Effects of Jadelle Used in Thai Women Aged between 20 and 45 Years in King Chulalongkorn Memorial Hospital

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Objective: *To study the menstrual patterns and side effects of Jadelle use in Thai women aged between 20 and 45 years.*
Study Design: *Prospective descriptive study.*
Setting: *Family Planning Clinic, Department of Obstetrics and Gynecology, King Chulalongkorn Memorial hospital.*
Material and Method: *A prospective clinical trial study was conducted at the Family Planning Unit, King Chulalongkorn Memorial Hospital in June 2005. The study duration was 6 months.The data was obtained from each patient's medical record.The descriptive statistics was frequency, percentage, mean, SD and 95% Confidence Interval (CI).The statistical analyses were performed by using the paired t test for comparison of means before and after 6 months of Jadelle used.*
Results: *A total of 59 women were recruited in a 6-month clinical study. Their mean age was 29.07 years. Most acceptors had completed secondary school. No accidental pregnancy occurred throughout the 6 months of use in the present study. The most common menstrual pattern was amenorrhea followed by irregular bleeding. The major side effect was irregular bleeding.There was no significant change in body weight, body mass index, and systolic-diastolic blood pressure during the 6 months follow up period. The common non menstrual adverse effects were headache, acne, alopecia.*
Discussion: *The most common menstrual patterns found in the present study were amenorrhea and irregular bleeding followed by a regular cycle. The common nonmenstrual adverse effects were headache, acne, and alopecia. There were no pregnancies in the 6-month follow-up period. Jadelle was an effective implant contraceptive method with an acceptable bleeding pattern. Over all acceptability was good.This should become another choice of contraception for Thai women.*

Keywords: *Jadelle, Contraception, Menstrual pattern, Side effects*

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There are many contraceptive methods for women. Norplant (a six-capsule subdermal implant system that releases levonorgestrel and has a duration of action of 5 years), showed that subdermal implants are very effective and are a reversible method of contraception[1,2]. However, because implants may be difficult to remove[3,4] new systems have been developed. There are currently several innovative contraceptive implant systems under development. Their main advantage is the reduction of the number of implants, which greatly facilitates insertion and removal. Jadelle is a system that consists of two implantable 43mm rods, each consisting of a drug-releasing core encased in thin-walled silicone rubber tubing sealed at both ends. The core of each rod consists of 50% by weight of levonorgestrel (75mg) and 50% of elastomer[5].

The calculated mean daily in vivo release rate of levonorgestrel provided by the implants is about 100 g/day at month 1 followed by a decline to about 40 g/day at 12 months and to about 30 g/day at 24 months with a stabilization thereafter at about 30 g/day[6].

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After placement of Jadelle implants, maximum levonorgestrel concentrations are reached in about 2 to 3 days, with the mean ± standard deviation being 772 ± 414 pg/mL at 2 days. After the initial phase, mean levonorgestrel concentrations slowly decline to approximately 435 ± 172 pg/mL at 1 month, 357 ± 155 pg/mL at 6 months, and 280 ± 123 pg/mL at 3 years. Concentrations at 4 and at 5 years are similar to those at 3 years[6].

Mechanism of action like other progestogens, levonorgestrel is thought to prevent conception through 2 main mechanisms:

1. Production of viscous cervical mucus that impairs sperm penetration[7,8].

2. Inhibition of ovulation by action on the hypothalamus and pituitary to suppress or reduce the surge of Luteinising Hormone (LH) that triggers ovulation[9,10].

The other 2 mechanisms are:

3. Suppression of endometrial function, interfering with implantation of the fertilised ovum[11].

4. Reduction of the natural production of progesterone by the ovary during post ovulatory (luteal phase).

Jadelle implants are indicated for the prevention of pregnancy and are a long-term (up to 5years) reversible method of contraception. Both implants must be removed by the end of the fifth year. New implants may be inserted at that time if continuing contraceptive protection is desired[6].

Most women using Jadelle implants can expect some variation in menstrual bleeding patterns. Irregular menstrual bleeding, prolonged episodes of bleeding and spotting, heavy bleeding, intermenstrual spotting and amenorrhea occur in some women.

There is little information of Jadelle effects in Thai women aged between 20 and 45 years. The objectives of the present study were to evaluate the menstrual patterns and side effects of Jadelle implant use in Thai women between 20 and 45 years of age during a 6 months follow- up period.

