Effect of a New Oral Contraceptive with Drospirenone on Vital Signs, Complete Blood Count, Glucose, Electrolytes, Renal, and Liver Function

Surasak Taneepanichskul MD*,
Unnop Jaisamrarn MD*, Vorapong Phupong MD*

** Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University*

Objective: *To evaluate the effect of a new oral contraception formulation with drospirenone (Yasmin®) on vital signs, complete blood count, glucose, electrolytes, and renal and liver function.*
Material and Method: *An open-label non-comparative clinical trial was conducted. One hundred women who were planning to use oral contraception for at least six months were recruited. The subjects received a blister pack which contained 21 tablets of 3 mg drospirenone /30 μg ethinyl estradiol for the first four cycles (1 cycle = 28 days). Cycle 5 and 6 blister packs were dispensed during the visit in cycle 4. Heart rate and blood pressure of each subject were checked at baseline and each visit. Serum from each subject was collected and sent for complete blood count, glucose, electrolytes, and renal and liver function tests at baseline and at cycle 6. Mean differences in these tests at cycle 6 compared to baseline were assessed.*
Results: *Ninety-two of the 100 subjects (92%) completed the present study. There was no significant change in heart rate, blood pressure, complete blood count, glucose, electrolytes, and renal and liver function tests at cycle 6 when compared to baseline.*
Conclusion: *Oral contraception formulation with drospirenone (Yasmin®) is well tolerated and has good contraceptive efficacy. It is safe, as it has no effect on heart rate, blood pressure, complete blood count, glucose, electrolytes, and renal and liver function.*

Keywords: *Oral contraception, Drospirenone, Vital signs, Blood count, Glucose, Renal, Liver*

J Med Assoc Thai 2007; 90 (3): 426-31
Full text. e-Journal: *http://www.medassocthai.org/journal*

Combined oral contraceptives (COC's) have now been in use for more than 40 years and have been proven a highly efficacious and safe method of contraception. However, their hormonal components, estrogens (usually ethinylestradiol, EE) and progestogens are known to have various metabolic effects, including effects on lipid and carbohydrate metabolism, and hemostatic variables. The influence on glucose metabolism increases with progestogen dominance[1-4]. In contrast, the adverse effects on hemostatic variables and associated risk of venous thrombosis are most likely to be influenced by the estrogen dose and not by the type of progestogen[5].

Although slight decreases in glucose tolerance and increases in insulin resistance have been reported for some COC's by means of oral or intravenous glucose tolerance tests or glucose clamps[6,7], evidence for an increased risk to develop diabetes has never been provided. However, a further investigation of long-term consequences of COC use on carbohydrate metabolism is important because any chronic, even mild hyperglycemia and/or hyperinsulinemia, in the fasting state as well as during a glucose load may contribute to ischemic vascular diseases[8-12].

Prolonged use of COC may lead to slight increases in mean body weight and blood pressure[13-15]. In this regard, there is no significant difference among

Correspondence to: Phupong V, Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University, Rama IV Rd, Pathumwan, Bangkok 10330, Thailand. Phone: 0-2256-4241, Fax: 0-2254-9292. E-mail: vorapong.p@chula.ac.th

various preparations containing 50 or 30 μg EE[16]. In rare instances, COC use may lead to severe or malignant hypertension[17-19].

Drospirenone (DSRP), a novel progestogen has a number of pharmacological properties combining progestogenic, antimineralocorticoid, and antiandrogenic activities[20-22]. The combination of 3 mg DRSP with 30 μg EE (Yasmin®) is characterized by a high contraceptive efficacy in combination with excellent cycle control and a low incidence of adverse effects[21,23]. Previous studies have provided evidence of favorable metabolic effects of this preparation[23-25]. However, more information is needed in order to appreciate its metabolic impact. Thus, the objective of the present study was to evaluate the effects of the combination of 3 mg DSRP and 30 μg EE in an OC (Yasmin®) on vital signs, complete blood count, glucose, electrolytes, renal and liver function.

Material and Method

The present study was conducted at the Family Planning Clinic, Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand. Women requesting contraception were enrolled into the present study. The inclusion criteria are as follows: 1) being 18-35 years old at the time of entry into the present study; 2) having regular menstrual cycles (25-34 days); 3) no use of injectable or implant hormonal contraceptives or OCs within 6 months prior to the present study; and 4) willing not to use any other form of hormonal treatment, including other hormonal contraception, for the duration of the present study. The exclusion criteria are as follows: 1) being suspected of pregnancy or having pregnancy; 2) breastfeeding; 3) being contraindicated under the WHO category 2, 3, and 4[26] and 4) having hypersensitivity to the active substances or any of the excipients of Yasmin®.

