

Desogestrel+ethinylestradiol versus levonorgestrel +ethinylestradiol

Which one has better affect on acne, hirsutism, and weight change

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ABSTRACT

الأهداف: عمل مقارنة بين المضاعفات المترتبة من استخدام الجيل الثالث من أقراص منع الحمل والمضاعفات المترتبة من استخدام الجيل الثاني من أقراص منع الحمل.

الطريقة: أُجريت هذه الدراسة العشوائية السريرية في عيادة طب الأسرة وتحديد النسل بمستشفى أمير وفي بعض المراكز الصحية الأخرى، سيمنان، إيران وذلك خلال الفترة من أكتوبر 2007م إلى أكتوبر 2008م. شملت هذه الدراسة 100 امرأة سليمة في سن الإنجاب، وقد تم تقسيمهن عشوائياً إلى مجموعتين وهما: المجموعة الأولى وتلقت العلاج بأقراص منع الحمل من الجيل الثالث (150 ملغ من ديزوجستريل و30 ملغ من إيثينيل استراديول)، فيما تلقت المجموعة الثانية العلاج بأقراص منع الحمل من الجيل الثاني (150 ملغ من ليفونورجستريل و30 ملغ من إيثينيل استراديول). تم عمل مقارنة بين المجموعتين بعد مرور 6 أشهر من أخذ العلاج وذلك فيما يخص التغيرات التالية: الوزن، وحب الشباب، ودرجة نمو الشعر، بالإضافة إلى تحليل نتائج مصل الغلوبولين المرتبط بالهرمون الجنسي وهرمون التسترون الحر.

النتائج: لقد قمنا بتقييم نتائج المجموعة الأولى التي تتكون من 45 مشاركة، والمجموعة الثانية التي تتكون من 46 مشاركة. أشارت نتائج الدراسة إلى ارتفاع مؤشر كتلة الجسم في المجموعة الثانية بالمقارنة مع المجموعة الأولى ($p=0.000$) وذلك بعد 6 أشهر من العلاج، كما أن درجة حب الشباب وفرط نمو الشعر قد قلت في المجموعة الأولى بشكل واضح ($p=0.000$). لقد كانت نتائج تحليل مصل هرمون التسترون ($p=0.967$) ومصل الغلوبولين المرتبط بالهرمون الجنسي ($p=0.916$) متشابهة في المجموعتين.

خاتمة: أظهرت الدراسة أن أقراص منع الحمل من الجيل الثالث تقوم بتقليل درجة حب الشباب وفرط نمو الشعر من دون التأثير على الوزن وذلك بالمقارنة مع أقراص منع الحمل من الجيل الثاني.

Objectives: To compare complications of third and second generation oral contraceptive pills (OCPs).

Method: In a randomized clinical trial from October 2007 to October 2008, 100 healthy women of reproductive age referred to Amir Hospital Family Planning Clinic and some health centers in Semnan, Iran were randomized in 2 equal groups. They received either a third generation OCP (150 µg desogestrel [DSG] + 30 µg ethinylestradiol [EE]) or a second generation type (150 µg levonorgestrel [LNG] + 30 µg EE). Six months later, changes of weight, acne, and hirsutism severity, as well as serum titers of sex hormone-binding globulin (SHBG) and free testosterone were compared between the 2 groups.

Results: Forty-five women were evaluated in the DSG+EE OCP group, and 46 women in the LNG+EE OCP group. The BMI was significantly higher in the second group ($p=0.000$) after 6 months duration. Likewise, the decrement of acne and hirsutism severity was significantly higher in the DSG+EE users ($p=0.000$). Mean changes of serum free testosterone ($p=0.967$) and SHBG ($p=0.916$) were comparable between the 2 groups.

Conclusion: In comparison with the LNG+EE OCP, the DSG+EE OCP is a contraceptive pill that significantly decreases the severity of acne and hirsutism, without any significant change in weight.

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Reproductive health requires careful use of effective contraceptive methods to prevent both pregnancy and sexually transmitted diseases. In hormonal contraceptive methods, female sex steroids, synthetic estrogen, and synthetic progesterone (progestin), or progestin only, are used. The most widely used hormonal contraceptive is the combination oral contraceptive pill (OCP).¹ Different kinds of oral contraceptives pills include: 1) First-generation oral contraceptive: products containing 50 mg or more of ethinylestradiol (EE). 2) Second-generation oral contraceptives: products containing levonorgestrel (LG), norgestimate, and other members of the norethindrone family and 20, 30, or 35 mg EE. 3) Third-generation oral contraceptives: products containing desogestrel (DSG) or gestodene with 20, 25, or 30 mg EE. The new progestins including DSG, gestodene, and norgestimate are more selective than other 19-norprogestins, they have no androgenic effects, or minimal androgenic effects. The androgenic effect of a product is an undesirable trait. The decreased androgenicity of the progestins in the new products is reflected in increased sex hormone-binding globulin (SHBG) and decreased free Testosterone concentrations to a greater degree than the older oral contraceptives. This difference could be of greater clinical value in the treatment of acne and hirsutism.² Complications such as weight gain, acne, and amenorrhea that are related to progestins in the use of second generation contraceptive pills are commonly seen in women. Progestins are essentially anabolic and cause weight gain.³ The Ferriman-Gallwey model determines hair growth extent in 9 anatomic key areas. This scoring includes zero score (lack of terminal hair) to 4 (maximum hair growth), and hirsutism is determined by a score of 8 or higher.⁴ Due to the high prevalence of complications such as weight gain, acne, and hirsutism in consumers of second generation contraceptive pills (EE+LG), which causes displeasure and sometimes discontinuation, and because this is the most commonly used contraceptive pill in this area, the objective of this study was to compare a third generation pill (150 µg DSG + 30 µg EE) with a second generation pill (150 µg LNG + 30 µg EE) in respect of their effect on weight gain, acne, and hirsutism.

