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Original article

Role of the Q36R polymorphism in the *KISS1* gene in female infertility

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ABSTRACT

Background: Infertility has evolved into a worldwide reproductive health concern that is distinctively constituted within various socio-cultural contexts. Female infertility is a global health concern ailment in couples who have been unable to conceive for a year. Kisspeptin (KISS1) is a peptide hormone that is important in women's health difficulties such as infertility. Based on previous studies, single nucleotide polymorphisms (SNPs) in *KISS1* gene can be a cause for infertility. The objective of this study is to explore into the Q36R SNP in the *KISS1* gene in Saudi infertile women.

Methods: In this case-control study, 96 cases of female infertile and 96 control women was selected. Deoxyribonucleic acid (DNA) was extracted to perform polymerase chain reaction and followed by restriction fragment length polymorphism analysis. All DNA products were run on 2% agarose and obtained data was imported into excel to perform the statistical analysis using SPSS software between cases and controls.

Results: The anthropometric analysis ($p > 0.05$), genotype (OR-3.60; 95 %CI:0.96–13.55; $p = 0.04$), allele (OR-2.49; 95 %CI: 0.86–7.21; $p = 0.08$) and different genetic models (AG + GG vs AA; OR-1.00; 95 %CI: 0.01–7.02; $p = 0.005$) showed negative association and fertility histories showed significant association ($p < 0.0001$). Anova analysis showed the positive association with weight ($p = 0.01$) and BMI ($p = 0.003$).

Conclusion: This study found no connection between the Q36R SNP in the *KISS1* gene and female infertility in Saudi Arabia.

1. Introduction

The definition of an infertility describes as the inability to conceive after 1 year or more of regular unprotected sexual intercourse. According to estimates, infertility affects 12–30 % of couples trying to conceive, and it can be ascribed on the male (30 %), women (55 %), or even both partners (40 %) (Koysombat et al., 2022). Infertility has become an issue for many couples as a worldwide health concern, and idiopathic infertility refers to a couple's failure to conceive even after an infertility work-up has been performed (Froment et al., 2022). Ovulation difficulties, fallopian tube damage (tubal infertility), cervical abnormalities (benign polyps or tumors), and hormonal imbalances can all contribute to female infertility. Polycystic ovarian syndrome (PCOS), premature ovarian failure, endometriosis, pelvic inflammatory disease and uterine fibroids are some of the hormonal conditions (Akbaribazm et al., 2021). Infertility affects around 70 million couples of reproductive age around the world, according to the World Health Organization (Wang et al., 2021). Ultrasonography is the primary imaging technology used to examine the pelvises of infertile women for symptoms of the aforementioned conditions. Ultrasounds are precise, non-invasive, and cost-effective diagnostic methods for identifying and classifying potential issues with female infertility (Khalid et al., 2022). Other possible causes of female infertility include family history, previous medical treatment, menstrual and sexual history and physical factors like decreased ovarian reserve or ovulatory dysfunction, thyroid problems or hyperprolactinemia. Other possible causes include tubal factors or uterine factors or other unidentified factors (Breitkopf and Hill 2019). Multiple variables, including inflammation, obesity, intermittent hypoxia, and sympathetic activation, can contribute to infertility (Lim et al., 2021). One of the risk factors is being overweight or obese and documented studies have found that obese and overweight women have lower levels of estrogen and progesterone, lower levels of luteinizing hormone and follicle-stimulating hormone, and higher levels of testosterone (Alshammary and Khan 2021, Joon et al., 2022). There is a lack of understanding regarding

