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The relationship between hypergonadotropic hypogonadism and gene variations? New mutations discovered by familial mutation screening and a review of the literature

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ABSTRACT

Hypergonadotropic ovarian failure with normal karyotype is a heterogeneously inherited disorder with Mendelian recessive inheritance in some cases. This condition is characterized by a wide range of clinical manifestations, ranging from primary amenorrhea associated with ovarian dysgenesis to post-pubertal secondary amenorrhea characterised by elevated gonadotropin levels and low estrogen levels. The objective of this study was to identify potential genetic mutations associated with ovarian dysfunction through genetic analysis in a 16-year-old female exhibiting a typical karyotype, who had previously been diagnosed with hypergonadotropic hypergonadism and sporadic ovarian failure, in addition to her first-degree relatives. Each of the seven family members underwent karyotype analysis for familial genetic screening. Using the Next Generation Sequencing (NGS) Sex Panel, a total of 41 genes were analysed. Five new gene variants (AMH [c.814C>G, rs546849156], SLC34A3 [c.1453C>T, rs145029982], FBN2 [c.8282C>T, rs201962592], NOTCH2 [c.6956C>T, rs373527990] and COL9A1 [c.1621G>A]) were identified in the proband. In the family screening of the proband, the karyotype analysis of the 14-year-old sister was found to be 46,XX,16qh+. The NGS scan of this sister revealed the same genetic mutations in the AMH, COL9A1, SLC34A3, FBN2, NOTCH2 and GP1BA genes as in the proband. These genetic variations play an important role in the regulation of many fundamental biological processes, including meiosis, follicular development, ovulation, cellular metabolism and regulation of the extracellular matrix. We suggest that these genetic variations may be directly or

indirectly related to the mechanisms of folliculogenesis and may represent novel candidate gene mutations in ovarian failure, an oligogenic disease.

Keywords: Hypergonadotropic hypogonadism, ovarian failure, novel mutation, AMH, NOTCH2.

1. INTRODUCTION

Hypergonadotropic hypogonadism (HH) is defined by elevated gonadotropin levels in individuals. Establishing a regular menstrual cycle is contingent upon the anatomical and biochemical integrity of the hypothalamic-pituitary axis. An adequate hormonal environment and a functional internal and external genital system are prerequisites (Aittomäki et al., 1995). The regulatory mechanism is controlled by pituitary gonadotropins, including luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Hypergonadotropic hypogonadism is characterized by elevated levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which is due to an inadequate ovarian response to gonadotropin stimulation. In individuals with hypergonadotropic hypogonadism, the ovaries fail to develop or respond to gonadotropin stimulation, resulting in arrested follicular development and follicular atresia.

Genetic alterations that cause ovarian defects may affect the ovary alone or be a syndrome component (Simpson et al., 1971). Hypergonadotropic hypogonadism, which is characterized by high levels of gonadotropins, low levels of sex steroids and menstrual abnormalities, has recently also been referred to as primary ovarian insufficiency (POI). The incidence of POI, a heterogeneous condition, is approximately 1% under 40, 1 in 10,000 in their 20s and 1 in 1,000 in their 30s (Beck-Peccoz and Persani, 2006). The premature depletion of the primordial follicle reservoir in individuals diagnosed with premature ovarian insufficiency (POI) may be due to abnormalities in the mechanisms of oocyte apoptosis.

This may lead to reduced follicular genesis, resulting in a reduced number of oocytes produced during ovarian maturation and accelerated follicular atrophy (Webber et al., 2016). POI can manifest as either primary or secondary amenorrhea, accompanied by perturbations in hormonal profiles, including elevated gonadotropin concentrations (FSH > 25 IU/L) and diminished levels of estradiol and anti-Müllerian hormone (AMH). Although many genes have been associated with premature ovarian insufficiency (POI), the specific genes responsible for POI have not yet been identified. In most cases (around 70 percent), the etiology of POI remains unclear. There is an apparent genetic predisposition to POI.

However, family studies have suggested a possible genetic association with idiopathic POI (Themmen, 2005). Studies using whole-exome or whole-genome sequencing techniques have successfully identified the underlying causes of POI in about 30-35% of cases. POI is a pathological condition characterized by markedly increased genetic heterogeneity (Gündüz et al., 2024). Many novel POI-related genes were identified, including X-linked genes such as SHOX, BMP15 and FMR1, and autosomal genes such as HFM1, FIGLA, FOXL2, STAG3 and FSHR (Rossetti et al., 2017).

