The efficacy, acceptability and continuation of postpartum, post-abortive progestin-only pill: a pioneering prospective multicentric study from Turkey

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Abstract

Objective: The aim of this study was to evaluate the efficacy, side-effects and continuation rate of the desogestrel-progestin-only-pill (POP) in postpartum and post-abortive Turkish women and its relation with breast-feeding.

Material and Methods: In this prospective multicentric study women who delivered (or had surgical abortion) and wanted to receive POP for contraception were recruited to the study. The follow-up visits were scheduled at the third, sixth and ninth months.

Results: Overall A total of 7,468 women (66.5% postpartum, 33.5% post-abortive) participated in the study. The number of women who attended follow-up visits in relation to the previous visit at the third, sixth and ninth months was 944/7,468 (12.6%), 406/944 (43%) and 121/406 (29.8%) respectively. The incidence of breastfeeding at all visits was between 54.8% and 68.4%. Out of the 7,468 women recruited only 6% continued with the method at the end of the ninth month. There was a statistically significant increase in hemoglobin level at the third month compared to initial values. Oligomenorrhea, spotting and headache were the three leading side-effects. There was no pregnancy among the patients who were followed up.

Conclusion: This study demonstrated that POP was an effective postpartum and post-abortive contraceptive method that had no negative impact on breast-feeding. A change in bleeding patterns was the most common side-effect. However, the possible causes of low contraceptive maintenance rates need to be investigated. (J Turk Ger Gynecol Assoc 2022; 23: 255-62)

Keywords: Breast-feeding, contraception, progestin-only pill, postpartum, post-abortive

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Introduction

Out of 211 million pregnancies that occur globally each year, 87 million are unintended and 46 million of these might end in induced abortion while unintended pregnancies constituted 40% of all pregnancies in 2012 (1,2). Unintended pregnancies and shorter pregnancy intervals result in maternal and fetal morbidity and mortality, and also increase social and economic burden (3-5). In various studies, short intervals between pregnancies were found to be associated with increased maternal risks, such as gestational diabetes, placental abruption, and uterine rupture while fetal problems include preterm delivery, low-birth weight or small for gestational age infants (6) and thus birth-spacing is strongly advised. While the World Health Organization (WHO) recommends an interpregnancy interval (time between delivery and conception

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of subsequent pregnancy) of 24 months, the American College of Obstetricians and Gynecologists emphasises the importance of avoiding an interpregnancy interval of less than six months and advises an interpregnancy interval of longer than 18 months (7,8).

Postpartum contraception is a life-saving issue for women who opt to delay the subsequent pregnancy. It is common for contraceptive service delivery to be delayed until the routine postpartum sixth week visit. However, this practice is criticized as most women experience sexual activity before this initial postpartum visit and may even ovulate, especially if they are not breast-feeding (9). The other problem related to the postpartum sixth week visit is the low uptake, as women might skip this visit due to various structural, social and economic problems (10). Although the context of the postpartum visit covers postpartum contraception in some settings, a Cochrane review reported that two-thirds of postpartum women have unmet needs for contraception (11).

Immediate postplacental and early postpartum intrauterine device (IUD) insertion is a convenient and reliable contraceptive method but the expulsion rate is higher than the interval insertion and immediate postplacental IUD insertion requires a trained practitioner (12). Progestin-bearing hormonal contraceptives (PHC) are effective without any negative impact on lactogenesis, breastfeeding rates, and milk supply during the postpartum period (6,13). PHC implants can also be used during the early postpartum period but insertion and removal requires a visit to a qualified health center, similar to IUDs (14). Progestin-only contraceptive pills (POP) are safe and effective. POPs are currently under-utilized although they are a good choice for almost any women but especially for postpartum and breastfeeding women and women with a higher risk of thromboembolism, such as diabetic, obese and smoking women who choose to use a hormonal method (15). Post-abortion contraception is an essential component of comprehensive abortion care in women who do not want to get pregnant immediately after abortion as a return of fertility is much shorter after surgical abortion and POP can be started at the time of abortion (16).