Material and Method

The present 6 months cohort study was conducted at the Family Planning Unit, Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University, Bangkok, beginning in June 2005. Fifty-nine women aged between 20 and 45 years were enrolled in the present study. The inclusion criteria for the study were age 20 years or above, normal medication history, no contra-indication for Jadelle use, normal physical and pelvic examination, normal Papanicolaou smear, no prior use of oral contraceptive or implanted contraceptive within 3 months, and no prior use of DMPA within 1 year. The exclusion criteria were breast-feeding, postpartum, pregnancy, and inability to follow up for 6 months. All participants voluntarily chose Jadelle after counseling and received two-rods of Jadelle insertion within 5 days after the onset of menstruation. All acceptors enrolled had physical and pelvic examination, including body weight, height, and blood pressure measurements. Follow-up visits were scheduled for the third and sixth months after implant placement.

At each follow-up visit, they were given a repeat physical and pelvic examination, including weight, and blood pressure. The menstrual bleeding patterns were recorded in a menstrual diary card, and subjective complaints as well as side effects were recorded on questionnaire forms. The period of follow-up was 6 months. Telephone calls and letters were used in cases of missed appointments. The insertion of Jadelle was performed by a doctor at the Family Planning Unit.

In the present study, amenorrhea was defined as the absence of menstruation for 3 months or longer. A regular cycle was defined as periodic withdrawal bleeding within 28 ± 7 days. Irregular cycles were defined as intermenstrual, prolonged, or heavy bleeding at irregular intervals (no regular cycle)[12].

Descriptive and analytic statistics were run on all data where appropriate. SPSS/PC for Window, a statistical package program, was used to analyze data. The sample size was calculated by using the formula for clinical study (P = 0.38, d=0.15, p-value = 0.05). The number of participants was approximately 50 cases. All data were coded, recorded, and analyzed by the investigators. The descriptive statistics were percentage, mean, SD, and 95%CI. The statistical analyses were performed by using the pair t-test for comparison of means before and after 6 months of Jadelle used. Significant difference was expressed at the level of 0.05 for all analyses.

Results

Jadelle was used by 59 women between 20-45 years of age. No women quit the project and all 59 women had a complete follow-up. The characteristics of Jadelle implants acceptors are shown in Table 1. The mean age was 29.1 ± 6.7 years. Most of the acceptors (39%) had completed secondary school, and 44.1% were employees. The most common contraceptive

Table 1. Characteristics of jadelle implants acceptors

Characteristics	n = 59	95%CI
Age (years) (mean ± SD)	29.10±6.7	27.3, 30.8
Education (%)		
Primary	33.9	21, 45
Secondary	39.0	27, 51
Above secondary	27.1	16, 38
Occupation (%)		
Housewife	15.3	6, 24
Employee	44.1	31, 57
Others	40.7	27, 53
Parity (%)		
None	10.2	2, 18
One	39.0	27, 51
Two	42.4	29, 55
Three	5.1	-1, 11
Four	3.4	-1, 7
Most recent contraception (%)		
None	11.9	3, 19
Oral pill	11.9	3, 19
DMPA	1.7	-2, 4
Condom	61.0	49, 73
IUD	3.4	-1, 7
Norplant	5.1	-1, 11
Implanon	5.1	-1, 11
Body weight at insertion (Kg)		
(mean ± SD)	55.38±12.51	52.12, 58.65
Body mass index (Kg/m)		
(mean ± SD)	23.28±4.32	22.15, 24.41
Blood pressure at insertion (mmHg)		
Systolic	112.95±7.85	110.90, 113.00
Diastolic	71.29±5.64	69.82, 72.76

method used by these acceptors prior to Jadelle insertion was condom (61%). There were no complications with the insertion procedure, and no pregnancy occurred during the 6- month follow up period. Considering the menstrual patterns,the most common bleeding pattern at three months was amenorrhea (54.2%), followed by an irregular cycle (40.7%), and a regular cycle (5.1%). The most common bleeding pattern at six months was amenorrhea (64.4%), followed by an irregular cycle (32.2%),and a regular cycle (3.4%) (Table 2). The major nonmenstrual side effects reported at six months of follow-up were irregular bleeding (32.2%), headache (11.9%), acne (11.9%), alopecia (6.8%) (Table3). When using the paired *t* test there were no significant differences in body weight, systolic or diastolic blood pressure between the time of insertion and the 6-month follow-up. The details are summarized in Table 4.

