



# Progesterone-Related Issues and Coping Strategies for Women Undergoing Assisted Reproductive Treatment

## Yardımcı Üreme Tedavisi Alan Kadınların Progesteron Kullanımına Bağlı Yaşadıkları Sorunlar ve Baş Etme Yöntemleri

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### ABSTRACT

**Objective:** This study aims to identify the problems experienced by women undergoing assisted reproductive treatment due to progesterone use, as well as their coping strategies.

**Methods:** The study included 145 women who were admitted to an infertility outpatient clinic of a university hospital between July 25 and August 8, 2022. The researchers collected data using a questionnaire designed to assess the problems that might arise due to the use of various types of progesterone-containing drugs and coping methods. The data were evaluated using descriptive statistics in the SPSS program.

**Results:** The mean age of the women was 30.76±5.53 years, and the mean duration of their marriages was 6.6±4.51 years. Of women 64.8% had primary infertility and 68.3% of women underwent assisted reproductive treatment (ART) at least once before. Women who received intramuscular progesterone treatment during ART frequently experienced pain, swelling, abscess, redness at the injection site. Women who received progesterone treatment vaginally experienced vaginal wetness, drying of the drug in the vagina, lumps, the drug leaving the body, the drug not being completely absorbed, vaginal itching. Women who received progesterone treatment orally experienced sleepiness, nausea, dizziness, headache, fatigue. Women coped with these problems using various methods.

**Conclusion:** The study revealed that women undergoing ART experienced many problems related to the use of progesterone and they attempted to address these issues through their own means. It

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**Amaç:** Bu araştırma ile yardımcı üreme tedavisi alan kadınların progesteron kullanımına bağlı yaşadıkları sorunların ve bunlarla baş etme yöntemlerinin belirlenmesi amaçlanmıştır.

**Yöntemler:** Araştırma, 25 Temmuz-08 Ağustos 2022 tarihleri arasında bir üniversite hastanesinin infertilite polikliniğine başvuran toplam 145 kadınla yürütülmüştür. Veriler, araştırmacılar tarafından progesteron hormonu içeren ilaçların farklı formlarının kullanımına bağlı yaşanabilecek sorunları ve bunlarla baş etme yöntemlerini sorgulamaya yönelik hazırlanmış bir anket formu aracılığı ile toplanmıştır. Veriler, SPSS programında tanımlayıcı istatistikler kullanılarak değerlendirilmiştir.

**Bulgular:** Kadınların yaş ortalaması 30,76±5,53 olup, evlilik süresi ortalaması 6,6±4,51 yıldır. Kadınların %64,8'i primer infertil iken %68,3'ü daha önce en az bir kez yardımcı üreme tedavisi (YÜT) almıştır. YÜT sırasında intramüsküler progesteron tedavisi alan kadınlar sıklıkla enjeksiyon bölgesinde ağrı, şişlik, apse, kızarıklık; vajinal yolla progesteron tedavisi alan kadınlar vajinal ıslaklık, ilacın vajinada kurumaması, topaklanması, ilacın vücut dışına çıkması, ilacın tamamen emilmemesi, vajinal kaşıntı ve oral yolla progesteron tedavisi alan kadınlar ise halsizlik, uyku hali, bulantı, baş dönmesi, baş ağrısı, yorgunluk gibi sorunlar yaşamıştır. Kadınlar bu sorunlar ile çeşitli yöntemler kullanarak baş etmişlerdir.

**Sonuç:** Araştırma YÜT alan kadınların progesteron kullanımına bağlı birçok sorun yaşadığını ve bu sorunlarla kendi yöntemleri ile baş etmeye çalıştıklarını ortaya koymuştur. Hastaların bilgilendirilmesi

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**Cite this article as:** Karadeniz H, Demirci N, Süzer Özkan F, Gülen Savaş H. Progesterone-Related Issues and Coping Strategies for Women Undergoing Assisted Reproductive Treatment.

Bezmialem Science 2023;11(3):300-7



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**Received:** 19.01.2023

**Accepted:** 11.05.2023

**ABSTRACT**

is necessary to inform patients and to plan nursing interventions to minimize/eliminate these problems.

**Keywords:** Coping, infertility, progesterone, assisted reproductive treatment

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ve yaşanan sorunların en aza indirilmesine/giderilmesine yönelik hemşirelik girişimlerinin planlanması gerekmektedir.