While traditional POP provides contraception through thickening of the cervical mucus and endometrial atrophy and therefore must be taken within a three-hour window at the same time every day, the new generation desogestrel POP inhibits ovulation besides these effects and has a range of 12 hours delay within the same day without jeopardizing its contraceptive efficacy (17).

Desogestrel POP was licensed in 2011 in Turkey and it was procured for the first time by the Ministry of Health and distributed to study sites for evaluation of the efficacy, acceptability and safety of this method among Turkish post-abortive and early postpartum women. In this pioneering Turkish study, this contraceptive drug was distributed free of charge to all post-abortive/postpartum women who had consented for POP use for the first time as a part of the Ministry of Health Reproductive Health and Women's Health Programme.

The aim of this study was to evaluate the efficacy, side-effects and continuation of the new generation desogestrel POP initiated in the early postpartum and post-abortive period and its relation with breast-feeding.

Material and Methods

This multicenter, prospective study was conducted in three centers: Ministry of Health Etlik Zübeyde Hanım Women's Health Training and Research Hospital; Ministry of Health Zekai Tahir Burak Women's Health Research and Training Hospital; and Adıyaman University Hospital Department of Obstetrics and Gynecology, between March 2016 and March 2017, in collaboration with the Ministry of Health Reproductive and Women's Health Department after obtaining Ethical approval from the Ethics Committee (approval number: 57536863-231.02.01). IUDs, depot-medroxyprogesterone injections, oral contraceptives and desogestrel POP (Cerazette® 75 μg, Merck Sharp & Dohme Pharmaceuticals Co.Ltd.) were procurred and delivered, free of charge, to women by the MOH. All women who delivered vaginally or had a cesarean section or had a surgical abortion (manual vacuum aspiration) for termination of pregnancy on demand up to 10 weeks of pregnancy (legal in Turkey) were counselled for all methods of postpartum, post-abortive contraception before discharge, as part of routine practice. Women who wanted to receive desogestrel POP (Cerazette 75 μg) and gave a written informed consent were recruited to the study. All recruits received counselling promoting full-breast-feeding and about POP at each visit. Women started using POP immediately after abortion or at 21 days postpartum. Not wanting to receive a contraceptive method or prefering another contraceptive method or having a stillbirth or having a contraindication for POP use according to WHO medical eligibility criteria and unwillingness to take part in the study were the exclusion criteria for recruitment to the study (18).

The patient's demographic characteristics and obstetric histories were recorded. They were given three packs of POP, sufficient for three months, and the initial follow-up was scheduled for three months after their discharge. Three follow-up visits were scheduled, at the third, sixth and ninth months. Women attending follow-up visits had their vital signs and weight measured and were asked about contraceptive method continuation, method satisfaction, side-effects and breast-feeding via questionnaire. Among them, women who opted to continue the method were given another three months POP supply at each follow-up. The study flow-chart is shown

in Figure 1. Contraceptive method continuation, method satisfaction/side-effects and the incidence of full breast-feeding during each visit were recorded and analyzed.

Statistical Analysis

The Statistical Package for Social Science, version 21 was used for statistical analysis (IBM Corporation, Armonk, NY, USA). Paired samples t-test was used for continuous variables and the data are given as mean ± standard deviation. Categorical variables were evaluated using Pearson chi-square test. Statistical significance was accepted as $p<0.05$ and the confidence interval was taken as 95%.

Results

Out of the 21,924 women from three centers who were counselled about contraception during the study period, 7,468 women (34.1%) who met the inclusion criteria were recruited to the study. Out of 7,468 women, 66.5% were postpartum (n=4963), while the remaining 33.5% were post-abortive. The average age of the patients was 30.03±6.76 years, the median number of pregnancies and number of children were 3 (range: 0-18) and 2 (range: 0-10) respectively. The mean body mass index was 26.8±4.7 kg/m^2, the systolic blood pressure was 110.4±11.4 mmHg and diastolic pressure was 70.9±8.8 mmHg. The average hemoglobin (Hb) and hematocrit values were 12.08±1.58 g/dL and 36.58±4.65% respectively. The percentage of women with systemic disease was 4.8%, including 134 (1.8%) women with hypertension, 21 (0.3%) with diabetes mellitus, and 201 (2.7%) with gestational diabetes. When contraceptive use prior to the last pregnancy was investigated, 24.1% were on a modern contraceptive while 63.8% were not using a method. The demographic and medical features of the women recruited is shown in Table 1.

