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Delayed first injection of a once-a-month injectable contraceptive containing 25 mg of medroxyprogesterone acetate and 5 mg of E_2-cypionate: effects on ovarian function

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Objective: To assess whether women who were administered the first injection of DMPA+E_2C on day 7 of their menstrual cycle (delayed injection) exhibit the same degree of ovarian suppression as women who receive it on day 5 of their menstrual cycle.

Design: Multicenter, randomized controlled trial.

Setting: Reproductive health clinics.

Patient(s): Women aged between 18 and 38 years (inclusive) willing to use DMPA+E_2C as their method of contraception.

Intervention(s): Participants received a DMPA+E_2C injection on day 5 (control group, n = 41) or day 7 (delayed-injection group, n = 117) of their menstrual cycle.

Main Outcome Measure(s): Ovarian activity and follicular development determined by serial serum progesterone levels and vaginal ultrasound.

Result(s): Participants who received DMPA+E_2C on day 5 of their menstrual cycle (control group) exhibited no more than limited follicular growth (no follicle >16 mm). Of those women who received DMPA+E_2C on day 7 of their menstrual cycle (delayed-injection group), 21 (18%) showed some follicular growth, of whom 4 (3%) ovulated.

Conclusion(s): The first injection of DMPA+E_2C given on day 7 of a menstrual cycle does not provide the same inhibition of ovarian activity as that observed when it is administered on day 5 of the menstrual cycle. (Fertil Steril® 2001;75:744–8. ©2001 by American Society for Reproductive Medicine.)

Key Words: Cyclofem, contraception, ovulation, progesterone, ultrasound, randomized controlled trial

The once-a-month injectable contraceptive that combines 25 mg of depot medroxyprogesterone acetate and 5 mg of estradiol cypionate (DMPA+E_2C; Cyclofem, Aplicaciones Farmacéuticas, Mexico City, Mexico and a registered trademark of the Concept Foundation, Seattle, WA) has been shown to be a highly effective and acceptable contraceptive method (1, 2). Current guidelines recommend that women receive the first injection of DMPA+E_2C within the first 5 days of their menstrual cycle. This differs from guidelines for depot medroxyprogesterone acetate (Depo-Provera, Kalamazoo, MI), which recommend that the first injection can be given up to the 7th day of the menstrual cycle (3).

Increasing the window in which the first DMPA+E_2C injection can be given to day 7 of the menstrual cycle would not only standardize recommendations for injectable contraceptive methods but also provide greater access for women. However, no studies to date have evaluated the consequences of extending the first injection of DMPA+E_2C to day 7 of the cycle. This randomized controlled trial assessed

TABLE 1

Characterization of ovulation.

Categories	Follicle size (mm)	Progesterone (ng/mL)
1. No activity	<10	<2.5
2. Limited follicular growth	10–16	<2.5
3. Follicular growth	≥16–30	<2.5
4. Enlarged follicle	>30	<2.5
5. Luteinized unruptured follicle	≥16	≥2.5
6. Disappearance of follicle without luteal activity	Disappearance of a follicle ≥16	<2.5 after disappearance
7. Uncertain ovulation	Limited or no follicular growth (follicle ≤16)	≥2.5
8. Ovulation	≥16 & rupture or abrupt disappearance of follicle	≥2.5

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whether women who were administered DMPA+E_2C on day 7 of their menstrual cycle (delayed injection) exhibited the same impaired fertility level as women who were administered DMPA+E_2C on day 5 of their menstrual cycle (control group).

MATERIALS AND METHODS

Study Population

A total of 160 women were enrolled at four centers, Campinas, Brazil (n = 48); Santo Domingo, Dominican Republic (n = 26); Santiago, Chile (n = 46); and Hangzhou, China (n = 40), between May 1998 and September 1999. The study was approved by the institutional review boards of the research sites, Family Health International, and the World Health Organization.

Eligible women were between 18 and 38 years of age (inclusive), had a normal medical history and physical examination, had not used hormonal contraception in the 4 months before entry to the study, and were not pregnant or breastfeeding. Written informed consent was obtained from women before enrollment and randomization.

The allocation sequence was computer generated using a permuted block randomization scheme. One hundred sixty women were randomly allocated to either an injection on day 5 (the control group) or day 7 (the delayed-injection group) of their menstrual cycle in a 1:3 ratio according to opaque-sealed, sequentially numbered envelopes opened at admission. Participants randomized to the control group established the level of ovarian activity suppression assumed to be adequate for contraceptive protection. The participants randomized to the delayed-injection group were considered the study group. Participants, clinic staff, and study monitors were not masked regarding the assignment group. Statisticians and medical reviewers were masked during the trial.

Participants made up to seven clinic visits (screening, admission, and five follow-up visits at 24 h and at 3, 5, 10, and 14 d after admission). The admission visit took place on days 5 or 7 after the onset of participant's menses. At each visit, blood samples were collected for progesterone levels, and a vaginal ultrasound was performed to document follicular development. The investigators from the four participating centers were trained in sample collection and ultrasound techniques to standardize the procedures.