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the genetic factors that contribute to female infertility, which is a complex disorder caused by genetic variations. Single nucleotide polymorphisms (SNPs), which are the most common of these variations, have been identified as the most significant of these variations (Asgari 2021). Previous studies from various ethnic origins examined at SNPs in several genes in female infertility (Altmäe et al., 2010, Ilgaz et al., 2015, Al-Mutawa 2018). Several genes have been related to the risk of hormonal abnormalities in women, which can eventually lead to infertility, with Kisspeptin-1 (KISS1) being one of them. It has recently been discovered that the hypothalamus contains a network of neurons that connects kisspeptin to neurokinin and dysorphin in the process of reproduction. Three exons of KISS1 are located on chromosome 1q32 and two of them, 145 amino acids, are translated into the 154-amino acid product, kisspeptin-54, as well as shorter physiologically active peptides, kisspeptin −14, −13 and −10 respectively (Siahpoosh et al., 2021). Previous studies have been carried out with *KISS1* gene with gynecological diseases such as female infertility and PCOS (Farsimadan et al., 2021, Siahpoosh et al., 2021). There are no studies conducted on Saudi infertile women. So, the aim of this study was to explore Q36R polymorphism in *KISS1* gene with Saudi women who had been diagnosed with female infertility.

2. Materials and methods

2.1. IRB approval

Ethical approval for this study was sanctioned from Institutional Review Board in College of Medicine at King Saud University. According to the 1975 Declaration of Helsinki as updated in 2008 (Puri et al., 2009), this study has been conducted in accordance with the informed consent form signed and completed by all participants.

2.2. Enrolment of infertile women

In this study a total of 192 Saudi women were recruited who have visited to Department of Obstetrics and Gynecology at King Khalid University Hospital. The 192 women were categorized into 96 infertile women (cases) and 96 controls. This study was carried out for 11 months in the year 2015 i.e., between January-November. The inclusion criteria for female infertility cases were based on family history of infertility and couples who had been unable to conceive for more than three years. Non-Saudi infertile women, Saudi fertile women, and women who did not sign the informed consent form were the exclusion criteria for female infertility cases. The inclusion criteria for control women were women who had conceived a child, had a regular menstrual cycle, and had no family history of infertility. This study excluded control participants with ovarian lesions/endometriosis and a family history of infertility, gestational diabetes (Khan et al., 2015), and low sperm count for male partners. The inclusion and exclusion criteria of this study subjects was already discussed (Al-Mutawa 2018).

2.3. Sample size

The Survey System Creative, Research Systems was one of the online tools was used to calculate the sample size, which was determined based on a formula, with the confidence level set at 95 % and the margin of error set at 5 %. It was estimated that each group had a sample size of 95 women. There was a total of 192 participants, comprising 96 women with female infertility and 96 healthy controls (Alqadri 2022).

2.4. Anthropometric measurements

Anthropmetric data such as age, weight, and height were recorded in this study to calculate body mass index (BMI) (Alshammary and Khan 2021), women experiencing infertility, and family history were recorded in both cases and controls.

2.5. Sample collection and DNA analysis

In this study, 2 ml of EDTA blood was collected from each woman who had visited our clinic after signing the informed consent form. Genomic DNA was extracted using Qiagen Kit from 192 woman based on the recommendation and company protocol (Alharbi et al., 2022). The genomic DNA (n = 192) samples were quantified using a NanoDrop spectrophotometer and stored at −80^{o}C for subsequent molecular analysis (Khan et al., 2015). Genotype analysis for Q36R (rs35431622) SNP was performed using inner and outer primers which was adopted (Vaziri et al., 2017). Primer sequence was shown below (F: CATCCCAGCTAAGGTGATCGT) and (R: CAGCTGGCTTCCTCGGT). The Q36R genotyping was performed with polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis using 50 µl of reaction mixture which consists of 4.0 µl of 20 ng of genomic DNA, 12.0 µl of distilled water, 4.0 µl of primer set and 30 µl of Qiagen master mix; which includes 10X buffer, $MgCl_2$, dNTPs and Taq DNA polymerase. The process of amplification was accomplished with an initial denaturation at 95^{o}C for 10 min, followed by denaturation at 94^{o}C for 30 s, annealing at 60^{o}C for 30 s, and 35 cycles were extended at 72^{o}C for 45 s. Final extension was finished for 10 min at 72^{o}C, and the complete reaction ended at 4^{o}C. After completing PCR amplification, 233 bp of PCR product was obtained, and RFLP analysis was performed using *NaeI* restriction enzyme, which was digested overnight at room temperature to obtain 233 bp as normal and 161/72 bp as variant bands. The heterozygous band is comprised of 233/161/72 bp. Both undigested and digested PCR products were run on 2 % agarose gel stained with ethidium bromide.

