A Double Blind Randomized Control Trial, Comparing Effect of Drospirenone and Gestodene to Sexual Desire and Libido

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Background: *Oral contraceptive is the most commonly used method of fertility control. Yasmin® is a combination of a novel progestogen with anti-androgenic and anti-mineralcorticoid activities (3 mg Drospirenone (DRSP) and 30μg ethinylestradiol (EE)). It has been shown in many clinical trials that Yasmin® is an efficacious oral contraceptive, lacking undesired effects as with other oral contraceptives such as weight gain. However, the effects of Yasmin® on sexual desire and libido have not been intensively investigated so far.*
Objective: *Investigate the effects of Yasmin® on sexual desire, libido and changes in the free androgen index (FAI) compare to Meliane® (75μg gestodene + 20μg ethinylestradiol).*
Material and method: *The authors' report the results of a double blind randomized controlled study using a translated version of the Female Sexual Function Index questionnaire (FSFI) for the assessment of the sexual function. The free androgen index was calculated from measurements of testosterone and sexual hormone binding globulin.*
Result: *The result shows statistically significant improvements regarding sexual desire, arousal and overall satisfaction in the Yasmin® group. Additionally, an increased frequency of orgasms in the Meliane® group was reported. Statistically significant differences between the two treatments regarding changes in the FSFI score and changes in the free androgen index have not been observed.*
Conclusion: *The novel oral contraceptive containing drospirenone (Yasmin®) and the non-anti-androgenic progestin containing oral contraceptive (Meliane®) do not show unfavorable effects on sexual response and libido.*

Keywords: *Drospirenone, Sexual desire, Libido*

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Oral contraceptive is commonly used for reversible fertility control throughout the world. Continuous research progress over the past decades has led to the development of low dose combinational oral contraceptives providing both a high degree of contraceptive efficacy and an excellent safety profile[1-3].

Drospirenone (DRSP), a novel progestogen, is a 17α-spironolactone analogue with unique pharmacological properties combining progestogenic, antimineralocorticoid, and anti-androgenic activities. The combination of 3 mg DRSP and 30 μg ethinylestradiol (Yasmin®) has been shown to be efficacious with regard to cycle control and relieve of premenstrual symptoms without having an undesired effect on the bodyweight in many clinical trials[1,3-6]. However, the effects of Yasmin® on sexual desire and libido have not been intensively investigated so far.

Human sexual desire and libido are complex phenomenon that is orchestrated by various internally and externally influenced biological, neurological psychological factors, and social mores. The interaction of these factors results in cascades of biochemical,

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hormonal, and circulatory changes determining the sexual desire and libido of human beings[7-9]. Oral contraceptives are believed to have some negative influence on the sexual desire. However, compared to intrauterine contraceptive devices (IUD), the reduction of sexual desire after the use of oral contraceptives is less predominant (12.1% in IUD groups versus 10.4% in oral contraceptives group)[10]

The modes of actions by which hormones influence sexual desire are not fully understood. However, androgens are known to play a key role for the activation and maintenance of sexual desire and libido in woman. Oral contraceptives increase the levels of sexual hormone binding globulin (SHBG) thereby leading to decreased levels of free androgens[11,12].

In order to investigate the effects of the DRSP containing oral contraceptive (Yasmin®) on sexual desire, libido and changes in the free androgen index compare to a non-anti-androgenic progesterone containing oral contraceptive (Meliane® (75µg Gestodene + 20µg ethinylestradiol)), we have performed this double blind randomized controlled study.

Material and Method

After achieving approval by the ethical committee of the faculty of medicine, Chulalongkorn University, Bangkok, Thailand, this double blind randomized controlled study was performed at the family planning clinic of the King Chulalongkorn Memorial Hospital. The nature of the clinical trial as well as possible risks and benefits were explained to the subjects in detail and appropriate time was given during which all questions of the subjects were answered. The subjects were informed about their right to withdraw from the study at anytime without giving explanation.

All subjects met the following inclusion criteria: all subjects were healthy volunteers and have signed written inform consent. All subjects were between 16-35 years old, were having sexual intercourse for at least four times per month, were requesting oral contraception for at least 3 months, and have not used hormones at least 3 months before entering the study. The subjects had agreed to regular medical check-ups and follow up according to the study protocol. None of the subjects met the following exclusion criteria: Suspected pregnancy or pregnancy, breastfeeding, serious physical or psychological disorder or use of alcohol, antidepressants, anxiolytic drugs, psychoactive drugs, or any illicit drugs. Subjects having contraindications for oral contraceptives according to WHO category 2, 3 and 4 were excluded from the study.

For the assessment of changes in the sexual desire and libido a Thai language version of the Female Sexual Function Index questionnaire (FSFI), which had already been tested for validity and reliability after translation. Thai version FSFI was answered by the subjects at baseline and after the third treatment cycle. The FSFI questionnaire is a well established and reliable tool to assess changes of sexual desire and libido by asking various questions regarding desire, arousal, lubrication, orgasm, overall satisfaction, and pain[14,15].