Table 2. Menstrual patterns at 3 and 6-month follow-up in Jadelle

Menstrual patterns	n = 59	%
3-month follow-up		
Amenorrhea	32	54.2
Irregular	24	40.7
Regular	3	5.1
6-month follow-up		
Amenorrhea	38	64.4
Irregular	19	32.2
Regular	2	3.4

Table 3. Side effects of Jadelle acceptors at 6-months follow up

Side effects	Number	Percent	95%CI
Irregular bleeding			
Yes	19	32.2	20, 44
No	40	67.8	55, 79
Headache			
Yes	7	11.9	3, 19
No	52	88.1	80, 96
Breast tenderness			
Yes	2	3.4	-1, 7
No	7	96.6	91, 101
Chloasma			
Yes	2	3.4	-1, 7
No	57	96.6	91, 101
Acne			
Yes	7	11.9	3, 19
No	52	88.1	80, 96
Alopecia			
Yes	4	6.8	0,12
No	5	93.2	86, 100

Discussion

Levonorgestrel-releasing Norplant contraceptive implants have a recorded history of successful use by more than 200,000 women in 30 countries[13]. The original system (Norplant-6), developed by the Population Council, comprises a set of six capsules each containing 36mg of levonorgestrel and has a contraceptive life of up to 5 years. Jadelle was also developed by the Population Council to improve the ease of insertion and removal. This system comprises two rods, each containing 75 mg levonorgestrel,with a contraceptive life of up to 5 years. Drug load is, therefore, 150 mg per set of two rods. Implant cores are covered with thin-walled silicone rubber tubing,

Table 4. Comparison of body weight and blood pressure at insertion and 6-month follow up

Variable	At insertion (n = 59) (mean ± SD)	at 6-month (n = 59) (mean ± SD)	95%CI
Body weight (Kg)	55.40±12.5	56.82±10.9	-3.9, 1.03
Body mass index (Kg/m	23.38±4.3	23.10±4.18	-0.06, 0.4
Blood pressure (mmHg)			
Systolic	113.00±17.8	111.90±6.2	-1.0, 3.1
Diastolic	71.30±5.6	72.20±5.9	-2.8, 0.9

* $p > 0.05$

whose ends are sealed with medical adhesive before the implants are sterilized. The rods are inserted in a superficial plane beneath the skin of the inner aspect of the upper arm. The principal benefit of contraception with levonorgestrel implants is its effectiveness in preventing pregnancy for extended periods after a single administration[14].

Alterations of menstrual function are associated with implant forms of contraception. During the course of using levonorgestrel implants, 75 to 90% of women reported changes in their menstrual patterns. These changes included prolonged episodes of bleeding and/or spotting, irregular bleeding, oligomenorrhoea and amenorrhoea. Heavy bleeding was also reported, however, it was much less common than the other disturbances. Alterations to menstrual patterns represented a substantial proportion of the reasons for discontinuation of implants within 5 years of initiation[14]. The present study has demonstrated that Jadelle use in women was highly effective. No pregnancy occurred during the study period. However, the most common menstrual patterns were amenorrhea, irregular bleeding and regular bleeding. A 5-year study in 594 females aged 18-40 showed that implantation of two levonorgestrel rods (Jadelle) was generally well tolerated. Over the 5-year study duration, 17.7% and 20.9% of patients discontinued treatment as a result of menstrual disorders and other medical problems, respectively[15].

Apart from menstrual disturbances the most frequently mentioned side effects of any progestogen-releasing implantable contraceptive were headache, weight gain, acne, dizziness, mood changes, including nervousness and depression, breast tenderness, nausea, lower abdominal pain, hair loss, loss of libido, and pain at implant site[16]. However, in the present study, it was demonstrated that weight gain during the 6-months period among Jadelle acceptors was not significant. A longer follow-up period should be done to evaluate the result of bodyweight gain.

The Norplant Surveillance study found a weight gain of 2.5 kg in Chinese women over 5 years. This relatively modest weight increase was, however, only 1.0 kg higher than the increase in nonhormonal controls ($p < 0.001$)[17]. Another large, 5-year Norplant-II study conducted in India reported that 43% of the women increased more than 5 kg, whereas 10% of the women in the multicenter Jadelle trial gained 9-10 kg in 5 years[18,19,20].

Acne was reported by 11.9% of users in the present study. In the international comparative study of Norplant and Jadelle, the proportion of women reporting acne was only 5.7% and 5.8%, respectively, whereas in the US Norplant trial, it was 21%, which is similar to a rate of 22% and 18% reported among women in the comparative trial between Norplant and Implanon, respectively[18,21,22].

Alopecia and melasma are less frequently mentioned side effects. The present study reported alopecia and melasma in 6.7% and 5.08% of users. Acne and alopecia are side effects that are usually attributed to an androgenic effect of progestogens.These side effects were a more frequent observation in Norplant implant users than nonhormonal controls. This suggested that these side effects are probably associated with the hormonal component and that they may occur more often in some women in the initial months of use, when the progestin levels are several-fold higher than in the later months. In the present study 11.9% of women with headache were observed. Headache is the frequent complaint of users of Implantable Contraceptive. The great majority of studies report figures within 10-30%. However, the percentage of women complaining of this condition ranged from 3 to 69% for the different Implantable Contraceptive[16].