The present study was been approved by the Ethics Committee of the Faculty of Medicine, Chulalongkorn University. Eligible subjects were required to sign in their informed consent form before enrolling in the present study. Each subject received a blister pack, containing 21 tablets of 3 mg DRSP/30 μg EE for the first four cycles (1 cycle = 28 days). They were instructed to take one tablet per day for 21 days followed by a 7-day tablet-free interval. The recommended dosing interval was not longer than 24 h. Compliance was assessed by pill count from the blister packs. For cycle 5 and 6, the blister packs were dispensed during the visit in cycle 4.

Vital signs of each subject were checked at baseline and during each visit. Blood samples were taken from each subject to assess complete blood count, fasting plasma glucose, electrolytes, renal and liver function at baseline and during the visit in cycle 6 from patients on fasting state before studying the drug administration. Analysis of the blood samples was performed at a central laboratory.

The primary measured outcome was the change in fasting plasma glucose levels from baseline to cycle 6. Other measured outcomes were the changes in vital signs, complete blood count, electrolytes, renal and liver function from baseline to cycle 6.

All data were collected, coded, and analyzed using SPSS version 12.0 software (SPSS, Chicago, IL). Descriptive statistics (mean, standard deviation, percentage) were used to analyze the demographic data. Student *t*-test was used to test the differences of mean vital signs, complete blood count, fasting plasma glucose, electrolytes, renal and liver function changes from baseline to cycle 6. p-value < 0.05 was considered statistically significant.

Results

One hundred subjects were recruited, screened, and enrolled. All subjects were included in the intention to treat (ITT) analysis. Of these 100 subjects, 92 (92%) completed the present study. Of the three subjects who prematurely discontinued before visit 2, two were relocated to other places that hindered them from follow-up and one decided to have pregnancy. For the rest of the subjects who did not follow up on visit 3, two subjects relocated to other localities and three developed adverse events. The adverse events included amenorrhea, cranial nerve VII neuritis, and nausea.

The mean $\pm$ standard deviation (SD) of the age of the subjects was 27.4 ± 4.2 years (ranged 19-35). The mean $\pm$ SD of subjects' weight was 53.3 ± 7.4 kg (39.5-76.0). Baseline vital signs were all normal. Changes in vital signs are presented in Table 1. Changes in complete blood count are presented in Table 2. Changes in fasting plasma glucose, electrolytes, renal function are presented in Table 3. Changes in liver function tests are presented in Table 4. There was no statistical significance of vital signs, complete blood count, glucose, electrolytes, and renal and liver function baseline to cycle 6. No pregnancy occurred during the present study.

Twenty-nine adverse effects were observed in 18 of 92 subjects of whom 19.6% (18 of 92) experienced

Table 1. Heart rate and blood pressure at baseline and after six cycles of DRSP + EE use

Variables	Reference range	Mean ± SD at baseline (n = 100)	Mean ± SD after 6 cycles (n = 92)	95%CI for the different between means	p-value
Heart Rate (beats/min)	60-100	74.8±7.0	76.1±6.5	-3.2-0.6	NS
Systolic BP (mmHg)	80-140	104.0±9.8	104.1±7.4	-2.6-2.4	NS
Diastolic BP (mmHg)	50-90	66.0±7.2	66.5±5.3	-2.3-1.3	NS

NS: no statistical significance

Table 2. Complete blood count at baseline and after six cycles of DRSP + EE use

Variables	Reference range	Mean ± SD at baseline (n = 100)	Mean ± SD after 6 cycles (n = 92)	95%CI for the different between means	p-value
Hemoglobin (g/L)	12.0-16.0	12.4±1.1	12.5±1.0	-0.4-0.2	NS
Hematocrit (%)	36.0-48.0	37.9±3.1	37.9±2.7	-0.8-0.8	NS
Leukocytes (10^9/uL)	4.5-11.0	6.4±1.7	6.6±1.9	-0.7-0.3	NS
Platelets (10^9/L)	150.0-450.0	269.1±56.4	270.9±55.3	-17.7-14.1	NS

NS: no statistical significance

Table 3. Fasting blood glucose, renal function, and electrolytes at baseline and after six cycles of DRSP + EE use