The percentage of women who came for a follow-up visit at the third-, sixth- and ninth-month follow-ups was 944 (12.6%),

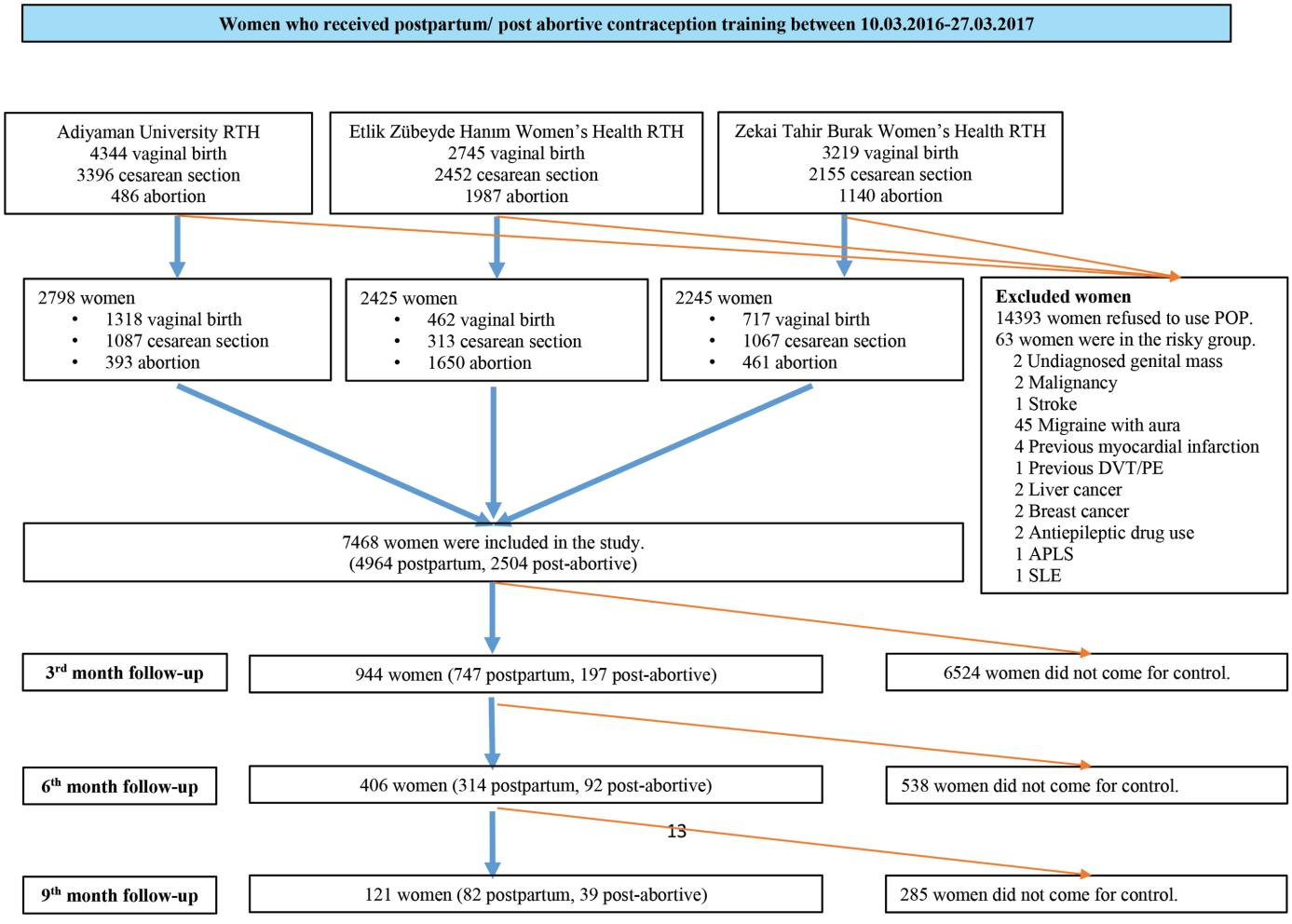

Figure 1. Study flow-chart

RTH: Research and Training Hospital, POP: Progestin-only contraceptive pills, DVT: Deep vein thrombosis, PE: Pulmonary embolism, APLS: Anti-phospholipid antibody syndrome, SLE: Systemic lupus erythematosus