Conclusion

Subdermal contraceptives offer women an effective method of birth control that is easy to use.

The present study demonstrated that Jadelle in Thai women did not have an adverse effect on systolic and diastolic blood pressure. Moreover, body weight, and body mass index were not changed. The most common menstrual patterns found in the present study were amenorrhea and irregular cycle followed by regular cycle. The nonmenstrual adverse effects were headache, acne and alopecia. There were no pregnancies in the 6-month follow-up period. Jadelle is a safe and effective implant contraceptive method with an acceptable bleeding pattern. Although irregular menstrual bleeding is more likely to occur than with combination methods, most patients find it acceptable. The lack of estrogen allows use by women who should not be exposed to systemic estrogen because of thrombotic risks. Overall acceptability was good. This should become another choice of contraception methods in Thai women. Effective counseling and explanation of the side effects and proper selection of women for Jadelle insertion should minimize the problems of side effects and improve continuation and acceptability.

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การศึกษาผลข้างเคียงของยาฝังคุมกำเนิด จาเดลล์ในสตรีไทยที่มีอายุ ระหว่าง 20 ปี ถึง 45 ปี ในโรงพยาบาลจุฬาลงกรณ์

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วัตถุประสงค์*: เพื่อศึกษาผลข้างเคียงของยาฝังคุมกำเนิด จาเดลล์ในสตรีไทยที่มีอายุระหว่าง 20 ปี ถึง 45 ปี ในโรงพยาบาลจุฬาลงกรณ์*

วัสดุและวิธีการ*: การวิจัยทดลองทางคลินิก สถานที่ทำการวิจัยใน หน่วยงานวางแผนครอบครัว โรงพยาบาลจุฬาลงกรณ์ กลุ่มตัวอย่าง สตรีไทยที่มีอายุระหว่าง 20 ปี ถึง45ปี ที่ต้องการคุมกำเนิดโดยการฝังจาเดลล์อย่างน้อย 6 เดือน จำนวน 59 คน ผู้เข้าร่วมงานวิจัยจะได้รับคำแนะนำและคำปรึกษาในการเข้าร่วมโครงการยาฝังจาเดลล์และฝังยา จาเดลล์บริเวณท้องแขนโดยแพทย์ภายใน 5 วันหลังมีประจำเดือนวันแรก ลงผลลักษณะประจำเดือนในแบบบันทึกลักษณะประจำเดือน โดยนิยามตัวแปรภาวะไม่มีประจำเดือนคือ การไม่มีประจำเดือนตั้งแต่ 3 เดือนขึ้นไปโดยไม่มีการตั้งครรภ์ ประจำเดือนสม่ำเสมอคือประจำเดือนที่มีระยะห่างของแต่ละรอบเดือน 28 $\pm$ 7 วัน ประจำเดือนไม่สม่ำเสมอ คือ มีภาวะที่ไม่ใช่ประจำเดือนสม่ำเสมอตรวจติดตามผลโดยการสัมภาษณ์ ตรวจร่างกายตรวจภายในและบันทึกข้อมูลลงในแบบสอบถามในเวลา 3 เดือน และ 6 เดือนหลังฝังจาเดลล์*

ผลการวิจัย*: สตรีไทยที่ติดตามครบ 6 เดือนทั้งสิ้น 59 คน มีอายุโดยเฉลี่ย 29.07 ปีส่วนใหญ่จบการศึกษาในระดับมัธยมศึกษา และไม่มีการตั้งครรภ์เกิดขึ้นในการศึกษานี้ลักษณะประจำเดือนที่พบมากที่สุดภาวะไม่มีประจำเดือนรองลงมา คือ ประจำเดือนไม่สม่ำเสมอ โดยผลข้างเคียงที่พบมากที่สุดคือภาวะประจำเดือน ไม่สม่ำเสมอ ในการศึกษานี้ไม่พบว่ามีการเปลี่ยนแปลงของน้ำหนักตัว ดัชนีมวลกายและความดันdiastolic ความดัน systolic ผลข้างเคียงอื่นคืออาการปวดศีรษะ สิว ผมร่วง คัดตึงเต้านม และ ฝ้า ตามลำดับ*

สรุป*: การใช้จาเดลล์ในสตรีไทยที่มีอายุระหว่าง 20 ปี ถึง 45 ปีมีประสิทธิภาพและ ปลอดภัย ดังนั้นการใช้จาเดลล์ในสตรีวัยนี้จึงอาจเป็นทางเลือกหนึ่งในสตรีที่มีข้อห้ามในการใช้ยาคุมกำเนิดชนิดรับประทาน*