**Anahtar Sözcükler:** Baş etme, infertilite, progesteron, yardımcı üreme tedavisi

**Introduction**

Infertility is defined as not being able to get pregnant while having regular sexual intercourse without using any birth control method for at least one year despite the couple's desire to have a child. Primary infertility is the inability to have any pregnancy, while secondary infertility is the inability to have a pregnancy after previously successful conception (1). The World Health Organization has reported that infertility is a health problem affecting 48 million couples and 186 million people worldwide (2). Of the couples worldwide who are at reproductive age 8-12% experience infertility issues, compared to 15% in the US and 10-20% in Turkey (3-5).

With the increase in its success rates, assisted reproductive technologies (ART) now present a significant opportunity for couples to have their own children. The most commonly used ARTs are Intrauterine Insemination (IUI), Intracytoplasmic Sperm Injection (ICSI) and in case of failure of previous assisted reproductive technologies, in vitro fertilization (IVF) (3,6). IUI is the direct introduction of sperm into the uterus with a thin cannula after special washing and preparation procedures. It is based on the hypothesis of increasing the chance of pregnancy by increasing the number of motile sperms in the fertilization area. In IVF, sperm cells from a man are placed around one of the egg cells from a woman in a laboratory and a sperm is expected to fertilize the egg spontaneously. This is similar to fertilization in a normal pregnancy. With ICSI, a sperm cell is injected into the egg cell with a micropipette and fertilization takes place (7).

The implantation stage of the embryo in ART cycles is a critical step limiting reproductive success and requires a perfect match between the embryo and the endometrium (8,9). The endometrium undergoes changes during the follicular phase due to estrogen and during the luteal phase due to progesterone. Progesterone has several physiological effects that prepare the endometrium for implantation, regulate the development of endometrial receptivity, and support pregnancy to delivery. Estradiol is involved in the epithelial, stromal, and glandular proliferation of the endometrium in this process (10,11). Contrary to natural cycles, supraphysiological estradiol and progesterone levels in the early luteal phase cause an anterior shift in endometrial development in gonadotropin-induced ART cycles. Therefore, asynchronization may occur between the embryo and endometrial development during the implantation period. Therefore, progesterone-containing drugs are frequently used as luteal phase support in the ART process (12).

Progesterone-containing medications come in a variety of forms that can be administered orally, intramuscularly, subcutaneously, and vaginally (13,14). Many studies have been conducted to investigate the relationship between various variables such as the effect of drugs containing progesterone on pregnancy outcomes, their ease of administration, and the tolerance levels of patients (13-22). However, no studies have been found illustrating the issues brought on by the use of progesterone-containing medications or the strategies used by women to cope with these issues.

The purpose of this cross-sectional and descriptive study was to identify the problems and coping strategies encountered by women receiving ART as a result of progesterone use. By adding to the body of knowledge, it is hoped that this study will advance the understanding and awareness of all healthcare professionals, particularly nurses who practice in the field. Therefore, the issues brought on by progesterone use during the ART process and the solutions that can be developed to lessen and manage these issues can be added to the patient's education, counseling, and care processes. It is believed that by doing so, the ART and use of progesterone, which is already a difficult process, will be made more comfortable for patients, contributing to patient compliance, treatment continuity, and even treatment success.

**Research Questions**

- What are the issues that women experience due to progesterone use during the ART process?
- How do women cope with these issues associated with the use of progesterone during the ART process?

**Methods****Research Design**

This is a descriptive and cross-sectional research study.

**Setting and Samples**

The study's population included all women between the ages of 18 and 45 who were admitted to a university hospital's infertility outpatient clinic between July 25 and August 8, 2022, were using progesterone-containing drugs, had no chronic diseases or communication barriers, and volunteered to participate in the research. The study's sample included 145 women who were admitted to the outpatient clinic between the dates specified and met the inclusion criteria.

**Data Collection Tools**

The data were gathered by the researchers using a questionnaire created after a review of the literature (12-24). A pre-application was made with 10 women to evaluate the intelligibility and usability of the questionnaire on the individuals in the sample group, and the pre-application data were not included in the research sample. It consisted of 44 questions and was structured to question the sociodemographic and obstetric characteristics of women, their ART history, the problems they experienced due to the use of different forms of progesterone-containing drugs (by intramuscular injection, injection into the subcutaneous fat tissue, vaginally, orally), and their coping methods.