406/944 (43%) and 121/406 (29.8%), respectively. Out of the 7,468 women recruited, only 6% continued with the method at the end of the ninth month (Table 2). Out of 944 women attending the initial third month visit, 37/944 (3.9%) wanted to discontinue, while this figure was 2/406 (0.5%) at sixth month and 16/121 (13.2%) at the ninth month.

The mean weight at the third month was significantly lower than the initial mean weight ($p<0.001$) but there was no difference between the third, sixth- and ninth-month follow-up mean weights and systolic and diastolic blood pressure measurements ($p>0.05$). The percentage of women who lost weight during POP use was high, most probably due to the expected postnatal weight loss. There was a significant increase in Hb level at the third month compared to the initial (postpartum/post-abortion) values (12.08±1.58 g/dL vs. 13.19±1.07 g/dL; $p<0.05$), with no significant change during subsequent follow-up visits. The incidence of breast-feeding during the three consecutive visits was 68.4%, 54.8% and 58.5%, respectively.

Although discontinuation rate was high, method satisfaction was also high among the women who continued to use the method. The main reasons for method discontinuation, based

Table 1. The demographic and medical features of the patient group

(n=7468)		
Name of the center, n (%)	ADYU	2798 (37.5)
	EZH	2425 (32.5)
	ZTB	2245 (30.0)
Age, (mean ± SD)		30.03±6.76
Age distribution, n (%)	<19 years	155 (2.1)
	20-34 years	5737 (76.8)
	35-39 years	1000 (13.4)
	>40 years	576 (7.7)
Method use prior to the last pregnancy,n (%)	No	4763 (63.8)
	CI	905 (12.1)
	Condom	553 (7.4)
	COC	319 (4.3)
	IUD	837 (11.2)
	Injection*	59 (0.8)
	POP	32 (0.4)
Height, cm (mean ± SD)		161.1±6.1
Weight, kg (mean ± SD)		69.5±12.5
BMI, (mean ± SD)		26.8±4.7
SBP, (mmHg) (mean ± SD)		110.4±11.4
DBP, (mmHg) (mean ± SD)		70.9±8.8
Hemoglobin, (mean ± SD)		12.08±1.58
Hematocrit, (mean ± SD)		36.58±4.65
Number of vaginal birth, (median, range)		1 (0-10)
Number of cesarean sections, [median (minimum-maximum)]		1 (0-6)
Gravidy, (median, range)		3 (0-13)
Parity, (median, range)		2 (0-18)
Number of living children, (median, range)		2 (0-10)
Number of abortions, (median, range)		0 (0-11)
Number of voluntary termination of pregnancies, (median, range)		0 (0-7)
Ectopic pregnancy, (median, range)		0 (0-3)
Disease history, n (%)	Hypertension	134 (1.8)
	Diabetes mellitus	21 (0.3)
	Gestational diabetes mellitus	201 (2.7)

SD: Standard deviation, ADYU: Adıyaman University Research and Training Hospital, EZH: Etlik Zübeyde Hanım Women's Health Research and Training Hospital, ZTB: Zekai Tahir Burak Women's Health Research and Training Hospital, CI: Coitus interruptus, COC: Combined oral contraceptive, IUD: Intrauterine device, POP: Progestin-only contraceptive pills, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, BMI: Body mass index. *All injection types (progesterone Injections, depot injections and DMPA)

on responses of the limited number of patients (n=55) who had discontinued but attended follow-up visits and answered the questionnaire were side-effects and dissatisfaction. Oligomenorrhea, spotting and headache were the three leading side-effects and the incidence of these had decreased by the ninth month follow-up. Apart from vaginal discharge, the incidence of almost all side-effects reported subsided gradually (Figure 2). None of the patients had method failure during POP use or had an adverse event. The percentage of women who resumed normal menstruation increased from 7.2% at the third month to 14.9% at the ninth month. The incidence of amenorrhea increased from 46.4% to 57% at the ninth month, while the incidence of oligomenorrhea decreased from 43.2% to 24.8%.

