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# EVALUATION OF SIDE EFFECTS OF LOW DOSE CONTRACEPTIVE PILLS ADMINISTERED BY THE VAGINAL ROUTE

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## ABSTRACT

Oral contraceptive pills have several side effects especially on the gastrointestinal tract and liver. Absorption of low dose (LD) pills by the vaginal route avoids the first pass of the steroids through these tracts and probably has fewer side effects. This study was a cohort study for evaluation of side effects and acceptability of LD pills administered by the vaginal route. In a clinical trial study, undesirable side effects such as nausea, dysmenorrhea, breast tenderness, gastrointestinal disorders, vertigo, headache, and breakthrough bleeding (BTB) were studied. The side effects, efficacy and acceptability were evaluated in 220 women using contraceptive pills containing 150mg levonorgestrel and 30mg ethinyl estradiol via the vaginal route in 660 cycles. The side effects among the patients who used the contraceptive pills vaginally were nausea in four subjects (1.8%), vertigo and headache in two subjects (0.9%), breast tenderness in four subjects (1.8%), dysmenorrhea in four subjects (1.8%), gastrointestinal disorders in one subject (0.5%), and BTB (breakthrough bleeding) in twelve subjects (5.5%). Most subjects in this study expressed a high level of acceptability with the vaginal route. There was only one unwanted pregnancy that occurred when the subject used the contraceptive pill incorrectly. Using contraceptive pills administered by the vaginal route appears to be a safe method with few side effects and high acceptability.
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**Key Words:** LD pill, Side effect, Acceptability, Vaginal route.

## INTRODUCTION

It is believed that oral contraceptive pills are superior to other methods of reversible contraceptions. However, the pills are not free from side effects. To minimize the side effects of oral contraceptive steroids as much as possible, especially on the gastrointestinal tract and liver, trials have been made to use steroid hormones as systemic contraceptives by administering them through the vagina.[1,2,3,4] The rationale behind vaginal administration of steroidal contraceptives was based on the assumption that absorption by this route avoids the first pass of the steroids through the liver, therefore reducing possible adverse effects of these compounds on liver function. Furthermore, as it was shown in several studies, ovulation suppression has occurred in most cases when the contraceptive pills were administered vaginally.[1,5,6,7,8,9]

This study is the first evaluation of the efficacy, side effects and the acceptability associated with the vaginal route of administration of contraceptive pills in Iran.

## MATERIAL AND METHODS

The subjects, 220 women, chosen from the family planning clinic, gave their consent to be included in the study. All of the women were fertile, having a regular menstrual cycle and were between 18 and 40 years old. They were not lac-

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tating, had no contraindications for using contraceptive pills and has not used any hormonal preparations in the past two months prior to the study.

All the women were given low dose combined pills containing 0.15 mg levonorgestrel and 0.03 mg ethinyl estradiol vaginally through 21 consecutive days starting on the fifth day of the treatment cycles for three months. After this period of time, side effects (nausea, dysmenorrhea, breast tenderness, vertigo, headache, gastrointestinal disorders, and BTB), efficacy and acceptability were evaluated in 660 cycles.

On admission into the study, the women were asked to complete a questionnaire which gave the details of demographic characteristics and on completion of the study, the women were asked to complete another questionnaire, which included their experiences about the side effects of the methods. The women were followed-up for three months and a total of 660 cycles were studied.

Statistical analysis was performed using Mac Nemar test for comparison before and after the administrations. P-value <0.05 was considered significant and all statistical analyses were done with $\alpha = 0.01$.

## RESULTS

As Table I shows, the majority of subjects are 26 to 35 years old, housewives, have secondary and high school educational status and are gravid 2.

Table II shows the frequency of complaints of vaginal administration of the contraceptive. It can be observed that the vaginal route of administration has few side effects.