**Data Collection**

Data were collected through face-to-face interviews in a quiet room in the outpatient clinic. The “Informed Consent Form”, which the participants read and approved after being informed about the study, allowed them to take part in it. Each woman’s data collection process took an average of 10 minutes.

**Data Analysis**

Data were evaluated by using descriptive statistics such as numbers, percentages, means, and standard deviations in SPSS 24 program.

**Results**

The mean age of the women participating in the study was 30.76±5.53, and their average marriage length was 6.6±4.51 years. Of the women 33.8 reported that they were high school graduates and 70.3 of them were not working. The vast majority of women (91.7%) had social security and 80.7% of them stated that they were in the middle-income bracket. Of the women 46.2% were housed in the city. While 23.6% of the women had never been pregnant, 32.4% had a history of pregnancy. While 64.8% of the women did not have children, 30.3% had one child (Table 1).

Of the women 23.4% had primary infertility and 68.3% of them had received ART at least once before. The ART they received were ovulation induction (31.7%), IUI (53.8%), and ICSI (24.1%). Of the women 62.8% stated that they got information about ART and 55.9% about the drugs used during ART, and the sources they got the most information from were health personnel (44.8% and 42.8%) and the internet (29.0% and 21.4%) (Table 2). While 97% of those who stated they obtained information from health personnel said that they got it from doctors, only 3% said that they got it from nurses.

The problems experienced by women undergoing ART due to progesterone use, and their coping strategies are shown in Table 3 and Table 4. According to this, the most common issues experienced by women during ART due to intramuscular progesterone use were pain at the injection site (56.0%), swelling, abscess, redness (44.0%), bruising (40.0%), weakness (36.0%), somnolence (32.0%), drowsiness (28.0%), and itching at the injection site (24.0%) (Table 3). The most common methods of

coping with these issues included resting and sleeping (30.0%), consulting a doctor (24.0%), applying pressure to the injection site (24.0%), applying cold (16.0%), walking (16.0%), and rubbing with cologne (12.0%) (Table 4).

Common issues experienced by women who received progesterone treatment vaginally were vaginal wetness (57.4%), the feeling of the drug getting out of the vagina (39.4%), weakness (36.0%), drowsiness (33.0%), incomplete absorption of the drug (30.9%), drying or lumping of the drug in the vagina (29.8%), and vaginal itching (20.2%) (Table 3). Among the methods of coping with these issues were resting and sleeping (30.9%), placing the drug towards the cervix and lying on the back (24.5%), consulting a doctor (22.3%), using pads (20.2%), changing underwear frequently (%6.4) (Table 4).

The most common issues experienced by women during oral progesterone use were weakness (76.5%), drowsiness (52.9%), nausea (51.0%), dizziness (39.2%), fatigue (35.3%), nervousness

**Table 1. Socio-demographic and obstetric characteristics of the participant women**

Variables	X̄± SD		
Age (years)	30.76 ± 5.53		
Marriage length (years)	6.6±4.51		
Body mass index (BMI)	26.99±5.51		
		N	%
Education	Primary school	23	15.9
	Middle school	32	22.1
	High school	49	33.8
	University or higher	41	28.2
Working status	Working	43	29.7
	Not working	102	70.3
Social security	Yes	133	91.7
	No	12	8.3
Income status	High	26	17.9
	Middle	117	80.7
	Low	2	1.4
Longest place of residence	Village	53	36.6
	Town	10	6.9
	City	67	46.2
	Big city	15	10.3
Number of pregnancies	0	34	23.4
	1	47	32.4
	2	33	22.8
	3 or more	31	21.4
Number of children	0	94	64.8
	1	44	30.3
	2	6	4.1
	3 or more	1	0.7
Total		145	100

X̄: Mean, SD: Standard deviation

(21.6%), and depression (19.6%) (Table 3). Among the methods of coping with these issues were sleeping and resting (62.7%), consulting a doctor (27.5%), doing nothing (9.8%), and quitting the treatment (5.9%) (Table 4).

**Discussion**

The use of progesterone hormone to support the luteal phase during the ART is accepted as a significant factor for successful reproductivity. Progesterone is believed to affect pregnancy rates positively by increasing endometrial receptivity while thickening endometrium (8,12). Along with the success rate of the progesterone form used during ART, its easy usability, fewer side effects, and tolerability significantly affect the success of the treatment (12). In the study, the issues experienced by women receiving ART due to the use of progesterone and their coping methods were examined, and the findings were discussed under three headings based on their application method in line with the literature.