2. MATERIALS AND METHODS

In this family study, a 16-year-old girl with hypergonadotropic hypogonadism who was admitted to Dicle University Faculty of Medicine, Gynaecology and Obstetrics Clinic in June 2023 and her family members were included. The study was approved by the Medical Ethics Committee. Dicle University Medical Faculty Ethics Committee (Ethical approval code: 125 Date: 06/02/2020). Before their inclusion in the study, each individual provided written informed consent. In this study, the lymphocyte tissue culture method, which is a modified form of the macroculture technique and is known as the microculture or whole blood technique, was used to obtain chromosomes. Preparations were made using the Giemsa banding technique and 30 cells were counted.

The extraction of genomic DNA was performed either from the blood cells of the patient. DNA extraction was performed with the QIAmp kit (QIAGEN, Hilden/Germany) in the QIAcube HT system (QIAGEN, Hilden, Germany) according to the manufacturer's instructions. A dsDNA HS assay kit (Invitrogen, Waltham, Massachusetts, USA) was used to measure the final DNA concentration fluorometrically in a Qubit™ instrument. Exon-intron junctions (±10 base pairs) were incorporated into the analysis. These regions were scrutinized with an average sequencing depth of 50x and a coverage rate of 97.56%.

The pathogenicity classification for the acquired data was executed according to the guidelines set forth by the American College of Medical Genetics and Genomics (PMIDs: 25741868; 27854360). This process was conducted utilizing a specifically tailored targeted next-generation sequencing (NGS) platform encompassing 41 genes: AMH, AMHR2, AR, ARX, ATRX, CDKN1C, CHD7, CUL4B, CYB5A, CYP11A1, CYP11B1, SGPL1, SOX10, SOX9, SRD5A2, SRY, STAR, CTU2, DHX37, ESR2, FGFR2, GATA4, HOXA13, MYRF, NR2F2, NR3C1, PAX8, PBX1, PPP1R12A, TCF12, TOE1, TSPYL1, WT1, ZFPM2, MAP3K1, NR0B1, NR5A1, POR, RPL10, RSPO1, SAMD9.

3. RESULTS

Our study included a family consisting of four females and three males. Genomic alterations were identified by NGS screening in a 16-year-old female (proband) who was referred to the Medical Biology and Genetics Center of Dicle University with an initial diagnosis of hypergonadotropic hypogonadism. As a result, we decided to continue screening the family (Figure 1).