Variables	Reference range	Mean ± SD at baseline (n = 100)	Mean ± SD after 6 cycles (n = 92)	95%CI for the different between means	p-value
Fasting blood glucose (mg/dL)	64.0-110.0	87.0±6.6	87.7±7.7	-2.7-1.3	NS
Creatinine (mg/dL)	0.5-2.0	0.7±0.1	0.7±0.1	-0.02-0.02	NS
Blood Urea Nitrogen (mg/dL)	10.0-20.0	9.7±2.2	9.6±2.2	-2.3-1.3	NS
Sodium (mEq/L)	135.0-145.0	138.7±3.0	137.9±2.8	-0.5-0.7	NS
Potassium (mEq/L)	3.5-5.5	3.9±0.4	3.9±0.3	-0.1-0.1	NS

NS: no statistical significance

Table 4. Liver function tests at baseline and after six cycles of DRSP + EE use

Variables	Reference range	Mean ± SD at baseline (n = 100)	Mean ± SD after 6 cycles (n = 92)	95%CI for the different between means	p-value
Bilirubin direct (mg/dL)	0.00-0.25	0.11±0.04	0.19±0.55	-0.2-0.02	NS
Bilirubin indirect (mg/dL)	0.00-1.00	0.64±0.26	0.64±0.30	-0.08-0.08	NS
ALT/SGPT (IU/L)	0.00-38.00	15.4±7.8	17.1±7.9	-3.9-0.5	NS
AST/SGOT (IU/L)	0.00-38.00	18.2±4.8	18.3±5.5	-1.6-1.4	NS

NS: no statistical significance

at least one adverse effect during the course of the present study. The most common adverse effect reported during the present study was nausea, which was reported by four (4.3%) subjects (8 events), followed by irregular bleeding, which was reported by three (3.3%) subjects (5 events). Three subjects discontinued the present study prematurely due to experience of adverse effects. Adverse effects of these subjects include amenorrhea, nausea, and neuritis (CN VII). No serious adverse effect was reported during the present study.

Discussion

In the present study, the authors investigated the effect of 3 mg DRSP/30 μg EE oral contraception on vital signs, complete blood count, glucose, electrolytes, renal and liver function during 6 cycles of using. The progestogen DRSP is a 17 α-spirolactone derivative with a unique pharmacological profile that combines potent progestogenic with anti-androgenic and anti-mineralocorticoid activity. DRSP + EE has no effect on vital signs, complete blood count, glucose, electrolytes, renal and liver function at cycle 6 when compared to baseline.

There was no significant change in heart rate, systolic and diastolic blood pressure in the present study. The stability in blood pressure was also found in the study of Gaspard et al[27]. From the study of Oelkers et al[24], blood pressure in OC containing DRSP groups fell slightly. The slight decrease or stability in blood pressure was due to a decrease in extracellular volume from antimineralocorticoid effect of DRSP[28].

The mean serum sodium and potassium levels were not significantly changed during 6 cycles in the present study. This is also similar to the study of Oelkers et al[24]. The mean serum creatinine was not significantly changed in the present study. However, this is contradictory to the study of Oelkers et al who found significant increase of serum creatinine at 6 cycles[24].

The mean fasting plasma glucose was not changed at 6 cycles from baseline in the present study. This is similar to previous studies[24,27,29]. However, they found a significant increase in glucose tolerance test in EE plus DRSP and EE plus levonorgestrel or desogestrel groups[24,27,29].

The means of hemoglobin, hematocrit, leukocytes and platelets counts showed no change at cycles 6 from baseline. In the study of Klipping et al[29], who evaluated hemostatic parameter and found changes in hemostatic parameters: increase in activation markers for thrombin (clotting activation) and fibrin (fibrinolytic activation) turnover, in (pro)coagulatory parameters, and in (pro)fibrinolytic parameters as well as a decrease in PAI-1 antigen levels. These suggested that the overall balance between factors influencing hemostasis were maintained on an up-regulated level in both study groups[29]. In addition, the means of liver function tests were not significantly changed at cycle 6 from baseline in the present study. This can confirm that DRSP + EE have no effect on liver function.

In conclusion, oral contraception formulation with drospirenone is well tolerated and has a good contraceptive efficacy. It is safe due to no effect on heart rate, blood pressure, complete blood count, fasting plasma glucose, electrolytes, renal and liver function.

