A comparison between monophasic levonorgestrel–ethinyl estradiol 150/30 and triphasic levonorgestrel–ethinyl estradiol 50–75–125/30–40–30 contraceptive pills for side effects and patient satisfaction: A study in Iran

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ABSTRACT

Objective: Oral contraceptive pills (OCPs) are one of the most effective reversible and accessible contraceptives, and patient acceptance for their use depends partly on the unfavorable adverse effects. The present study compared the two kinds of OCPs (monophasic; levonorgestrel (LNG)–ethinyl estradiol (EE) 150/30 versus triphasic; LNG–EE 50–75–125/30–40–30) for adverse effects and patient satisfaction.

Study design: A randomized clinical trial was performed on 314 women who used OCPs for the first time, as their contraception, for 6 months. Overall, 1884 cycles were studied. In the monophasic group (n = 159 who finally finished the study), monophasic pills LNG–EE 150/30 mcg, and in the triphasic group (n = 155 who finally finished the study), triphasic pills LNG–EE 50–75–125/30–40–30 mcg were used. Statistical analysis was performed using SPSS 10: Chi square test, Fisher exact test and Student’s t-test were used.

Results: There were no significant differences between the two groups for common side effects, including nausea, headache, nervousness, facial hyperpigmentation (chloasma), and body weight (increase or decrease) but breakthrough bleeding and spotting (BTB/S) were less in the triphasic group, occurring in 30 cycles (18.86%) versus 10 cycles (6.45%), P = 0.009*. Patient satisfaction for the two OCPs was similar and high. The rates of side effects were low.

Conclusion: It seems that the monophasic and triphasic pills are similar according to patient satisfaction and side effects; therefore there is no benefit of one over the other except for BTB/S, for which triphasic is superior.

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1. Introduction

Combined estrogen–progestogen oral contraceptive pills (OCPs) are amongst the most effective and reliable methods of contraception, used by many women throughout the world [1]. Concerns regarding the metabolic and cardiovascular adverse effects of OCPs resulted in the production of new formulations with the least (but at the same time effective) necessary steroids [2]. In these new formulations the amount of ethinyl estradiol (EE), which is the most common estrogenic agent of OCPs, is about 20–40 mcg. This reduction in the amount of steroids has been used for the progestogenic component also, and new OCPs contain less than 10% of the progestogens of the former pills [1]. Also, the progestogens have been changed in order to reduce side effects [4] and, at the present time, OCPs have less metabolic effect compared to earlier formulations. However, with decreasing amounts of estrogens and progestogens in OCPs, the adverse effects of “unscheduled bleeding/spotting” or breakthrough bleeding/spotting (BTB/S) would increase if their amounts are not enough to maintain endometrial stability [1].

Triphasic pills have been produced in order to decrease the total amount of consumed steroids as much as possible. These pills have three phases which, in every phase, have different amounts of progestogens [5] and in some formulations, the amount of estrogen will be increased during the second phase also. The aims of producing these new pills were to decrease their metabolic side effects and, at the same time, to minimize bleeding problems while preserving their efficacy [6].

In studies that compared monophasic and triphasic pills with each other, their risk/benefit profiles were almost similar [1,6]. Studies have shown that about 50% of pill consumers discontinue pill-taking within 24 months, mostly due to their common side effects [7]. Therefore finding pills with the least adverse effects and thus higher acceptability for women in every society is a necessity [8] in order to decrease the discontinuation
rate of women taking OCPs. At the same time triphasic pills with different progestogens should be compared with monophasic pills containing the same progestogen, to omit the effect of variability between steroids in order to find the most appropriate pill for consumers. The purpose of the present study was to compare monophasic and triphasic pills with the same progestogen, with regard to frequent side effects and patient satisfaction.

2. Materials and methods

The study was conducted as a randomized clinical trial. The population of the study were women who applied to public health centers for contraception. Inclusion criteria were: married women, age between 17 and 40 years, regular menstruation with normal bleeding, not having any signs and symptoms similar to the adverse effects of pills before using them and not using OCPs before, and they were new start patients for pills.