**Table 2.** Characteristics of women regarding assisted reproductive treatments

Variables		N	%
<b>Infertility type</b>	Primer infertility	34	23.4
	Secondary infertility	111	76.6
<b>Received ART before?</b>	Yes	99	68.3
	No	46	31.7
<b>ART history*</b>	Ovulation induction (OI)	46	31.7
	Intrauterine insemination (IUI)	78	53.8
	Intracytoplasmic sperm injection (ICSI)	35	24.1
<b>Got information about ART?</b>	Yes	91	62.8
	No	54	37.2
<b>Sources of information about ART*</b>	Health personnel	65	44.8
	Internet	42	29.0
	Friends	19	13.1
	Mother/sister/aunt/neighbors	15	10.3
	TV, newspaper	9	6.2
	Books	3	2.1
	School, class	2	1.4
<b>Got information about the drugs used during ART?</b>	Yes	81	55.9
	No	64	44.1
<b>Sources of information about the drugs used during ART*</b>	Health personnel	62	42.8
	Internet	31	21.4
	Friends	8	5.5
	Mother/sister/aunt/neighbors	3	2.1
	TV, newspaper	2	1.4
<b>Total</b>		145	100

\*Multiple responses were available

**Oral Progesterone Use**

Progesterone taken orally has the benefits of being inexpensive and easy to use for patients (18). However, because oral progesterone has low absorption rates, it is worth noting that current studies mostly focus on intramuscular and vaginal progesterone use (12,15,16,24). According to studies, oral progesterone causes more side effects (such as sedation, dizziness, and drowsiness) than other forms due to the metabolites that occur during its use (12,25,26).

In a study conducted by Boelig et al. (26) with groups receiving oral progesterone and those receiving a placebo, patients receiving oral progesterone reported side effects such as dizziness, sleepiness, and vaginal dryness. A meta-analysis of patients taking oral and vaginal progesterone found that pregnancy outcomes were similar in both groups, and that drug selection should be based on cost and side effects (16). Another study found that oral progesterone can be preferred over vaginal progesterone in patients with appropriate indications due to its ease of use and lower treatment cost (18). Similar to the findings of other studies in the literature, this study discovered that patients using oral progesterone experienced more systemic side effects (such as weakness, sleepiness, headache, dizziness, nausea, vomiting, nervousness, and depression) that were more difficult to cope with when compared to other progesterone forms, and that they mostly coped with these side effects by sleeping/resting or consulting a doctor. It was worth noting that the majority of studies in the literature were aimed at evaluating treatment success rather than treatment process (12,16,18,23,26), and the lack of any study on coping methods with problems encountered due to the use of oral progesterone during ART limited the discussion of this section. These are significant in terms of demonstrating the importance of conducting studies in different groups, specific to the route of administration, and with larger samples to determine the drug administration problems experienced by women during ART. Furthermore, it is an important finding in terms of revealing the need for experimental studies involving various nursing interventions to deal with these issues.

**Intramuscular Progesterone Use**

Until recently, the most commonly used form of progesterone for luteal phase support has been intramuscular injections (12). However, using this form by administering natural progesterone in an oil solution causes side effects such as inflammatory reactions, pain, and abscess at the injection site. Furthermore, it is difficult to use because health personnel is required to perform the application. This has led to research into the use of alternative forms and their impact on pregnancy outcomes (12,24,27).

Some studies found that using vaginal or intramuscular progesterone had no effect on pregnancy outcomes and that using vaginal progesterone was more useful and less painful for patients. Due to its discomfort and side effects, the intramuscular form was not recommended as the first choice for luteal phase support in studies (12,15,24). In the study by Devine et al. (27), patients stated that intramuscular progesterone administration was very painful and likely to irritate the application site, and

that they required assistance with intramuscular progesterone administration. Patients reported that intramuscular progesterone administration was significantly stressful and that they were twice less satisfied than with vaginal progesterone (27). In this

study, pain, swelling, abscess, redness, bruising, and numbness at the injection site were the most common side effects observed during the use of intramuscular progesterone. As a result, it is advised to make a decision in favor of the patient, taking into

