Z edited and revised the final manuscript. All authors read and approved the final manuscript.

Conflicts of interest

The authors declared no conflicts of interest.

Funding

There was no external funding for this study.

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