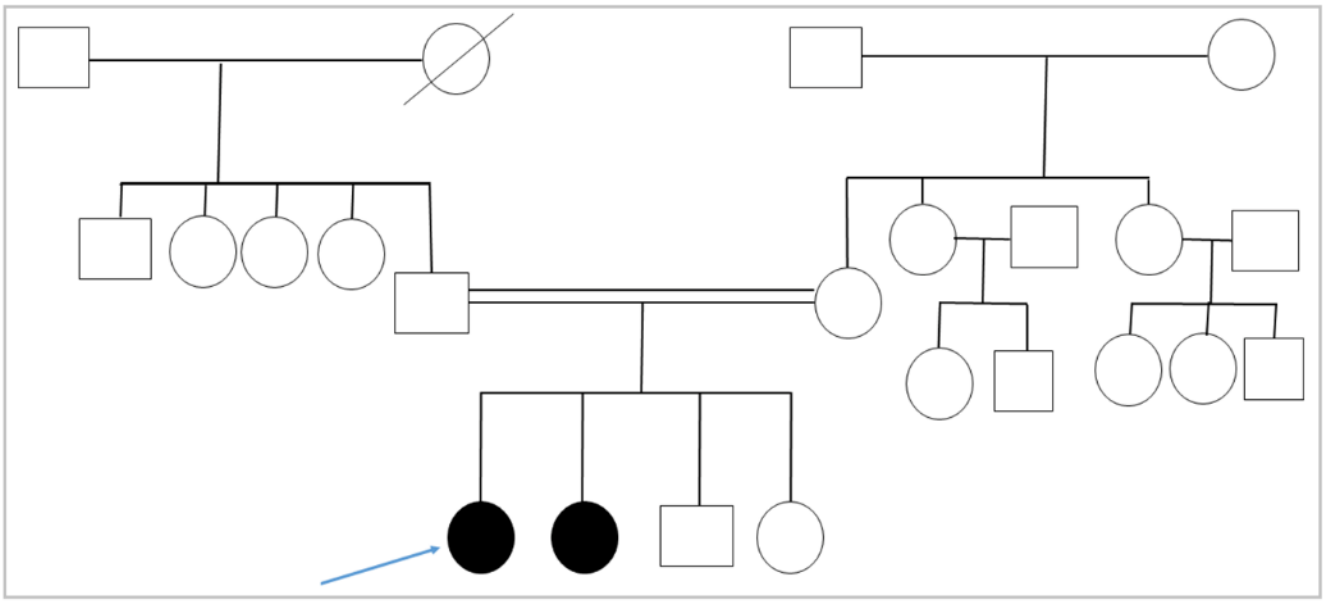

Figure 1 Pedigree chart

Physical examination of the proband revealed a height of 157 cm and a weight of 57.4 kg, which were within normal limits for her age. She had Tanner stage IV breast development and Tanner stage IV pubic hair. The pelvic ultrasound showed that the pelvic organs were significantly reduced for her age and a pelvic MRI was ordered. According to the pelvic MRI, the dimensions of the uterus were 1.2X2.6X3.9 cm, the uterus was hypoplasic and the ovaries were not observed. The proband's baseline serum gonadotropin levels were elevated, consistent with a diagnosis of hypogonadotropic hypogonadism (HH). In particular, follicle-stimulating hormone (FSH) was 91 U/L (normal range 2.2-10.1 U/L) and luteinising hormone (LH) was 33.3 U/L (normal range 1.9-2.3 U/L). Family screening revealed that her 14-year-old sister had the same condition.

The affected sister's height was 152 cm and her weight was 48 kg, within normal limits for her age. Breast development was normal and no pubic hair growth was noted. On pelvic MRI, the bladder was normal, uterine dimensions were 58x20x20mm, myometrium was homogeneous with average thickness and endometrial thickness was approximately 5 mm. The right ovary showed a follicular cyst measuring 17x13mm and approximately 1cm in diameter. The left ovary was not visualized (atrophy?). Gonadotropin levels were above average normal with FSH = 18.21 U/L [normal range 2.2-10.1 U/L] and LH = 2.89 U/L [normal range 1.9-2.3 U/LThe serum estradiol concentration was below the normal range in the proband (5 pg/mL [normal range 22-215 pg/mL]) and in the sister (8 pg/mL [normal range 22-215 pg/mL]). The serum AMH concentration was 0.01 U/L in both siblings, which was below the normal range.

Both siblings were followed for 12 months. Low-dose estrogen therapy (2 μg/day ethinyl estrodiol) was started and the estrogen dose was increased by 2 μg from the sixth month. During this time, the subject experienced three menarchees, while her affected sister

experienced two menarchees. At the end of the twentieth month, the healthcare provider decided to add progesterone to the ongoing treatment regimen. The proband's karyotype was identified as 46,XX following a comprehensive 50-metaphase analysis (Figure 2). The chromosomal analysis of the affected 14-year-old sister is 46,XX,16 qh+ (increased heterochromatin on the q arm of chromosome 16) (Figure 3). For the patient and her sibling, 41 genes were analyzed as part of the gender panel, and the genes with mutations are shown in (Table 1).