Table III demonstrates the frequency of alterations in the

**Table I.** Demographic characteristics of the subjects.

| Characteristics | N (%) | Mean ± SD |
|---|---|---|
| Age (year) | | |
| 18-25 | 62 (28.2%) | 29.7 ± 5.7 |
| 26-35 | 113 (51.3%) | |
| 36-40 | 45 (20.5%) | |
| Occupation | | |
| Housewife | 198 (90%) | |
| Worker | 22 (10%) | |
| Educational status | | |
| Illiterate & Elementary school | 55 (28%) | |
| Junior-high & High School | 153 (69.5%) | |
| University | 12 (5.5%) | |
| Gravidity | | |
| ≤ 2 | 159 (72.3%) | 2±1 |
| 3-4 | 48 (21.8%) | |
| ≥ 4 | 13 (5.9%) | |

**Table II.** Comparison of complaints before and after treatment (Mac Nemar test).

| Complaints | Nausea n (%) | | Vertigo & Headache n (%) | | Breast tenderness n (%) | | Dysmenorrhea n (%) | | Gastrointestinal disorder n (%) | | BTB n (%) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| After the treatment / Before the treatment | Pos | Neg | Pos | Neg | Pos | Neg | Pos | Neg | Pos | Neg | Pos | Neg |
| Pos | 6 (2.7%) | 43 (19.5%) | 18 (8.2%) | 63 (28.6%) | 21 (9.6%) | 41 (18.6%) | 43 (19.6%) | 95 (43.2%) | 11 (5%) | 38 (17.2) | 0 | 0 |
| Neg | 4 (1.8%) | 167 (76%) | 2 (0.9%) | 137 (62.3%) | 4 (1.8%) | 154 (70%) | 4 (1.8%) | 78 (35.4) | 1 (0.5%) | 17 (77.3%) | 12 (5.5%) | 208 (94.5%) |
| P value | *P*<0.0001 | | *P*<0.0001 | | *P*<0.0001 | | *P*<0.0001 | | *P*<0.0001 | | | |

**Table III.** The duration and severity of menstrual bleeding after the use of vaginal contraceptive pills.

| | Duration (n%) | Flow |
|---|---|---|
| Without change | 107 (48.8%) | 88 (40.1%) |
| Decreased | 92 (42%) | 102 (46.3%) |
| Increased | 21 (9.2%) | 30 (13.6%) |

duration of menstrual bleeding and in the menstrual flow. It is observed that there are not any changes in the majority of women.

Table IV demonstrates medical and non-medical reasons for discontinuing use of vaginal contraceptive pills by women. 79.8% of subjects reported that vaginal use of contraceptive pills is a suitable method and were willing to continue it in the future.

In 660 cycles of vaginal administration, one pregnancy happened in the subject who used the contraceptive pill incorrectly. There was not any pregnancy except that case throughout the study.

## DISCUSSION

Vaginal administration of contraceptive steroids offers potential advantages over oral administration because the steroids are absorbed gradually into the systemic circulation and can reach the target organs in the hypothalamic-pituitary-ovarian (HPO) axis without first passage through the liver; high concentrations of some steroids can alter liver function.[10]

Ovulation suppression in women following vaginal administration of all kinds of oral contraceptive tablets has been shown in many researches.[1,5,6,7,8,9]

A study was done by Elsimar et al.[11] comparing the efficacy, acceptability and occurrence of side effects associated with the oral versus vaginal route of administration of contraceptive pills which contained 250 mg levonorgestrel and 50mg ethinyl estradiol. It was also shown that the vaginal route of administration appears to be as acceptable and efficacious as the oral route.

In another study[12] Elsimar and colleagues compared the efficacy and acceptability of two widely used oral contraceptive tablets, one containing 250mg levonorgestrel and 50mg ethinyl estradiol and the other containing 150mg desogestrel and 30mg ethinyl estradiol administered by the vaginal route. They found the effectiveness of both these tablets when administered by the vaginal route. They conducted another multicenter, international, randomized, comparative trial[13] to assess the acceptability, efficacy and safety of two different schedules of contraceptive pills, containing 250mg levonorgestrel and 50mg ethinyl estradiol administered by the vaginal route (intermittent versus continuous use). They showed that continuous use of vaginal contraceptive pills may offer some advantage over the traditional intermittent use and could be recommended to women who bleed excessively during menstruation.

**Table IV.** Medical and nonmedical reasons for discontinuing use of the vaginal contraceptive pill.

| Reasons | n (%) |
|---|---|
| Difficulty in using the method | 6 (2.8%) |
| Desire for pregnancy | 5 (2.3%) |
| Family objection | 10 (4.6%) |
| Traveling | 7 (3.2%) |
| BTB | 10 ( 4.6%) |
| Breast tenderness | 1 (0.46%) |

Eschenbach et al.[14] examined the effect of oral contraceptive use on vaginal discharge, epithelium, and flora and they found that OC did not change the gross, colposcopic or histologic appearance of the vaginal epithelium or characteristics of vaginal or cervical discharge.