Changes in free androgen levels were determined by measuring testosterone and sexual hormone binding globulin at baseline, and after the third treatment cycle, by using the electrochemiluminescence method (Elecsys 1010 machine; Belinger) followed by calculations of the free androgen index. In order to filter out diurnal fluctuations of androgen levels, blood work was always performed between 10:00 am and 12:00 am.

Between March 2005 and February 2006, 86 Thai women were enrolled into the trial. At baseline, medical and gynecological histories including FSFI questionnaire were obtained from each subject and physical examination and blood work including the measurements for the calculation of free androgen index were performed. The subjects were then randomly chosen to receive either three blinded blisters containing 21 tablets of 3mg DRSP/30µg EE (Yasmin®) in sachet label A or three blinded blisters of 21 tablets 75µg Gestodene/20µg EE (Meliane®) in sachet label B. The analyzer and subjects knew only the pills were A or B. The subjects were advised to take one tablet per day for 21 consecutive days followed by a 7 day pause for three consecutive treatment cycles. The first treatment cycle started on the first day of menstruation. After completing three treatment cycles, the subjects repeated the translated FSFI questionnaire and blood work to complete the protocol.

Statistical analysis

For statistical analyses, SPSS version 12.0 was used. Baseline characteristic were calculated and compared by using unpaired t-test for parametric data and non-parametric data were calculated by using Chi-square test and Mann Whitney-U and Wilcoxson test. Free androgen index and translated FSFI score were compared before and after intervention by paired t-test and differences compared between the two groups by ANCOVA test The results were regarded to

be statistically significant when p-values were smaller than 0.05 ($p < 0.05$).

Results

Between March 2005 and February 2006, 86 women were enrolled into the study. Subjects were randomly assigned to receive either Yasmin® (Sachet A, 42 subjects) or Meliane® (Sachet B, 44 subjects). At baseline both groups were well balanced regarding general characteristics, FSFI scores and free androgen indices (Table 1).

After three treatment cycles, FSFI scores and the values of the free androgen index were obtained and compared to the baseline findings. Thereby, statistical significances were calculated for changes in the predefined domains and in the summary scores of the FSFI as well as for the changes regarding the values of the free androgen index.

In the Yasmin® group statistically significant increases were seen regarding sexual desire, arousal, and overall satisfaction as well as in the FSFI summary score. In the Meliane® group, a statistically significant increase in the frequency of orgasms was additionally observed (Table 2).

In both groups, the pre- and post-treatment values for the free androgen index were not statistically different (Table 2). Furthermore, no statistically significant differences regarding values of the free androgen index were seen when both groups were compared with each other (Table 3). The pre- and post-treatment values of the various domains of the FSFI score were also not statistically different when both groups were compared with each other (Table 3).

Discussion

In human beings, various factors including biological, psychological, and social factors as well as the method of contraception may influence sexual desire and libido[7-10]. This double blind randomized controlled trial was performed in order to investigate the effects of a new drospirenone containing oral contraceptive (Yasmin® (3mgDRSP/30µgEE)) on the sexual function in Thai women compared with a well established non-anti-androgenic progestin containing oral contraceptive (Meliane®(75µg gestodene 20µgEE)). Yasmin® was shown to be efficacious with regard to cycle control and relief of premenstrual symptoms without having an undesired effect on the body weight in many clinical trials[1,3-6]. However, the effects of Yasmin® on sexual desire and libido have not been intensively investigated so far.

Among biological factors, that may influence sexual desire and libido, androgens are considered the most important hormones[9,11,12]. Oral contraceptives may increase the levels of sex hormone binding globulin (SHBG) thereby leading to decreased levels of free

Table 1. General characteristics of both groups

Characteristics		Yasmin	Meliane	Significance
Family status	Single	5	3	NS
	Married	37	41	
Income	<10000	22	27	NS
	10000-20000	14	15	
	>20000	6	2	
Contraception	Pills	6	10	NS
	IUD	0	1	
	Condom	27	23	
	No	9	10	
Sexually transmitted disease	Yes	1	2	NS
	No	41	40	
	Not sure	0	2	
Age (yr)		25.7±4.8	24.8±4.8	NS
Children (yr)		0.8±0.7	1.0±0.6	NS
Age of children (yr)		1.2±2.6	1.6±2.0	NS
Duration of Marriage (yr)		3.4±3.1	4.2±4.0	NS
Number of marriages		1.0±0.3	1.0±0.3	NS
Age at 1st Intercourse (yr)		19.2±4.7	18.9±4.0	NS
Number of partner		1.2±1.0	1.1±0.4	NS
Frequency of Intercourse per week		2.7±1.2	2.8±1.1	NS

Table 2. Free androgen Index and FSFI change in separate domain and sum score before and after use in the same groups