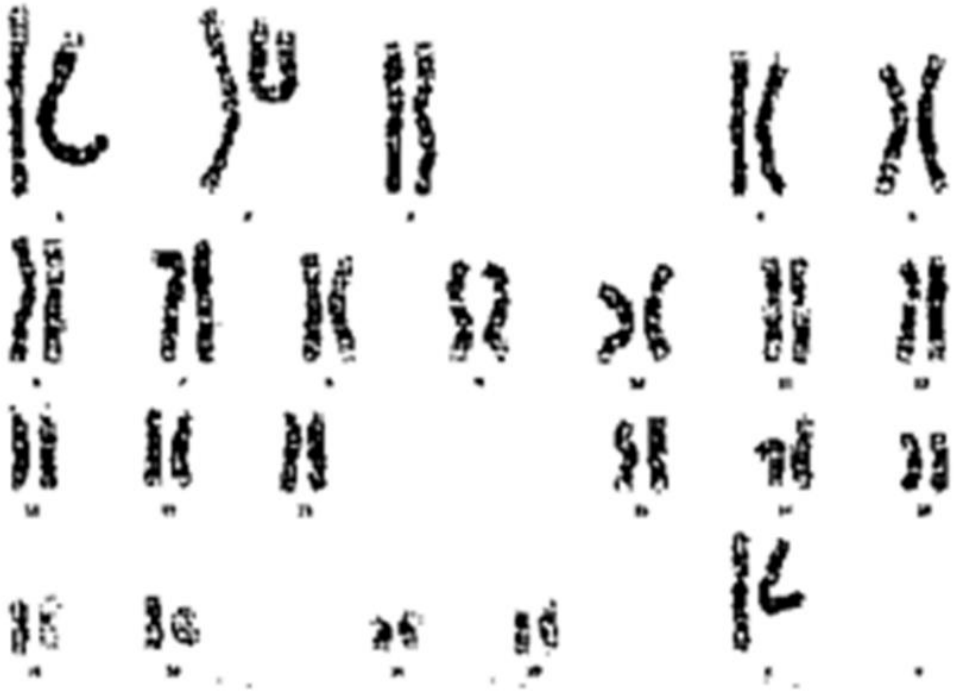

Figure 2 Karyotype analysis of proband

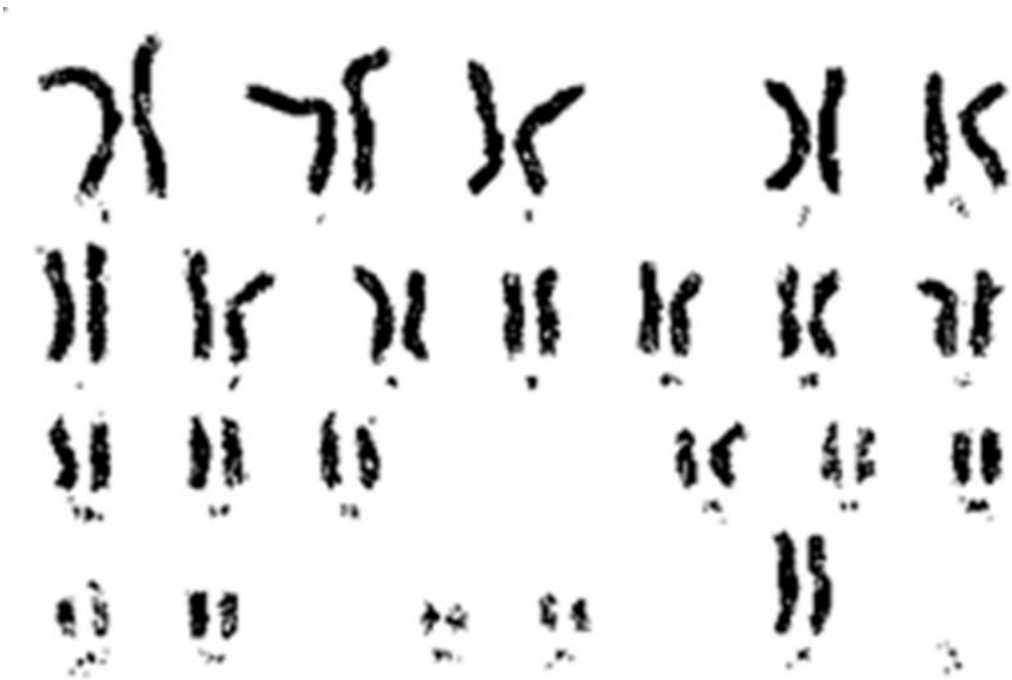

Figure 3 Karyotype analysis of affected sibling

Table 1 The results of a specially designed targeted next-generation sequencing (NGS) panel of 41 genes for family members