Discussion

POP prevents pregnancy through causing cervical mucus to become impermeable to sperm, inducing endometrial changes that interfere with implantation, inhibiting ovulation and changing tubal motility. These contraceptive actions vary according to the dose and type of the progestin involved. Desogestrel is a third generation progestin that inhibits ovulation, in addition to thickening cervical mucus and reducing tubal motility, when taken continuously without a break at a dose of 75 µg. This contrasts with older oral formulations containing levonorgestrel and norethisterone that are not able to supress ovulation effectively (19,20). As these pills are estrogen-free, they can be used in various conditions when combined hormonal contraceptive use is contraindicated, such as early postpartum women, lactating women, women with cardiovascular risks (obesity, smoking), thromboembolic risks (family history, thrombophilia) and specific arterial risks

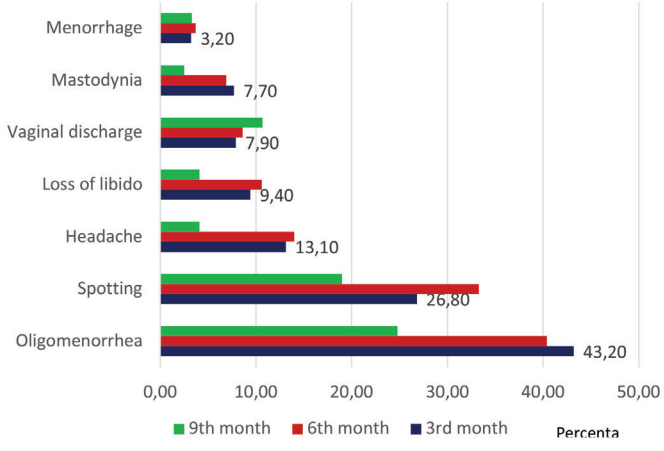

Figure 2. The incidence of major side-effects related to desogestrel-progestin-only-pill use in the third, sixth- and ninth months

POP: Progestin-only contraceptive pills

(valvular heart disease, past ischemic heart disease). They have a limited number of contraindications, the main ones being breast cancer, active liver disease, and benign and malignant liver tumors. Desogestrel POPs should be taken continuously. With a crude Pearl index of 0.41, its efficacy is similar to combined oral contraceptives and the incidence of ovulation inhibition is 97% when a 75 µg dose/day is used (21,22). None of the patients followed up in our study experienced pregnancy during the use of desogestrel POP.

Disturbance of menstrual bleeding patterns effects the compliance of women on progestin-only contraceptives. In natural ovulatory cycles, the estrogenic effect leads to endometrial proliferation in the first phase prior to ovulation and this is followed by a secretory transition of the estrogen-primed endometrium due to progestagenic activity (20). At the end of the menstrual cycle, mensturation is triggered by progesterone withdrawal. In women on progestin-only contraceptives, breakthrough bleeding is thought to arise from the fragile vascular structures, adjacent to the uterine lumen, that have lost their integrity and also a change in angiogenic factors (23,24). In a double-blind, randomized, multicenter trial comparing desogestrel-POP with levonorgestrel-POP, a higher incidence of amenorrhea and infrequent bleeding was encountered in the desogestrel-POP group but there was also a higher incidence of lessened bleeding over time in this group (22). In a study comparing desogestrel-POP with drospirenone-POP, women on desogestrel-POP experienced a higher proportion of different bleeding patterns, such as amenorrhea, infrequent bleeding, frequent bleeding and prolonged bleeding. However, from cycles 2 to 9 subjects who had no bleeding or spotting increased from 26.0 to 54.7% in the desogestrel group (25). In our study, the proportion of women who were amenorrheic increased as the duration of use of desogestrel POP increased. Zigler and McNicholas (26) suggested that the high incidence of discontinuation with the method might be related to the high incidence of unscheduled bleeding that occurs in 20% of the women using progestin-only contraceptive methods, even though method satisfaction is high. In our study group, the women who came for an initial follow-up visit and stated that they were satisfied with the method was relatively high, but the number coming for a second and third follow-up for continuation of the method decreased and this may have been due to the change in bleeding patterns.