The main objective of this study was to express that systemic side effects such as nausea, breast tenderness, vertigo, headache, gastrointestinal disorders, dysmenorrhea, and BTB commonly experienced with low dose oral contraceptives (LD pill) could be reduced if the same pills were administered by the vaginal route.

In this study these side effects, when compared with symptoms in women receiving the contraceptive pill orally in the text,[15] were very low (nausea in 1.8%, vertigo headache in 0.9 %, breast tenderness in 1.8%, dysmenorrhea in 1.8%, gastrointestinal disorders in 0.5% and BTB in 5.5%).

As shown in the results, nausea, dysmenorrhea, breast tenderness, vertigo, and gastrointestinal disorders after using contraceptive pills decreased significantly. These symptoms are probably due to premenstrual syndrome (PMS), that occurred only in the luteal phases of the subjects before treatment and shows that vaginal contraceptive pills can be used in the treatment of PMS.

The study was also designed to show the level of acceptability of the vaginal route of administration. Most women in this study expressed a high level of satisfaction with the vaginal route and the major reasons for discontinuation were family objection and difficulty in using the method.

The vaginal route of administration should be encouraged, and an appropriate aesthetic pill applicator or dispenser should be developed to enhance acceptability of this route of administration for Iranian women.

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## REFERENCES


1. Coutinho EM, Coutinho EJ, Gonealves MTR, Barabosa IC: Ovulation suppression in women following vaginal administration of oral contraceptive tablets. Fertil Steril 38(3): 380-1, 1982.
2. Souka AR, Kamel M, Einen M, Saleh F, Sallam H: Vaginal administration of combined oral contraceptive containing norethisterone acetate. Contraceptive 31(6): 571-583, 1985.
3. Nelson MS, Kuller JA, Zacur HA: Clinical use of oral contraceptives administered vaginally: a case report. Fertil Steril 52(5): 864-866, 1989.
4. Grow DR, Ahmed S: New contraceptive methods. Obstet Gynecol Clin North Am 27(4): 901-16, 2000.
5. Coutinho EM, Silva AR, Carreira C, Borbosa IC: Ovulation inhibition following vaginal administration of pills containing norethindrone and mestranol. Contraception 29: 197-9, 1984.
6. Ziaei S, Lamyian M, Mahdavian F: The study of two effective mechanisms on contraception in vaginal usage of LD pill (30mg ethinyl estradiol & 150mg levonorgestrel). Daneshvar 26: 33-38, 2000.
7. Alvares F, Faundes A, Johansson E, Coutinho EM: Blood levels of levonorgestrel in women following vaginal placement of contraceptive pills. Fertil Steril 40(1): 120-123, 1983.
8. Souka AR, Sokkary HEI, Kamel M, Hassan M: The effect of vaginal administration of low-dose oral contraceptive tablets on human ovulation. Contraception 33(4): 365-371, 1986.
9. Ballagh SA: Vaginal ring hormone delivery system in contraception and menopause. Clin Obstet Gynecol 44 (1):106-13, 2001
10. Mackinnon M, Sutherland E, Simon FR: Effects of ethinyl estradiol on hepatic microsomal proteins and turnover of cytochrome p-450. J Lab Clin Med 90: 1069, 1977.
11. Coutinho EM, Mascarenhas I, Acosta OM, et al: Comparative study on the efficacy, acceptability, and side effects of a contraceptive pill administered by the oral and the vaginal route: an international multicenter clinical trial. Clin Pharmacol Ther 54: 540-5, 1993
12. Coutinho EM, Souzaj C, Silva AR, et al. Comparative study on the efficacy and acceptability of two contraceptive pills administered by the vaginal route: an international multicenter clinical trial. Clin Pharmacol Ther 53: 65-75, 1993.
13. Coutinho EM, Dwyer EO, Barbosa LC, et al: Comparative study on intermittent versus continuous use of a contraceptive pill administered by vaginal route. Contraception 51: 355-358, 1995.
14. Eschenbach DA, et al: Effects of oral contraceptive pill use on vaginal flora and vaginal epithelium. Contraception 62(3): 107-12, 2000.
15. Speroff L, Glass RH, Kase NG: Oral contraception. In: Clinical Gynecologic Endocrinology and Infertility. Baltimore: Williams and Wilkins, pp. 867-947, 1999.