References

1. Hedon B. The evolution of oral contraceptives. Maximizing efficacy, minimizing risks. Acta Obstet Gynecol Scand Suppl 1990; 152: 7-12.
2. Shoupe D. Effects of desogestrel on carbohydrate metabolism. Am J Obstet Gynecol 1993; 168: 1041-7.
3. Speroff L, DeCherney A. Evaluation of a new generation of oral contraceptives. The Advisory Board for the New Progestins. Obstet Gynecol 1993; 81: 1034-47.
4. Spellacy WN. Carbohydrate metabolism during treatment with estrogen, progestogen, and low-dose oral contraceptives. Am J Obstet Gynecol 1982; 142: 732-4.
5. Conard J. Biological coagulation findings in third-generation oral contraceptives. Hum Reprod Update 1999; 5: 672-80.
6. Crook D, Godsland IF, Worthington M, Felton CV, Proudler AJ, Stevenson JC. A comparative metabolic study of two low-estrogen-dose oral contraceptives containing desogestrel or gestodene progestins. Am J Obstet Gynecol 1993; 169: 1183-9.
7. Watanabe RM, Azen CG, Roy S, Perlman JA, Bergman RN. Defects in carbohydrate metabolism in oral contraceptive users without apparent metabolic risk factors. J Clin Endocrinol Metab 1994; 79: 1277-83.
8. Eschwege E, Fontbonne A, Simon D, Thibult N, Balkau B, Saint-Paul M, et al. Oral contraceptives, insulin resistance and ischemic vascular disease. Int J Gynaecol Obstet 1990; 31: 263-9.
9. Laakso M. Hyperglycaemia as a cardiovascular

risk factor. Int Diabetes Monit 2000; 12: 1-5.
10. Coutinho M, Gerstein HC, Wang Y, Yusuf S. The relationship between glucose and incident cardiovascular events. A metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. Diabetes Care 1999; 22: 233-40.
11. Glucose tolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria. The DECODE study group. European Diabetes Epidemiology Group. Diabetes epidemiology: collaborative analysis of diagnostic criteria in Europe. Lancet 1999; 354: 617-21.
12. Laakso M. Insulin resistance and coronary heart disease. Curr Opin Lipidol 1996; 7: 217-26.
13. Weir RJ. When the pill causes a rise in blood pressure. Drugs 1978; 16: 522-7.
14. Crane MG, Harris JJ. Estrogens and hypertension: effect of discontinuing estrogens on blood pressure, exchangeable sodium, and the renin-aldosterone system. Am J Med Sci 1978; 276: 33-55.
15. The WHO multicentre trial of the vasopressor effects of combined oral contraceptives: 1. Comparisons with IUD. Task Force on Oral Contraceptives. WHO Special Programme of Research, Development and Research Training in Human Reproduction. Contraception 1989; 40: 129-45.
16. The WHO multicentre trial of the vasopressor effects of combined oral contraceptives: 2. Lack of effect of estrogen. Task Force on Oral Contraceptives. WHO Special Programme of Research, Development and Research Training in Human Reproduction. Contraception 1989; 40: 147-56.
17. McAreavey D, Cumming AM, Boddy K, Brown JJ, Fraser R, Leckie BJ, et al. The renin-angiotensin system and total body sodium and potassium in hypertensive women taking oestrogen-progestagen oral contraceptives. Clin Endocrinol (Oxf) 1983; 18: 111-8.
18. Petitti DB, Klatsky AL. Malignant hypertension in women aged 15 to 44 years and its relation to cigarette smoking and oral contraceptives. Am J Cardiol 1983; 52: 297-8.
19. Lim KG, Isles CG, Hodsman GP, Lever AF, Robertson JW. Malignant hypertension in women of childbearing age and its relation to the contraceptive pill. Br Med J (Clin Res Ed) 1987; 294: 1057-9.
20. Krattenmacher R. Drospirenone: pharmacology and pharmacokinetics of a unique progestogen. Contraception 2000; 62: 29-38.
21. Foidart JM. The contraceptive profile of a new oral contraceptive with antimineralocorticoid and antiandrogenic effects. Eur J Contracept Reprod Health Care 2000; 5(Suppl 3): 25-33.
22. Oelkers W. Drospirenone - a new progestogen with antimineralocorticoid activity, resembling natural progesterone. Eur J Contracept Reprod Health Care 2000; 5(Suppl 3): 17-24.
23. Parsey KS, Pong A. An open-label, multicenter study to evaluate Yasmin, a low-dose combination oral contraceptive containing drospirenone, a new progestogen. Contraception 2000; 61: 105-11.
24. Oelkers W, Foidart JM, Dombrovicz N, Welter A, Heithecker R. Effects of a new oral contraceptive containing an antimineralocorticoid progestogen, drospirenone, on the renin-aldosterone system, body weight, blood pressure, glucose tolerance, and lipid metabolism. J Clin Endocrinol Metab 1995; 80: 1816-21.
25. Gaspard U, Endrikat J, Desager JP, Buicu C, Gerlinger C, Heithecker R. A randomized study on the influence of oral contraceptives containing ethinylestradiol combined with drospirenone or desogestrel on lipid and lipoprotein metabolism over a period of 13 cycles. Contraception 2004; 69: 271-8.
26. World Health Organization. Improving access to quality care in family planning. Medical eligibility criteria for contraceptive use methods. Geneva: World Health Organization; 1996.
27. Gaspard U, Scheen A, Endrikat J, Buicu C, Lefebvre P, Gerlinger C, et al. A randomized study over 13 cycles to assess the influence of oral contraceptives containing ethinylestradiol combined with drospirenone or desogestrel on carbohydrate metabolism. Contraception 2003; 67: 423-9.
28. Oelkers W, Berger V, Bolik A, Bahr V, Hazard B, Beier S, et al. Dihydrospirorenone, a new progestogen with antimineralocorticoid activity: effects on ovulation, electrolyte excretion, and the renin-aldosterone system in normal women. J Clin Endocrinol Metab 1991; 73: 837-42.
29. Klipping C, Marr J. Effects of two combined oral contraceptives containing ethinyl estradiol 20 microg combined with either drospirenone or desogestrel on lipids, hemostatic parameters and carbohydrate metabolism. Contraception 2005; 71: 409-16.