There are few studies on the metabolic effects of desogestrel-POPs. In a systematic review and meta-analysis conducted by Glisic et al. (27), POPs were found to demonstrate no effect on blood pressure and, moreover, oral progestin-only contraceptives did not increase the risk of developing cardiometabolic syndrome, in contrast to injectable progestin-only contraceptives. In our series there was no significant

change in mean blood pressure measurements at any of the three follow-up points.

The most frequent side effects related to progestagens are acne, mild hirsutism, depressive mood, sexual pain, and weight gain (20). Vaginitis has also been reported to be a side-effect in a collaborative study (22). In our patient group, none of the women complained of acne, hirsutism, or depressive mood changes. Vaginal discharge was one of the side-effects reported and the incidence did not change through follow-up visits.

There are few studies on the effect of POPs on sexuality. In a double-blind, placebo-controlled study the effect of combined oral contraceptives on well-being and sexuality was compared with women on progestin-only pill and no adverse effect of POP on sexuality was found, while some improvement in well-being was noted (28). In our study the incidence of loss of libido was 9.4% but decreased to 4.1% at the ninth month. In a study from Germany, 403 women who experienced estrogen-related symptoms during combined oral contraceptive use and 403

Table 2. Findings of desogestrel progestin-only pill users at the third-, sixth- and ninth-month follow-ups

		Third month	Sixth month	Ninth month
		(n=944)	(n=406)	(n=121)
Weight, kg (mean ± SD)		67.83±12.47[β]	67.55±12.89	68.61±13.55
Systolic blood pressure, mmHg (mean ± SD)		112.53±10.89	113.54±10.59	112.89±12.68
Diastolic blood pressure, mmHg (mean ± SD)		71.35±8.19	72.43±8.08	70.23±8.39
Hemoglobin, g/dL (mean ± SD)		13.19±1.07*	13.31±1.40[Ω]	13.28±1.23
Cycle characteristics, n (%)	Amenorrhea	438 (46.4)	185 (45.6)	69 (57.0)
	Oligomenorrhea	408 (43.2)	164 (40.4)	30 (24.8)
	Normal mensturation	68 (7.2)	42 (10.4)	18 (14.9)
	Menorrhagia	30 (3.2)	15 (3.7)	4 (3.3)
Breast-feeding, n (%)		511 (68.4)	172 (54.8)	48 (58.5)
Method satisfaction, n (%)	Very satissfied	248 (26.3)	84 (20.7)	27 (22.3)
	Satisfied	677 (71.7)	313 (77.1)	84 (69.4)
	Not satisfied	19 (2.0)	9 (2.2)	10 (8.3)
Reason for method discontinuation, n (%)	Side-effects	10 (1.1)	1 (0.3)	4 (3.3)
	Not happy with the method	14 (1.5)	1 (0.3)	7 (5.8)
	Forgets taking pills	8 (0.9)	0 (0.0)	1 (0.8)
	Friends, -neighbours do not approve of the method	5 (0.5)	0 (0.0)	0 (0.0)
	Wants to get pregnant	0 (0.0)	0 (0.0)	4 (3.3)
Side-effects, n (%)	Mastodynia	73 (7.7)	28 (6.9)	3 (2.0)
	Headache	124 (13.1)	57 (14.0)	5 (4.1)
	Oligomenorrhea	408 (43.2)	164 (40.4)	30 (24.8)
	Spotting	253 (26.8)	135 (33.3)	23 (19.0)
	Menorrhage	30 (3.2)	15 (3.7)	4 (3.3)
	Vaginal discharge	75 (7.9)	35 (8.6)	13 (1.7)
	Loss of libido	89 (9.4)	43 (10.6)	5 (4.1)
	Difficulty in swallowing the pill	4 (0.4)	0 (0.0)	0 (0.0)
	Nausea	4 (0.4)	2 (0.5)	0 (0.0)
	Dizziness	3 (0.3)	1 (0.3)	0 (0.0)
	Hirsutism	1 (0.1)	0 (0.0)	0 (0.0)
	Itching, and rash	1 (0.1)	0 (0.0)	0 (0.0)
	Pelvic pain	3 (0.3)	0 (0.0)	0 (0.0)
Weight change, n (%)	Weight loss	481 (50.9)	263 (6.8)	84 (69.4)
	Weight gain	463 (49.1)	143 (35.2)	37 (30.6)