2.6. Statistical analysis

Statistical analysis was carried out using SPSS program (Version 20.0). Clinical features were compared between cases of female infertility and controls. Mean and standard deviation (MSD) were used to describe categorical variables, while percentages were used to represent numerical variables. The chi-square test was used to compare female infertility patients and controls. The Q36R SNP was subjected to a Hardy Weinberg equilibrium (HWE) analysis. The odds ratio (OR), 95 % confidence intervals (CIs), and significant p values were calculated for genotype, genetic models of genotypes, and allele frequencies. BMI and three types of genotypes were analyzed using one-way ANOVA (Khan et al., 2019). If the P value was<0.05 ($p \leq 0.05$), it was considered significant.

3. Result

3.1. Clinical features

The mean age of the women in the cases was 30.82 ± 5.39, while the mean age of the women in the control group was 29.96 ± 5.12. The anthropmetric factors such as age (p = 0.61), gender (p = 1.00), weight (p = 0.72), height (p = 0.87) and BMI (p = 0.63) were not associated when comparing female infertility cases and control women (p > 0.05) However, there was a strong association between infertile women and family history of infertility in an

infertile woman ($p < 0.0001$). Table 1 describes the details for cases and control subjects.

3.2. HWE analysis

When the genotype distribution of the Q36R SNP in the *KISS1* gene was investigated in the control group, it was determined to be consistent with HWE analysis ($\chi^2 = 14.15$ and $p = 0.0001$). The HWE analysis details was described in Table 2.

3.3. Q36R genotyping analysis

The genotype frequencies for female infertile women were 88.5 % and 10.4 % in AA and AG genotypes (Fig. 1), whereas 95.8 % and 3.1 % in AA and AG genotypes in the control group. In all cases and controls, the GG genotype was determined to be 1.1 %. The A allele was found in 93 % and 97 % of female infertility cases and controls, respectively, while the G allele was found in 7 % and 3 % of cases and controls. The genotype frequencies of A36R SNP were shown in Table 3. Genotype analysis confirmed the negative association with genotypes (GG vs AG: OR-1.08: 95 %CI [0.06–17.57]; p = 0.003), genetic models such as (AG + GG vs AA: OR-2.97: 95 %CI [0.91–9.70]; p = 0.003; AA + AG vs GG: OR-1.00: 95 %CI [0.06–16.22]; p = 0.00; AG vs AA + GG: OR-0.09: 95 %CI [0.01–0.72]; p = 0.005 and allele frequencies (G vs A: OR-2.49: 95 %CI [0.86–7.21]; p = 0.08). Statistical analysis was shown in Table 4.

3.4. Anova analysis

A one-way Anova analysis was performed in this study between Q36R cases and anthropometric parameters such as age, weight, height, and BMI. The Anova analysis explored the positive association between weight (p = 0.01) and BMI (p = 0.003) as rather than to age (p = 0.64) and height (p = 0.17). Table 5 shows the statistical analysis of Anova.