Exclusion criteria included: absolute and partial contraindications to pills, any known systemic disorders or drug use, breastfeeding, having delivered less than 3 weeks previously, history of having injectable contraceptives within 6 months prior to entering the study, history of implants within the 3 months before entering the study, abnormal Pap smear, abnormal blood level of cholesterol and triglycerides, and being illiterate. Further exclusion criteria during the study were: omitting one or more pills during the cycles, stopping taking pills, using other contraceptives along with OCPs, acute severe diarrhea and vomiting, and pregnancy.

A sample size of 300 patients was sufficient to obtain a power of 80% ($\alpha = 0.05$, $1 - \beta = 0.085$) with a significance level of 5% considering common side effects of triphasic pills = 0.26, and common side effects of monophasic pills = 0.41. Regarding the probable drop-out rate as about 10%, 330 patients were considered sufficient, and 360 eligible women were invited to participate in the study. Written informed consent was obtained from all participants.

Fig. 1. The consort E-flowchart.
342 women who fulfilled the inclusion criteria were divided into the two groups randomly (4 parts, block random using sealed, sequentially distributed envelopes to which the letters A, B, C, and D had been allocated: the letters A and C to the monophasic group and the letters B and D to the triphasic group). The patients chose one of the envelopes which was opened by the investigator and according to the letters, the groups of patients were determined. This envelope was then removed by the investigator, so women did not choose one letter more often than another.

In the monophasic group (n = 171) monophasic pills containing 30 mcg ethinyl estradiol (EE) and 150 mcg levonorgestrel (LNG) were prescribed. In the triphasic group (n = 171) triphasic pills containing EE–LNG (the first 6 days of cycle EE–LNG 30/50 mcg, in the second 5 days EE–LNG 40/75 mcg and in the last 10 days EE–LNG 30/125 mcg, therefore just the amounts of steroids were different). The two groups used pills for 6 consecutive months, with any adverse effects reported monthly during this time. At first, the frequency of side effects were considered separately for each month and also for 6 months.

Finally, 314 (159 in monophasic group and 155 in triphasic group) women finished the study (Fig. 1). Overall, 1884 cycles were filled in by the women and checked again by the investigator at periodic visits monthly.

Women’s satisfaction was evaluated using a scale ranging from very dissatisfied (with the score of 1), to very satisfied with the score of 6. The means of the scores of women in the two groups were considered separately for each month and also for 6 months totally.

Statistical analysis was performed using SPSS 10: Chi square test, Fisher exact test and Student’s t-test were used.

### 3. Results

The women of the two groups did not have statistically significant differences in age, weight, gravidity, being employed, or level of education for women and their husbands (Table 1).

There were no statistically significant differences between the two groups according to side effects, except for BTB/S. During months 1–6 of the study, there were no other difference between the 2 groups for adverse effects and patient satisfaction (Table 2).

The numbers of adverse effects were very low and BTB/S, nausea, headache and nervousness (except hyperpigmentation), gradually disappeared within 6 months. Patient satisfaction was good without any significant differences between the 2 groups.

For the evaluation of weight changes in each group, repeat variance test showed significant differences between the 2 groups, but the differences were very low and really did not have any clinical importance (Table 3). At the same time, the changes in weight of the women did not reveal significant difference within 6 months (Table 4). During this study, women did not show any serious side effects like thromboembolism.