**Table 3.** Issues experienced by women due to progesterone use\*

Coping methods	Intramuscular application (N=50)	Vaginal application (N=94)	Oral application (N=51)
	n (%)	n (%)	n (%)
Weakness	18 (36.0)	27 (28.7)	39 (76.5)
Sleepiness	16 (32.0)	31 (33.0)	27 (52.9)
Tiredness	12 (24.0)	14 (14.9)	18 (35.3)
Nausea	7 (14.0)	12 (12.8)	26 (51.0)
Dizziness	6 (12.0)	10 (10.6)	20 (39.2)
Nervousness	8 (16.0)	11 (11.7)	11 (21.6)
Depression	8 (16.0)	6 (6.4)	10 (19.6)
Indigestion	5 (10.0)	7 (7.4)	7 (13.7)
Vomiting	6 (12.0)	5 (5.3)	7 (13.7)
Insomnia	4 (8.0)	9 (9.6)	9 (17.6)
Edema	3 (6.0)	5 (5.3)	5 (9.8)
Fever	2 (4.0)	2 (2.1)	2 (3.9)
Backache	4 (8.0)	2 (2.1)	-
Headache	1 (2.0)	-	8 (15.7)
Speech impairment	1 (2.0)	-	3 (5.9)
Pain at injection site	28 (56.0)	-	-
Swelling, stiffness, abscess at the injection site	22 (44.0)	-	-
Bruising at the injection site	20 (40.0)	-	-
Numbness at injection site	14 (28.0)	-	-
Itching at the injection site	12 (24.0)	-	-
Redness at the injection site	11 (22.0)	-	-
Burning at the injection site	9 (18.0)	-	-
Leg pain	3 (6.0)	-	-
Diarrhea	2 (4.0)	-	-
Blurred vision	1 (2.0)	-	-
Vaginal wetness	-	54 (57.4)	-
The sensation of the drug coming out of the vagina	-	37 (39.4)	-
Sensation of incomplete absorption of the drug	-	29 (30.9)	-
Drying, lumping of the drug in the vagina	-	28 (29.8)	-
Itching in the genitals	-	19 (20.2)	3 (5.9)
Urinary tract infection	-	11 (11.7)	-
Constipation	-	4 (4.3)	-
Stomach ache	-	1 (1.1)	-
Epigastric burning	-	1 (1.1)	-
Increase vaginal secretion	-	-	4 (7.8)
Breast fullness	-	-	3 (5.9)
Palpitation	-	-	2 (3.9)
Difficulty in breathing	-	-	1 (2.0)
Skin rash	-	-	1 (2.0)

\*Percentages are based on N values for different drug administrations. Multiple responses were available

**Table 4.** Methods of coping with the issues experienced due to progesterone use\*

Issues	Intramuscular application (N=50)	Vaginal application (N=94)	Oral application (N=51)
	n (%)	n (%)	n (%)
I rest/sleep	15 (30.0)	29 (30.9)	32 (62.7)
I consult a doctor	12 (24.0)	21 (22.3)	14 (27.5)
I do nothing about it	9 (18.0)	24 (25.5)	5 (9.8)
I change my stance	6 (12.0)	23 (24.5)	-
I walk	8 (16.0)	4 (4.3)	-
I apply pressure/massage	12 (24.0)	-	-
I apply cold	8 (16.0)	-	-
I rub the area with cologne	6 (12.0)	-	-
I take a painkiller	3 (6.0)	-	-
I use pad	-	19 (20.2)	-
I increase my fluid intake	-	2 (2.2)	-
I change my underwear more often	-	6 (6.4)	-
I quit treatment	-	-	3 (5.9)

\*Percentages are based on N values for different drug administrations. Multiple responses were available

account the findings of clinical experimental studies. There is no study in the literature that addresses the issues associated with the use of intramuscular progesterone. However, symptoms such as leakage, bleeding, and hematoma, particularly pain were reported to be reduced in intramuscular applications by using new methods such as ventrogluteal site selection, airlock technique, z technique, comfortable positioning during the procedure, local ice application before and after the procedure, cold spray, Buzzy, ShotBlocker, and Coolsense method (28-32). It is recommended that experimental studies are carried out with larger sample sizes and that pre-application training is organized to lessen symptoms.