	Gene	Location	Sequence variation	Variant ID or rs number
Proband	AMH	chr19:2250997 (exon 4)	c.814C>G	Rs 546849156
	SLC34A3	chr9:140130521 (Exon 13)	c.1453C>T	Rs145029982
	FBN2	chr5:127597510 (Exon 70)	c.8282C>T	Rs201962592
	NOTCH2	chr1:120458389 (Exon 34)	c.6956C>T	Rs373527990
	COL9A1	chr6:70964710 (Exon 24)	c.1621G>A	Not found
Affected sibling	AMH	chr19:2250997 (exon 4)	c.814C>G	Rs 546849156
	SLC34A3	chr9:140130521 (Exon 13)	c.1453C>T	Rs145029982
	FBN2	chr5:127597510 (Exon 70)	c.8282C>T	Rs201962592
	NOTCH2	chr1:120458389 (Exon 34)	c.6956C>T	Rs373527990
Other family members	No mutation was detected			

4. DISCUSSION

Hypergonadotropic hypogonadism occurs as a result of primary gonadal failure, although the hypothalamic-hypophyseal axis is normal. In partial or incomplete cases, puberty begins but cannot be maintained. In particular, FSH is very high in primary gonadal failure. This increase becomes apparent from the age of eight to nine years. Even in the absence of suspicious genitalia, karyotype analysis is recommended in these patients. Chromosomal abnormalities should be kept in mind in these patients and specific hormones of the hormone-secreting gonads (FSH, estrogen, etc.) should be evaluated if necessary (Benk-Şilfeler et al., 2014). The serum FSH level of the proband was 91 U/L, which was above average, while that of his affected sibling was 8.21 U/L, which was within normal limits.

The female reproductive system in mammals goes through a fascinating developmental journey, starting with the complex Müllerian ducts and extending to the fallopian tubes, the uterus, the cervix and the upper part of the vagina. Any disruption in the formation of these Müllerian structures can result in many a number of congenital abnormalities of the female genital tract. These abnormalities can manifest as agenesis, atresia or irregular septation of the fallopian tubes, uterus, cervix or vagina. They originate from the Müllerian duct (Yatsenko and Rajkovic, 2019). The reason for the uterine atrophy and absence of ovaries on MRI in the proband and affected sibling can be attributed to this condition. Hypergonadotropic hypogonadism is a complex condition with a hereditary element. Numerous well-defined genes are involved in forming the Müllerian duct (Yan et al., 2019).

Variations in either the AMH or AMH receptor type II gene, which impede the growth of the female reproductive system, have been linked to levels of estradiol during the follicular phase, indicating a possible function for AMH in FSH-induced steroidogenesis in the human ovary (Kevenaar et al., 2007). AMH possesses the capacity to control the commencement of primordial follicular maturation as well as follicular atresia triggered by follicle-stimulating hormone (FSH) (Durlinger et al., 2001). AMH is synthesized by granulosa cells originating from the pre-antral and antral follicles in females. The initiation of AMH expression takes place in the granulosa cells of primary follicles during follicular growth Itreaches its highest levels in the granulosa cells of preantral and small antral follicles and then decreases as the follicles continue to grow (Weenen et al., 2004).

Differences in AMH levels during childhood and adolescence are minimal, and each young woman maintains a constant relative level throughout puberty (Lindhardt-Johansen et al., 2013). In adult females, the presence of circulating Anti-Müllerian Hormone (AMH) levels functions as a marker for the number of primordial follicles yet to be developed (Grossman et al., 2008). AMH plays a role in the controllingsteroid hormone production in the ovaries by hindering the activity of aromatase and diminishing the levels of oestradiol within the follicles (Nielsen et al., 2011). Typically, individuals with AMH mutations exhibit reduced levels of AMH in their serum (Josso et al., 2005). Both siblings had → deficientserum AMH levels (0.1 μg/l) and the same mutation in the AMH gene (c.814C>G).

In two recent studies investigating AMH variants in patients with POI, no apparent discrepancy in the frequency of menopause-related distribution was observed compared to age-matched controls (De-Kat et al., 2021). SNP rs10407022 represents the sole documented variation within the AMH gene that has undergone functional analysis (Kevenaar et al., 2008). In their study, identified three defective AMH variations among patients with premature ovarian insufficiency (POI), one of which had not been previously → characterized. An in vitro functional evaluation revealed that two of the three variations (G264R and R444H) exhibited a loss of function, whereas the third variation (D288E) displayed a reduction or impairment in secretion (Josso et al., 2005). Our study identifies AMH rs546849156 variants in two sisters with the same mutation, the prevalence of which remains undefined or extremely rare.