[β]The mean weight at the third month was significantly lower when compared to the initial mean weight ($p<0.001$). *There is a significant increase compared to the first hemoglobin ($p<0.001$). [Ω]Sixth month hemoglobin value was higher than at the third month ($p=0.008$), SD: Standard deviation

women with dysmenorrhea received 5 μg/d desogestrel-POP and remarkable resolution or improvement of the estrogen-related symtoms, such as nausea, breast-tenderness, estrogen-related headache and oedema, was noted in 70% (29). However, in the presented study group, 13.1% of the women experienced headache while this incidence decreased to 4.1% at the ninth month follow-up. Merki-Feld et al. (30) reported improvement in migraine frequency, migraine intensity and use of pain medication for migraine in women on desogestrel 75 μg/d POP. This finding was supported by the meta-analysis conducted by Warhurst et al. (31). None of the women in the presented group was diagnosed as having migraine nor were recieving any treatment for migraine.

POP is a good choice for lactating patients, as are the other progestin-only contraceptive methods. In a Cochrane review, analysis of published trials comparing combined oral contraceptives with POPs showed no difference in duration of breast-feeding, milk volume or composition (32). Goulding et al. (33) reported that women using POPs were most likely to breast-feed when compared to using combined hormonal contraceptives, even at the ninth month. In our patient group the incidence of breast-feeding did not change among the group who continued with the contraceptive method.

In our study, we found the follow-up rate at the first visit (third month) to be only 12.6%.

Study limitation

This high loss rate is the most important limitation of our study. As this was a hospital-based study, women's transportation to the hospital besides the difficulties in obtaining a suitable appointment from the hospital for a breast-feeding mother are obstacles that might have contributed to the lower follow-up rate. In the second phase of the project in order to improve the service delivery for the women, the reproductive health service providers working at the primary health care facilities were trained by the Ministry of Health Reproductive Health and Women's Health Division and the POPs were made available for use in the primary health services.

Conclusion

Progestin-only contraceptives are safe, effective methods of contraception and can be used by most women, as the contraindications for their use are very few. Progestin-only intrauterine systems and implants are long-acting contraceptive methods but their cost and the need for medical services for initiation and discontinuation is a burden for some women. New generation, POPs are very effective due to their inhibitory effect on ovulation. However, public awareness of the availability and advantages of this is method is still low. The menstrual changes related to progestin-only contraceptive methods might lead to a higher incidence of discontinuation. Therefore, pre-POP counselling sessions should address this and can include the information that the incidence of menstrual changes decreases with longer use of the contraceptive method. This sudy also demonstrated that POPs progestin-appear to be a good choice for breast-feeding women.

According to the latest Turkish Demographic Health Survey (TDHS 2018) (34), out of the 70% of currently married women using a method of contraception, 49% are using a modern method. The unmet need for family planning among currently married women has reached 12%. The percentage of women using the pill is only 5% and has not changed since 2013. The proportion of subjects still using the desogestrel-POP use at the end of the ninth month of the study was still higher than the overall rate of pill use reported by the TDHS 2018. Increasing awareness about POP will provide women with another choice, especially if they have contraindication, for combined hormonal contraceptives and are breast-feeding.

Ethics Committee Approval: *This study was carried out with the permission of the Ministry of Health, Reproductive and Women's Health Department (approval number: 57536863-231.02.01).*

Informed Consent: *It was obtained.*

Peer-review: *Externally peer-reviewed.*

Author Contributions: *Surgical and Medical Practices: B.D., M.B., S.D., N.Y.; Concept: B.D., S.S.; Design: B.D., S.D., N.Y., S.S.; Data Collection or Processing: B.D., M.B., S.D., N.Y.; Analysis or Interpretation: B.D., M.B., S.D.; Literature Search: B.D., M.B., N.Y.; Writing: B.D., M.B.*

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

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