Methods. This clinical trial study included 18-35 year old women referred to Amir Hospital Family Planning Clinic and some health centers in Semnan, Iran from October 2007 to October 2008. Women with no contraindications to OCP use, and that had not used hormonal methods such as Norplant, depot medroxy progesterone acetate, or OCP in the past 6 months were included in the study. The purpose of the study was explained to all the participants, and written consent was obtained. This study was approved by the ethical

committee of Semnan University of Medical Sciences. Exclusion criteria included lack of cooperation with continued treatment, irregular consumption of pills, pregnancy while using pills, affection to an underlying disease which is an OCP contraindication, prolonged and uncontrollable abnormal uterine bleeding. Before beginning treatment, the women's weight was recorded using a scale with an accuracy of 0.1 kg. If there were acne, the number of lesions was measured and was recorded in the questionnaire. If there were hirsutism, hirsutism severity was determined based on the Ferriman-Gallwey scoring. A 4 ml blood sample was obtained from all participants to evaluate SHBG and free serum testosterone levels. Sampling was performed in Amir Hospital Laboratory and derivates serum was sent to the Pasteur Laboratory for evaluation. The SHBG and free testosterone measurement was performed using the ELIZA technique with an IBL® company kit (Aburaihan Pharmaceutical Co., Tehran, Iran). All the data were recorded in a questionnaire. Selected women were randomly given DSG+EE (Aburaihan Pharmaceutical Co., Tehran, Iran), or LNG+EE (Aburaihan Pharmaceutical Co., Tehran, Iran) and for this purpose a random number table was used. As the sample size was 100, 50 numbers were randomly selected from 1 to 100 and were randomized to the DSG+EE group, and the other numbers randomized to the LNG+EE group. At the end of 6 months treatment, weight, number of acne lesions, hirsutism score, SHBG, and free serum testosterone levels were evaluated. Finally, all the information was gathered from questionnaires and final results were obtained by statistical analysis. All those evaluating the women were not informed of their categorization.

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS Inc, Chicago, IL, USA) version 15. Quantitative variables were compared by using student T-test (independent samples) or Mann-Whitney (based on data distribution) and qualitative variables (categorical) were compared using contingency tables, chi-square test, or Fisher's exact test, and $p \leq 0.05$ was considered statistically significant.

Results. One hundred healthy women of reproductive age divided into 2 groups of 50 cases were evaluated in this study. Nine cases not fulfilling the inclusion criteria were excluded. Finally, 45 cases in the DSG+EE group, and 46 cases in the LNG+EE group remained. The two groups were matched with regard to age, parity, and menstrual irregularity (abnormal uterine bleeding) before and after the study (Table 1). At the end of the study, a 2.5 kg increase in mean weight was recorded in the LNG+EE group, while there was no increase in mean weight in the DSG+EE group. Thus,

the difference between the 2 groups was significant in this aspect ($p=0.000$). A one kg/m^2 increase in mean BMI was found in the LNG+EE group, while there was no increase in mean BMI in the DSG+EE group, and the difference between the 2 groups was significant ($p=0.000$). At the end of the study, in the DSG+EE group, it was found that the mean number of acne lesions decrease was 3, while in the LNG+EE group, there was a 0.4 number increase in the mean number of acne lesions, thus, this difference was statistically significant ($p=0.001$). At the end of the study, the mean hirsutism severity score decreased by 1.7 in the DSG+EE group, and increased by 0.3 in the LNG+EE group, and this difference was statistically significant ($p=0.000$). At the end of study, the mean SHBG level increased by 1.1 nmol/l in the DSG+EE group, and by 0.6 nmol/l in the LNG+EE group, this difference

was not statistically significant. The mean SHBG level changes, before and after intervention in both groups were not statistically significant. At the end of study, the free testosterone mean level decreased 0.5 pg/ml in both groups, so this difference was not statistically significant. The free testosterone mean level changes, before and after intervention in both groups were not statistically significant (Table 2).