4. Discussion

The definition of an infertility is described as failure to become pregnant after at least 12 months of regular, unprotected sexual contact is a sign of infertility for both sexes. Infertility is classified as (i) Primary infertility is the inability to conceive at all, whereas (ii) secondary infertility is the inability to conceive after prior successful conception. Female infertility can be caused by a variety of conditions, including complications with the ovaries, uterus, fallopian tubes, or endocrine system. According to WHO records, infertility affects 48 million couples and 186 million individuals. In Saudi Arabia, the prevalence of female infertility was 18.93 %, with the majority of infertility observed in younger women, and the average duration of married life being 5 years (Al-Turki 2015). In this study, the mean age of 192 women was found to be on average of 30 years. The current fertility rate of Saudi Arabia is 2.24 children per woman, dropping from 7.29 in 1971 (Khalid et al., 2022). Based on the limited studies in molecular genotype data, this study was designed to investigate the role of Q36R SNP in the *KISS1* gene in Saudi women who had female infertility. The current study results confirmed that there is a negative association was found between clinical characteristics, genotype and allele frequencies ($p > 0.05$). Histories related infertility was found to be associated ($p < 0.0001$). Anova analysis confirmed the positive association with BMI and weight when compared with three genotypes in Q36R SNP ($p < 0.05$). A previous study by Daghestani et al showed the relation between *KISS1* gene and BMI (Daghestani et al., 2020).

Previous studies with Q36R SNP and KISS1 gene polymorphism was carried out in infertility women (Anna et al., Vaziri et al., 2017, Rehman et al., 2019, Siahpoosh et al., 2021) and the current study was found to be in agreement with the previous studies (Anna et al., Vaziri et al., 2017, Rehman et al., 2019). The different polymorphisms in *KISS1* gene was studies in PCOS (Branavan et al., 2019, Farsimadan et al., 2021, Zhao et al., 2022), that too in Saudi Arabia women (Albalawi et al., 2018, Daghestani et al., 2020, Daghestani et al., 2020) and also in male infertility (Poursharif et al., 2017, Al-Kalabi et al., 2021).

Table 1
Clinical characteristics between female infertility cases and controls.

	Female infertility (n = 96)	Fertile women (n = 96)	P values
Age (Years)	30.82 ± 5.39	29.96 ± 5.12	0.61
Female Gender	96 (100 %)	96 (100 %)	1.00
Weight (kgs)	73.91 ± 11.33	71.56 ± 10.92	0.72
Height (cms)	157.71 ± 5.11	157.68 ± 5.03	0.87
BMI (Kg/m2)	29.36 ± 4.44	28.86 ± 4.23	0.63
Infertile women	96 (100 %)	0 (0 %)	<0.0001
Family History	52 (54.1 %)	0 (0 %)	<0.0001

Table 2
Calculation of HWE analysis in Q36R genotype.

Q36R	HWE	X^2	P value
Controls	0.03	14.15	0.0001
Cases	0.06	1.18	0.27

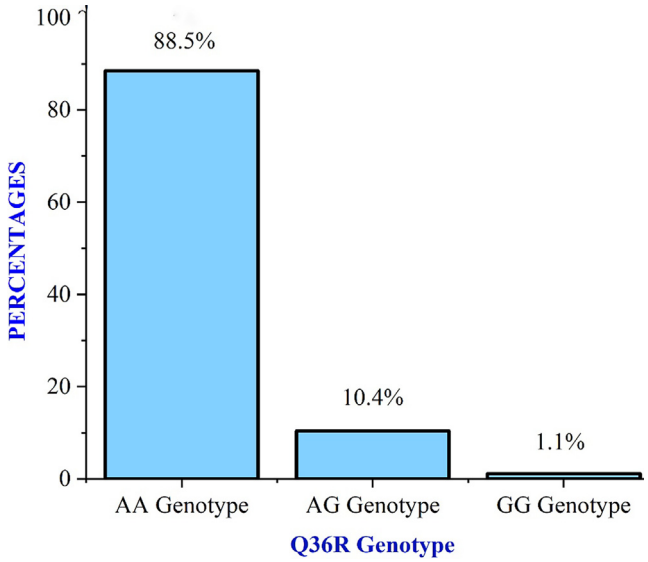

Fig. 1. Description of genotype frequencies in female infertility cases.