### Vaginal Progesterone Use

Vaginal progesterone has advantages such as no hepatic first-pass effect, no effect on the central nervous system, rapid absorption, and relatively high bioavailability. Furthermore, its most tangible advantage is that it has a local endometrial effect, also known as the uterine first pass effect. It was reported that despite low circulating progesterone levels, it reached high endometrial concentrations due to direct transport from the vagina to the uterus (23). In addition, some studies in the literature indicated that vaginal progesterone caused local irritation, itching, discharge, and bleeding and that it could be affected by coitus because absorption decreased after intercourse (33,34).

In the study of Boelig et al. (35), it was reported that no serious side effects were observed due to the use of vaginal progesterone, one participant reported mild headache and another participant reported hives on the legs, which was thought to be related to the sheets, not progesterone (35). In another study comparing patient satisfaction, ease of use, and side effects, itching and discharge were reported as the most common side effects for the vaginal form. It was also reported that the vaginal form could be

preferred in terms of patient satisfaction and ease of use (24). The use of vaginal progesterone was reported as more useful and less painful, more satisfying by the patients (12,24,27). In the study of Chi et al. (36), it was reported that there was no difference in efficacy when compared with intramuscular progesterone. The most common problems encountered by the patients in this study were vaginal wetness, drying and lumping of the drug in the vagina, the feeling of the drug leaving the body, incomplete absorption of the drug, and vaginal itching. The methods used by the patients in the study to cope with these problems are given in Table 4. The absence of any study in the literature on dealing with the problems associated with vaginal progesterone use, as in other forms, limited the discussion of this section. It is recommended that nurses working in the field conduct individual interviews with women during the ART, cooperate with them, and support the treatment process while planning and informing them about coping with these problems.

In general, couples face a difficult, complex, and exhausting process when undergoing ART (37-39). According to studies, women who undergo ART face numerous challenges while on progesterone treatment and try to cope with these difficulties. These issues caused by the use of progesterone may place an additional burden on women and jeopardize the treatment process. In addition to many coping strategies preferred by patients in the face of these issues, frequent doctor visits may increase the burden on the health system. The findings in Table 4 supported our view that patients consulted a doctor to cope with the problems they experienced during treatment and even discontinued the treatment. At this point, it is critical to identify the most useful, tolerable, effective form of progesterone for the benefit of patients and to inform them about these issues.

The majority of the studies in the literature focused on the success of treatments rather than the ART process. However, families face numerous challenges during the ART process and

struggle to cope with these challenges (37-39). According to Yılmaz's study (40), the practices that nurses performed the most as practitioners in the ART process were patient preparation/care before and after invasive procedures, 80.7% of the nurses provided training/consultancy in their institutions, and oral and/or subcutaneous administration was the subject they provided the most training/consultancy on (40). In this study, it was found that infertile women received information about progesterone use mostly from the doctors. The proportion of patients who received information from nurses was very low. One of the most important responsibilities of infertility nurses is to make the process as easy and comfortable for families as possible. Nurses can serve as practitioners, trainers/consultants, and researchers (37).

### Study Limitations

The study's findings were limited to a cross-section of a university hospital and a relatively small number of patients.

### Conclusion

This study discovered that women undergoing ART experienced numerous problems due to progesterone use and that the patients attempted to deal with these issues on their own. It is critical to inform patients about potential problems that may arise during treatment to reduce stress and plan nursing interventions to minimize/eliminate problems. It is recommended to work in different centers and with larger sample groups to increase generalizability, use other measurement tools to evaluate the effects of progesterone-related problems, and conduct advanced experimental studies to solve these problems.

### Ethics

**Ethics Committee Approval:** Düzce University Non-interventional Health Research Ethics Committee (decision no: 2022/144, date: 25.07.2022).

**Informed Consent:** Data were collected through face-to-face interviews in a quiet room in the outpatient clinic. The "Informed Consent Form", which the participants read and approved after being informed about the study, allowed them to take part in it. Each woman's data collection process took an average of 10 minutes.

**Peer-review:** Externally peer reviewed.

### Authorship Contributions

Concept: H.K., N.D., F.S.Ö., H.G.S., Design: H.K., F.S.Ö., H.G.S., Data Collection or Processing: H.K., Analysis or Interpretation: H.K., N.D., F.S.Ö., Literature Search: H.K., N.D., F.S.Ö., H.G.S., Writing: H.K., N.D., F.S.Ö., H.G.S.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

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