Group		Mean ± SD		Significance
		Pre	Post	
Yasmin	Free androgen index (FAI)	1.5±1.7	1.3±2.0	NS
	Sexual desire	2.9±0.7	3.5±1.0	p <0.05
	arousal	3.3±0.8	3.8±1.4	p <0.05
	lubrication	3.1±0.4	3.0±1.0	NS
	orgasm	3.2±0.6	3.4±1.1	NS
	Overall satisfaction	3.5±0.9	4.2±1.2	p <0.05
	pain	3.6±0.7	4.1±1.5	NS
	Summary score	19.6±3.0	21.9±5.8	p <0.05
Meliane	Free androgen indexFAI	1.7±2.6	1.2±1.4	NS
	Sexual desire	3.0±0.6	3.4±0.7	p <0.05
	arousal	3.3±0.7	3.8±0.9	p <0.05
	lubrication	3.0±0.7	3.4±1.5	NS
	orgasm	3.2±0.6	3.5±0.5	p <0.05
	Overall satisfaction	3.6±0.7	4.1±1.0	p <0.05
	pain	3.9±0.8	4.0±0.8	NS
	Summary score	19.9±2.9	22.2±3.3	p <0.05

Table 3. Free Androgen Index (FAI) and FSFI score between 2 groups before and after use oral contraceptive pills

Factors		Mean ± SD		Significance
		Yasmin	Meliane	
FAI	Pre	1.5±1.8	1.7±2.6	NS
	Post	1.3±2.0	1.2±1.4	NS
Sexual desire	Pre	2.9±0.7	3.0±0.6	NS
	Post	3.5±1.0	3.4±0.7	NS
Arousal	Pre	3.3±0.8	3.3±0.7	NS
	Post	3.8±1.4	3.8±0.9	NS
Lubrication	Pre	3.1±0.4	3.0±0.7	NS
	Post	3.0±1.0	3.4±1.5	NS
Orgasm	Pre	3.2±0.6	3.2±0.6	NS
	Post	3.4±1.1	3.5±0.5	NS
Overall Satisfaction	Pre	3.5±0.9	3.6±0.7	NS
	Post	4.2±1.2	4.1±1.0	NS
Pain	Pre	3.6±0.7	3.9±0.8	NS
	Post	4.1±1.5	4.0±0.8	NS
Summary score	Pre	19.6±3.0	19.9±2.9	NS
	Post	21.9±5.8	22.2±3.3	NS

androgens[11,12]. In this study, none of the used oral contraceptives was shown to have a statistically significant effect on values of the free androgen index. In line with these results, no undesired effects on sexual response and libido were seen after the use of one or the other oral contraceptive. Further, no statistically significant differences regarding sexual desire and libido were seen when the anti-androgen containing oral contraceptive (Yasmin®) was compared to the non-anti-androgen containing oral contraceptive (Meliane®). Therefore, a possible negative effect of the anti-androgenic component seems to be negligible.

Overall the pre- and post-treatment comparison of parameters reflecting the sexual desire and libido

has shown that the use of Yasmin® was associated with statistically significant increase in sexual desire, arousal and overall satisfaction score and the use of Meliane® was additionally associated with a statistically significant increase in the domain of orgasm in FSFI score.

However, with regard to the complex regulation of sexual functions, confounders that may have influenced the current results could not be fully excluded. In addition, no conclusions regarding long-term effects on sexual functions can be drawn out of findings of this study. Therefore, consolidating trials as well as investigations of long-term effects of drospirenone containing oral contraceptives are warranted.

In conclusion, the results of this study have not shown unfavorable properties of the new drospirenone containing oral contraceptive (Yasmin®) and of the well established non anti-androgenic progestin containing oral contraceptive (Meliane®) regarding sexual response and libido in Thai women.

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การศึกษาเปรียบเทียบผลของฮอร์โมนดรอสไพรีโนนและเจสโตรดีนต่อความต้องการทางเพศ

ชินา โอฬารรัตนพันธ์, สุรศักดิ์ ฐานีพานิชสกุล

ยาเม็ดคุมกำเนิดเป็นวิธีคุมกำเนิดที่ใช้กันทั่วไป ยาเม็ดคุมกำเนิดยาสมิน ซึ่งเป็นยาเม็ดคุมกำเนิดชนิดใหม่ที่ประกอบด้วยฮอร์โมนดรอสไพรีโนน มีผลดีในด้านของการต้านฤทธิ์ของฮอร์โมนเพศชาย อย่างไรก็ตามไม่มีผลการศึกษาที่ชัดเจนในด้านที่มีผลต่อความต้องการทางเพศของสตรีที่รับประทานยาเม็ดคุมกำเนิดชนิดนี้ วัตถุประสงค์ของการศึกษานี้เพื่อศึกษาเปรียบเทียบผลของฮอร์โมนดรอสไพรีโนนและฮอร์โมนเจสโตรดีนต่อความต้องการทางเพศ จากการศึกษาพบว่า ยาเม็ดคุมกำเนิดที่ประกอบด้วยฮอร์โมนดรอสไพรีโนนและฮอร์โมนเจสโตรดีน ไม่มีผลกระทบต่อความต้องการทางเพศ