Discussion. Although there is a general tendency in the world toward, the use of the third generation contraceptive pills, the differences between these 2 groups regarding 2nd and 3rd generation on the efficacy and complications is not yet well known, and there is no general agreement in this field.⁵

In the current study, it was noted that after 6 months, weight and BMI increase in the second generation OCP user were greater, and hirsutism severity and acne lesion decrement were more in the DSG+EE user. The mean serum level changes of SHBG and free testosterone between the 2 groups were not statistically significant. Rosen et al,⁶ in a study on 34 women compared the effect of third and second generation OCPs on acne severity, SHBG, and serum testosterone level, and found that after 9 months treatment the acne severity significantly decreased, and the SHBG mean serum level increased in both groups. However, the testosterone serum level change was not significant. On the other hand, a significant difference in acne severity between the 2 groups at the end of study was not reported. Unlike our study although the acne severity changes in each group were significant, at the end of the study there was no difference between the 2 groups. This may be because of a lower sample size in Rosen's study (34 cases).⁶ However, the results of Rosen's study,⁶ with regard to the effect on free testosterone serum level are in agreement with our study.

Moreau et al⁷ compared the complications of these 2 OCP groups in reproductive aged women, and found no significant difference between the groups in terms of weight changes.⁷ The main limitation of this study, as has been emphasized by the authors, is no randomization. Therefore, the results of Moreau's study are not in agreement with our study. Breikopf et al⁸ compared the effects of second and third generation OCPs on hirsutism. Twenty-three cases on second generation OCPs, and 24 cases on third generation OCPs were treated and the results were compared 9 months later. Although both drugs reduced hirsutism severity, there was no significant difference between the groups. Small sample was one of the limitations of Breikopf's study. However, serum SHBG level However, increase of serum SHBG level and decrease of serum free testosterone level in third generation group was

Table 1 - Demographic characteristics of patients.

Variable	DSG+EE	LNG+EE	P-value
Age (years)	5.3±26.7	5.4±26.1	0.553
Parity	1.2±1.0	1.0±1.4	0.934
AUB (before)	16 (35.6%)	14 (30.4%)	0.603
AUB (after)	2 (4.4%)	4 (8.7%)	0.607

LNG - levonorgestrel, EE - ethinylestradiol, DSG - desogestrel, AUB - abnormal uterine bleeding

Table 2 - Base and terminal evaluated parameters and their changes in the 2 groups.

Parameters	LNG+EE	DSG+EE	P-value
Base weight (kg)	63.2±15.6	65.3±10.6	0.576
Terminal weight (kg)	65.8±15.6	65.3±11.0	0.902
Weight changes (kg)	3.3±3.6	0.0±2.5	0.000
Base BMI (kg/m^2)	25.0±5.7	25.7±4.1	0.462
Terminal BMI (kg/m^2)	26.0±5.7	25.7±4.3	0.827
BMI changes (kg/m^2)	1.0±0.9	0.0±1.0	0.000
Base number of acne	4.3±7.0	48.±8.2	0.758
Terminal number of acne	4.7±6.7	1.8±3.6	0.011
Number of acne changes	0.4±3.3	-3.0±6.2	0.001
Base hirsutism severity	2.5±4.3	2.7±4.4	0.836
Terminal hirsutism severity	2.8±4.2	1.0±2.0	0.012
Hirsutism severity changes	0.3±1.8	-1.7±2.9	0.000
Base SHBG (nmol/L)	35.6±24.8	35.8±25.2	0.971
Terminal SHBG (nmol/L)	36.2±22.6	37.0±31.2	0.904
SHBG changes (nmol/L)	0.6±19.6	1.1±25.1	0.916
Base free testosterone (pg/ml)	4.4±4.6	3.0±4.1	0.018
Terminal free testosterone (pg/ml)	3.8±4.4	2.4±3.3	0.093
Free testosterone changes (pg/ml)	-0.5±2.2	-0.5±2.3	0.967

BMI - body mass index, SHBG- sex hormone binding globulin, DSG - desogestrel, LNG - levonorgestrel, EE - ethinylestradiol

statistically significant.⁸ As observed in the above study, third generation OCPs increased SHBG and decreased the free testosterone. In this study, although SHBG and free serum testosterone levels changes were predicted, these changes in both groups were not significant.

Although one of the main mechanisms of the effect of OCPs on androgenic complications is to change these 2 serum parameters,⁹⁻¹¹ it seems that this effect is not always present, as confirmed by the results of this study and other research. In this study, we have shown that the DSG+EE OCP is better than the LNG+EE OCP with regards to complications such as acne, hirsutism, and weight gain. Other studies are also in agreement with our findings.¹²⁻¹⁷

Gaspard¹⁸ and Oelkers¹⁹ introduced the effect of third generation OCPs on fat metabolism and lipid profile status, and also their more antiminerocorticoid effect, as factors that participate in lack of weight gain in consumers of these pills. However, some studies have shown that the third generation OCPs in comparison with older generations, may increase the risk of venous thrombosis and thromboembolic events.²⁰ Therefore, more study with regard to these complications are necessary.

The unavailability of drugs in pharmacies, cooperation of patients in follow up, and discontinuation of drugs by patients were the main limitations of this study.

In conclusion, DSG+EE is favorable to LNG+EE with regard to reduction in acne, hirsutism severity, and weight gain, and so its use in healthy reproductive aged women is recommended. Further studies with more cases and more accurate selection of patients for evaluation of the DSG+EE effect on SHBG and free testosterone levels are suggested.

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