Table 3
Genotype and allele frequencies between female infertility cases and controls.

Genotypes/Alleles	Cases (n = 96)	Controls (n = 96)	P value
AA	85 (88.5 %)	92 (95.8 %)	**Reference**
AG	10 (10.4 %)	03 (3.1 %)	0.04
GG	01 (1.1 %)	01 (1.1 %)	0.95
AG + GG vs AA	11 (11.5 %)	04 (4.2 %)	0.05
AA + AG vs GG	95 (98.9 %)	95 (98.9 %)	0.00
AG vs AA + GG	86 (89.6 %)	95 (95.9 %)	0.005
A allele	180 (0.93 %)	187 (0.97 %)	**Reference**
G allele	12 (0.07 %)	05 (0.03 %)	0.08

Table 4
Genotype analysis between infertile and fertile women.

(rs35431622)	OR	95 %CIs	P value	Chi-Square
AA Genotype	**Reference**	**Reference**	**Reference**	**Reference**
AG Genotype	3.60	0.96–13.55	0.04	4.02
GG Genotype	1.08	0.06–17.57	0.95	0.003
AG + GG vs AA	2.97	0.91–9.70	0.05	3.52
AA + AG vs GG	1.00	0.06–16.22	0.00	0.99
AG vs AA + GG	0.09	0.01–0.72	0.005	7.77
A allele	**Reference**	**Reference**	**Reference**	**Reference**
G allele	2.49	0.86–7.21	0.08	3.01

Table 5
Anova analysis performance between BMI and Q36R genotypes in female infertility subjects.

Variables	QQ (n = 85)	QR (n = 10)	RR (n = 01)	P value
Age (Years)	30.83 ± 5.53	31.30 ± 4.35	26.00 ± 1.00	0.64
Weight (Kg)	72.73 ± 11.32	83.20 ± 6.46	82.00 ± 1.00	0.01
Height (Cms)	157.98 ± 5.20	156.10 ± 3.63	150.00 ± 1.00	0.17
BMI (Kg/m^2)	28.74 ± 4.29	33.92 ± 1.93	36.40 ± 1.00	0.003

Lee et al discovered the Kisspeptin gene as a metastasis inhibiting gene in melanoma cell lines in 1996 (Lee et al., 1996). Many SNPs have been documented in the KISS1 gene which is connected with precocious puberty, female infertility and PCOS. Earlier studies in the past had linked *KISS1* gene to various processes, such as aging, adipose physiology, and perhaps as a molecular conduit between metabolism and reproduction. The relation between infertility in women and KISS1 gene was shown in previous studies. Idiopathic hypogonadotropic hypogonadism (IHH) patients have been found to have SNPs in *KISS1* gene. Impaired pubertal maturation and reproductive function can be caused by decreased GnRH signaling and low levels of circulating gonadotropins in IHH patients. The hypothalamic KISS1/KISS1R (KISS1 receptor) system is responsible for the pulsatile release of gonadotropin-releasing hormone. As a result, KISS1 and the KISS1R receptor play an important role in determining when puberty begins and how hormones are released from the reproductive axis (Anna et al., Vaziri et al., 2017, Rehman et al., 2019, Siahpoosh et al., 2021). The rs35431622 (Q36R) SNP was found in the exon 2 region of the KISS1 gene. The functional role was discovered to be non-synonymous, and the amino acid region at Gln36Leu was altered. The mRNA location was identified to be 261 with a minor allele frequency of 0.075. The heterozygosity rate was determined to be 0.103 (Daghestani et al., 2020).

This study has certain strength and limitations such as follows. The main strength of this study was to recruit all Saudi women from single tertiary center between the age range of 20–40 years. The limited limitations of this study were to enroll single SNP, missing validation and biochemical parameters.