Another intra-ovarian factor, fibrillin (FBN), regulates transforming growth factor beta (TGF-β) activity during ovarian development. Expression of FBN1-3 changes during fetal development and influences stromal cell behavior and collagen deposition, which are critical for proper ovarian function. FBN1, FBN2, and FBN3 are involved in regulating TGF-β activity (Maylem et al., 2021). TGF-β induces aromatase expression in granulosa cells, which affects estradiol production and normal ovarian function (Banerjee et al., 2023). Type IX collagen is essential, in the regulating of type II fibril growth. It is a trimeric protein consisting of three polypeptide chains, a 1(IX), a 2(IX) and a 3(IX), derived from the COL9A1, COL9A2 and COL9A3 genes respectively. Within the cartilage collagen domain, type IX collagen contains three collagen (COL1-3) and four non-collagen (NC1-4) domains. It is noteworthy that the NC4 domain encoded by COL9A1 is larger than those encoded by COL9A2 or COL9A3.

The NC4 domain is adept at interacting with cartilage proteoglycans, thereby contributing to the stabilization of the cartilage extracellular matrix, facilitating the remodelling of the ECM to function as a vital conduit for the transport of nutrients, hormones, and signaling molecules within the ovary. This facilitates germ cell maturation and follicle development. It also forms the primary collagen scaffold within the ovarian tissue and serves as an important site for transporting essential nutrients, hormones, and signaling molecules (Cheng et al., 2021). The FBN gene and its isoform COAL9A 1-3, known for its involvement in the TGF-β signaling pathway, strongly correlate with various ovarian physiological processes such as regulation of granulosa cell proliferation, ovulation, and/or follicular development. In this study, mutations in the FBN2 (c.8282 C>T) and COL9A1 (c.1621G>A) genes were found in both sisters.

In addition, an SLC34A3 (c.1453C>T) Vus mutation was found in both sisters. Mutations in the SLC34A3 gene, which is responsible for regulating phosphate homeostasis, play a role in the tumourigenesis of ovarian, lung and breast cancer (Czarny-Ratajczak et al., 2001). A total of three distinct mutations have been discovered within the NOTCH2 gene, which encodes one of the four single-pass transmembrane type I (SPTI) receptors in the NOTCH family (Andersson et al., 2011). The mutations NotCH2-P Ser1804Leu, p.Gln1811His, and p.Leu2408His, identified in a separate investigation, are located in the cytoplasmic domain of the protein that translocates to the nucleus, where it modulates processing and repression (Patiño et al., 2017). There is a possibility that the alternative variants identified in NOTCH2 in our research may lead to dysregulation in the expression of essential target genes associated with oocyte development.

5. CONCLUSION

In the realm of clinical practice, there is an observation that individuals afflicted with premature ovarian failure (POI) exhibit common characteristics in specific female family members, indicating a potential hereditary origin. As part of our investigation, we present five novel genetic alterations that may be associated with the phenotype mentioned above, identified in identical variations in two siblings. It appears that mutations in low-frequency genes in the sex panel, such as AMH, COLA1, FBN, NOTCH 2, and SLC34A3, may contribute to a significant proportion of POI patients with a familial history of ovarian failure. The study of these mutations will facilitate the formulation of more critical conclusions regarding the effect of these genes on the pathogenesis of POI, especially in large groups of POI patients with a familial history. It is essential to study the identified mutations in patients with similar problems to determine the effect of these genes on the disease.

It is crucial to analyze the identified mutations in individuals with similar clinical manifestations to determine the impact of these genetic alterations on the disorder's pathogenesis. Elucidation of the aetiology and molecular basis of premature ovarian insufficiency (POI) is essential not only for understanding ovarian function but also for genetic counseling and reproductive health recommendations. The ability to predict the onset of menopause is expected to improve with the discovery of additional genetic variations in POI. Individuals with certain POI conditions may be able to achieve oocyte preservation through age-appropriate assisted reproductive technologies. In addition, correction of hormonal parameters may delay the age of menopause.

Ethical approval

Dicle University Medical Faculty Ethics Committee (Ethical approval code: 125 Date: 06/02/2020).

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Conflicts of interest

There are no conflicts of interest

Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

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