ผลของยาเม็ดคุมกำเนิดชนิดใหม่ที่ประกอบด้วยโดสไปรีโนนต่อสัญญาณชีพ เม็ดเลือด น้ำตาล เกลือแร่ การทำงานของไตและตับ

สุรศักดิ์ ฐานีพานิชสกุล, อรรณพ ใจสำราญ, วรพงศ์ ภู่พงศ์

วัตถุประสงค์: *เพื่อศึกษาถึงผลของยาเม็ดคุมกำเนิดชนิดใหม่ที่มีโดสไปรีโนน (Yasmin®) เป็นส่วนประกอบต่อสัญญาณชีพ เม็ดเลือด น้ำตาล เกลือแร่ การทำงานของไตและการทำงานของตับ*

วัสดุและวิธีการ: *เป็นการศึกษาที่ไม่มีกลุ่มเปรียบเทียบ โดยคัดเลือกหญิงที่วางแผนใช้ยาเม็ดคุมกำเนิดเป็นเวลาอย่างน้อย 6 เดือนจำนวน 100 คน ซึ่งหญิงที่เข้ารับการศึกษาจะได้รับแผงยาเม็ดคุมกำเนิดที่มียาจำนวน 21 เม็ดที่แต่ละเม็ดประกอบด้วยโดสไปรีโนน 3 มิลลิกรัมและเอทินิลเอสตราไดออล 30 ไมโครกรัมทั้งหมด 4 รอบระดู (หนึ่งรอบระดูเท่ากับ 28 วัน) สำหรับแผงยาในรอบระดูที่ 5 และ 6 หญิงที่เข้ารับการศึกษาจะได้รับยาในการนัดครั้งที่สอง ได้มีการวัดอัตราการเต้นของหัวใจและความดันโลหิตเมื่อเริ่มเข้าร่วมโครงการและทุกครั้งที่นัดหมาย หญิงที่เข้ารับการศึกษาจะได้รับการเจาะเก็บซีรัม เพื่อส่งตรวจเม็ดเลือด น้ำตาล เกลือแร่ การทำงานของไต และการทำงานของตับเมื่อเริ่มเข้าร่วมโครงการและที่สิ้นสุดรอบระดูที่หก โดยจะมีการประเมินค่าเฉลี่ยของความแตกต่างของค่าดังกล่าวระหว่างการสิ้นสุดรอบระดูที่หกกับเมื่อ เริ่มเข้าร่วมโครงการ*

ผลการศึกษา: *จากหญิงที่เข้ารับการศึกษาทั้งหมด 100 คน มี 92 คน (ร้อยละ 92)ได้เข้าร่วมจนจบการศึกษา พบว่าไม่มีความแตกต่างของการเปลี่ยนแปลงของอัตราการเต้นของหัวใจ ความดันโลหิต เม็ดเลือด น้ำตาล เกลือแร่ การทำงานของไตและการทำงานของตับเมื่อเปรียบเทียบระหว่างการสิ้นสุดรอบระดูที่หกกับเมื่อเริ่มเข้าร่วมโครงการ*

สรุป: *ยาเม็ดคุมกำเนิดชนิดใหม่ที่มีโดสไปรีโนนเป็นส่วนประกอบ มีประสิทธิภาพดีในการคุมกำเนิด และไม่มีผลต่อสัญญาณชีพ เม็ดเลือด น้ำตาล เกลือแร่ การทำงานของไตและการทำงานของตับ*