5. Conclusion

The findings of this study confirm that the Q36R SNP plays no function role in Saudi infertile women. However, similar SNP was found to be associated with PCOS women in Saudi women. Additional studies are required to rule out the discrepancies in results between female infertility and PCOS women. One of the key causes for the disparities in outcomes was the selection of patient criteria.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Akbaribazm, M., Goodarzi, N., Rahimi, M., 2021. Female infertility and herbal medicine: an overview of the new findings. Food Sci. Nutr. 9 (10), 5869–5882.

Albalawi, F.S., Daghestani, M.H., Daghestani, M.H., et al., 2018. rs4889 polymorphism in KISS1 gene, its effect on polycystic ovary syndrome development and anthropometric and hormonal parameters in Saudi women. J. Biomed. Sci. 25 (1), 1–6.

Alharbi, K.K., Alsaikhan, A.S., Alshammary, A.F., et al., 2022. Screening of mitochondrial mutations in Saudi women diagnosed with gestational diabetes mellitus: A non-replicative case-control study. Saudi J. Biol. Sci. 29 (1), 360–365.

Al-Kalabi, F.K., Al-Azzawie, A.F., Al-Wasiti, E.A., 2021. Role of Kisspeptin gene polymorphism in idiopathic male infertility in Iraq. Iraqi J. Sci. 62 (10), 3428–3435.

Al-Mutawa, J., 2018. Interaction with angiotensin-converting enzyme-encoding gene in female infertility: insertion and deletion polymorphism studies. Saudi J. Biol. Sci. 25 (8), 1617–1621.

Alqadri, N., 2022. Independent case-control study in KCNJ11 gene polymorphism with Type 2 diabetes Mellitus. Saudi J. Biol. Sci. 29 (4), 2794–2799.

Alshammary, A.F., Khan, I.A., 2021. Screening of obese offspring of first-cousin consanguineous subjects for the angiotensin-converting enzyme gene with a 287-bp Alu sequence. J. Obes. Metab. Syndr. 30 (1), 63.

Altmäe, S., Stavreus-Evers, A., Ruiz, J.R., et al., 2010. Variations in folate pathway genes are associated with unexplained female infertility. Fertil. Steril. 94 (1), 130–137.

Al-Turki, H.A., 2015. Prevalence of primary and secondary infertility from tertiary center in eastern Saudi Arabia. Middle East Fertil. Soc. J. 20 (4), 237–240.

Anna, R., V. Hamidreza and F. Roya, The association of the Q36R polymorphism in KISS1 gene with female infertility.

Asgari, R., 2021. The role of ESR1 PvuII T/C variant in the female reproductive process: a review. Central Asian J. Med. Pharma. Sci. Innov. 1 (1), 22–27.

Branavan, U., K. Muneeswaran, W. Wijesundera, et al., 2019. Association of Kiss1 and GPR54 gene polymorphisms with polycystic ovary syndrome among Sri Lankan women. BioMed Research International. 2019.

Breitkopf, D.M., Hill, M., 2019. Infertility workup for the women's health specialist. Obstet. Gynecol. 133 (6), E377–E384.

Daghestani, M., Daghestani, M., Daghistani, M., et al., 2020. Relevance of KISS1 gene polymorphisms in susceptibility to polycystic ovary syndrome and its associated endocrine and metabolic disturbances. Br. J. Biomed. Sci. 77 (4), 185–190.

Daghestani, M.H., Daghestani, M.H., Daghistani, M., et al., 2020. Influence of KISS1 gene polymorphisms on the risk of polycystic ovary syndrome and its associated variables, in Saudi women. BMC Endocrine Disorders 20 (1), 1–10.

Farsimadan, M., Moammadzadeh Ghosi, F., Takamoli, S., et al., 2021. Association analysis of KISS1 polymorphisms and haplotypes with polycystic ovary syndrome. Br. J. Biomed. Sci. 78 (4), 201–205.