### 4. Comments

In the present study, the side effects of monophasic pills were greater than triphasic pills (though both types were low) and this difference did not have any statistical significance, except for BTB/S, which was significantly less in the triphasic group. This may be a benefit of triphasics over monophasic pills. Women’s satisfaction in both groups was similar and discontinuation of pills was low. The frequency of side effects was lower than in other studies, but it was for both kinds of pills, which might rule out biases in this study. It might be in part be due to more patience and forbearance in our population. At the same time, the point should be considered.
that oral contraceptive pills are not very popular in Iran and are amongst the last options for women, so when a woman chooses pills as a contraceptive method, she is highly motivated on its use and never discontinues it for simple reasons. In this group of women, pills must have very serious adverse effects to cause stopping their use, and this might be another reason for the very low “lost to follow up” and “discontinued study” rates. In addition, the researchers explained carefully to the women about the probable occurrence of BTB/S, especially during the first 3 months, and asked them seriously not to stop pill-taking just for this reason. This is the other probable reason for the low “discontinued” rate. The duration of the study was 6 months and if it had been longer, maybe the discontinuation rate would have been higher.

Cedars [1] compared different kinds of triphasic pills with monophasic pills and concluded that the risk/benefit profiles for both pills were similar and favorable, which is in accordance with monophasic pills and concluded that the risk/benefit profiles for the present study and the progestogens of the two pills were different, maybe the discontinuation rate would have been higher.

A Cochrane review [11] of different researches on the comparison between monophasic and triphasic pills concluded that present evidence is not enough to prove a difference between these two kinds of OCPs, according to their effects on BTB/S and discontinuation of pills. It also suggested that monophasic pills should be the first option for starting the pill as a contraceptive and concluded that more studies should be performed on monophasic and triphasic pills with the same progestogens to be able to judge better their differences. In the present study the progestogenic portion of two pills were the same, just their amounts were different, and a significant difference between two different pills was shown for BTB/S, suggesting that less progestogen means less BTB/S.

Table 3

<table>
<thead>
<tr>
<th>Month</th>
<th>Monophasic group, n = 159</th>
<th>Triphasic group, n = 155</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Decrease</td>
<td>Increase</td>
</tr>
<tr>
<td>1</td>
<td>0 (0%)</td>
<td>58 (36.47%)</td>
</tr>
<tr>
<td>2</td>
<td>1 (0.64%)</td>
<td>74 (46.54%)</td>
</tr>
<tr>
<td>3</td>
<td>0 (0%)</td>
<td>73 (45.91%)</td>
</tr>
<tr>
<td>4</td>
<td>0 (0%)</td>
<td>73 (45.91%)</td>
</tr>
<tr>
<td>5</td>
<td>0 (0%)</td>
<td>72 (45.28%)</td>
</tr>
<tr>
<td>6</td>
<td>0 (0%)</td>
<td>86 (54.08%)</td>
</tr>
</tbody>
</table>

Repeat variance test: 0.0001

Table 4

<table>
<thead>
<tr>
<th>Months</th>
<th>Monophasic, n = 159</th>
<th>Triphasic, n = 155</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>154.14 ± 234.65</td>
<td>149.68 ± 234.41</td>
<td>0.866</td>
</tr>
<tr>
<td>2</td>
<td>194.26 ± 250.70</td>
<td>159.87 ± 226.69</td>
<td>0.203</td>
</tr>
<tr>
<td>3</td>
<td>183.43 ± 223.27</td>
<td>159.23 ± 222.73</td>
<td>0.337</td>
</tr>
<tr>
<td>4</td>
<td>175.79 ± 210.12</td>
<td>171.23 ± 198.73</td>
<td>0.847</td>
</tr>
<tr>
<td>5</td>
<td>199.35 ± 241.34</td>
<td>177.07 ± 222.42</td>
<td>0.397</td>
</tr>
<tr>
<td>6</td>
<td>227.06 ± 236.39</td>
<td>219.74 ± 253.29</td>
<td>0.791</td>
</tr>
<tr>
<td>Total</td>
<td>188.48 ± 163.85</td>
<td>172.82 ± 198.69</td>
<td>0.447</td>
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</tbody>
</table>

Conflict of interest

There was no conflict of interest.

Acknowledgements

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References

[10] Chavez A, DelConte A. A comparison of cycle control with monophasic levonorgestrel/ethinylestradiol 100 micrograms/20 micrograms versus triphasic norethindrone/ethinylestradiol 500–750–1000 micrograms/35 micro-