Froment, P., Plotton, I., Giulivi, C., et al., 2022. At the crossroads of fertility and metabolism: the importance of AMPK-dependent signaling in female infertility associated with hyperandrogenism. Hum. Reprod. 37 (6), 1207–1228.

Ilgaz, N.S., Aydos, O.S.E., Karadag, A., et al., 2015. Impact of follicle-stimulating hormone receptor variants in female infertility. J. Assist. Reprod. Genet. 32 (11), 1659–1668.

Joon, T.L., Pillai, N., Yap, C.G., et al., 2022. Obesity and female infertility—a review on mechanisms (Endocrinology). Open Access Library J. 9 (6), 1–20.

Khalid, N.H.M., Ahmed, I.A.M., Ahmed, S.A.F., 2022. Evaluation of causes of female infertility using ultrasonography in Najran, Saudi Arabia. Afr. J. Reprod. Health 26 (5).

Khan, I.A., Kamineni, V., Poornima, S., et al., 2015. Tumor necrosis factor alpha promoter polymorphism studies in pregnant women. J. Reprod. Health Med. 1 (1), 18–22.
Khan, I.A., Shaik, N.A., Pasupuleti, N., et al., 2015. Screening of mitochondrial mutations and insertion–deletion polymorphism in gestational diabetes mellitus in the Asian Indian population. Saudi J. Biol. Sci. 22 (3), 243–248.
Khan, I.A., Jahan, P., Hasan, Q., et al., 2019. Genetic confirmation of T2DM meta-analysis variants studied in gestational diabetes mellitus in an Indian population. Diabetes Metab. Syndrome: Clin. Res. Rev. 13 (1), 688–694.
Koysombat, K., Abbara, A., Dhillo, W.S., 2022. Current pharmacotherapy and future directions for neuroendocrine causes of female infertility. Expert Opin. Pharmacother., 1–11
Lee, J.-H., Miele, M.E., Hicks, D.J., et al., 1996. KiSS-1, a novel human malignant melanoma metastasis-suppressor gene. JNCI: J. Nat. Cancer Inst. 88 (23), 1731–1737.
Lim, Z.W., Wang, I.-D., Wang, P., et al., 2021. Obstructive sleep apnea increases risk of female infertility: a 14-year nationwide population-based study. PLoS ONE 16 (12), e0260842.
Poursharif, A., Shabani, S., Vaziri, H.R., et al., 2017. polymorphism in KISS1 receptor gene was correlated with idiopathic male infertility in Guilan province, Iran. Gene Rep. 6, 112–115.
Puri, K., Suresh, K., Gogtay, N., et al., 2009. Declaration of Helsinki, 2008: implications for stakeholders in research. J. Postgrad. Med. 55 (2), 131.
Rehman, R., Fatima, S.S., Alam, F., et al., 2019. Kisspeptin and attributes of infertile males and females: a cross-sectional study in a subset of Pakistani population. Andrologia 51 (9), e13370.
Siahpoosh, Z., Farsimadan, M., Pazhohan, M., et al., 2021. KISS1R polymorphism rs587777844 (Tyr313His) is linked to female infertility. Br. J. Biomed. Sci. 78 (2), 98–100.
Vaziri, H., Rafeie, A., Siapoosh, Z., 2017. Q36R (rs 35431622) Polymorphism in KISS1 gene and idiopathic female infertility in a Northern Iranian population. Gene, Cell Tissue 4 (3).
Wang, W., Wang, W., Xu, Y., et al., 2021. FBXO43 variants in patients with female infertility characterized by early embryonic arrest. Hum. Reprod. 36 (8), 2392–2402.
Zhao, T., Zhang, Q., Xiao, X., et al., 2022. Associations of the KiSS-1 and GPR54 genetic polymorphism with polycystic ovary syndrome in Yunnan, China. Gynecol. Endocrinol., 1–5