Outcome Measures

Progesterone serum levels were measured with direct enzyme immunoassay kits provided by the World Health Organization Collaborating Center for Research and Reference Services in the Immunoassay of Hormones in Human Reproduction (London, UK). The interassay coefficient of variation for low (1.0 ng/mL), middle (3.1 ng/mL), and high (12.6 ng/mL) pools were 28.7%, 13.4%, and 14.6%, respectively. One center did not participate in the joint quality control scheme. The interassay coefficient of variation for this center ranged from 3.9 to 9.7%.

Vaginal ultrasound examinations were performed using a real-time scanner and a vaginal probe of 5 MHz. The technique for performing measurements has been described elsewhere (4, 5). Briefly, the follicle measurement was made in three diameters, and the mean was noted. Follicles that disappeared or that were reduced in size by >50% after reaching a diameter of 15 mm were considered to have ruptured.

Ovarian activity was categorized using an eight-level classification system developed by the authors (Table 1). The classification system combines progesterone values with vaginal ultrasound findings to categorize ovarian activity. The classification of each participant within these categories was based on the highest level of ovarian activity observed in each woman during the course of the study. Using these categories, two dichotomous variables were defined: *ovarian activity* (categories 3–8) vs. no ovarian activity (categories 1 and 2) and *ovulation* (categories 7 and 8) vs. no ovulation (categories 1–6).

For each variable, a one-tailed Fisher's exact test comparing the proportion observed in the delayed-injection group with the proportion observed in the control group was done at a significance level of 0.05.

The primary group for the analysis, the treated population,

TABLE 2

Baseline characteristics.

Characteristic	Brazil	Chile	China	Dominican Republic	Control group	Delayed-injection group	Total
Age (yr)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
18–24	15 (32)	15 (33)	1 (2)	12 (46)	11 (27)	32 (27)	43 (27)
25–29	14 (30)	6 (13)	16 (40)	4 (15)	12 (29)	28 (24)	40 (25)
30–34	13 (28)	12 (27)	15 (38)	8 (31)	12 (29)	36 (31)	48 (30)
35–38	5 (10)	12 (27)	8 (20)	2 (8)	6 (15)	21 (18)	27 (17)
	mean (SD)	mean (SD)	mean (SD)	mean (SD)	mean (SD)	mean (SD)	mean (SD)
Age (yr)	27.9 (5.0)	28.3 (7.4)	31.0 (4.0)	27.0 (5.4)	28.5 (5.9)	28.7 (5.8)	28.6 (5.8)
Body mass index[a]	24.5 (4.5)	24.3 (3.7)	21.0 (2.5)	26.6 (6.5)	23.7 (4.5)	24.0 (4.7)	23.9 (4.7)

[a] Body mass index = [weight (kg)/height (m)^2]

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was defined as women who were randomized to the study, received the DMPA+E_2C injection, were not subsequently found to be pregnant before injection, and contributed some follow-up assessment information. During analysis, one participant was found to be in the midluteal phase of her menstrual cycle at baseline. Because the initial definition of ovarian activity was designed to categorize women entering the study during the follicular phase, it was difficult to classify this participant. Hence, she was excluded from the treated population.

RESULTS

A total of 160 participants was randomized to receive DMPA+E_2C: 41 in the control group and 119 in the delayed injection group. One participant was found to be ineligible (outside age range) for the study after randomization but before DMPA+E_2C injection. She did not receive the injection and was therefore excluded from the treated population. Another participant was excluded from the treated population because she was found to be in the midluteal phase of her cycle after review of her progesterone level at baseline (18.6 ng/mL) and ultrasound results. Both of these participants were in the delayed-injection group. Thus, the treated population was comprised of 158 women: 41 in the control group and 117 in the delayed-injection group. The average age of the participants was 29 years, and their average body mass index was 24 (Table 2).

All participants in the control group were categorized as either having no activity (category 1) or having limited follicular activity (category 2) during the course of the study (Table 3). At baseline, 80% were categorized as having no activity and 20% as having limited follicular activity. After the DMPA+E_2C injection, 68% had no activity, and 32% had limited activity.

In contrast, in the delayed-injection group, 7 women (6%) were categorized as having follicular growth at baseline. After injection, three participants (3%) were categorized as

TABLE 3

Baseline and maximum ovarian activity postinjection.

	Control group		Delayed-injection group	
	Baseline	Max postinjection	Baseline	Max postinjection
Categories	n (%)	n (%)	n (%)	n (%)
1. No activity	33 (80)	28 (68)	65 (56)	55 (47)
2. Limited growth	8 (20)	13 (32)	45 (38)	40 (34)
3. Follicular growth			7 (6)	6 (5)
4. Enlarged follicle				
5. Luteinized unruptured follicle				2 (2)
6. Follicular disappearance with no luteal activity				9 (8)
7. Uncertain ovulation				1 (1)
8. Ovulation				3 (3)
Total	41 (100)	41 (100)	117 (100)	116[a] (100)

[a] One participant in the delayed-injection group (day 7) did not receive any follow-up visits after injection but before discontinuing early.

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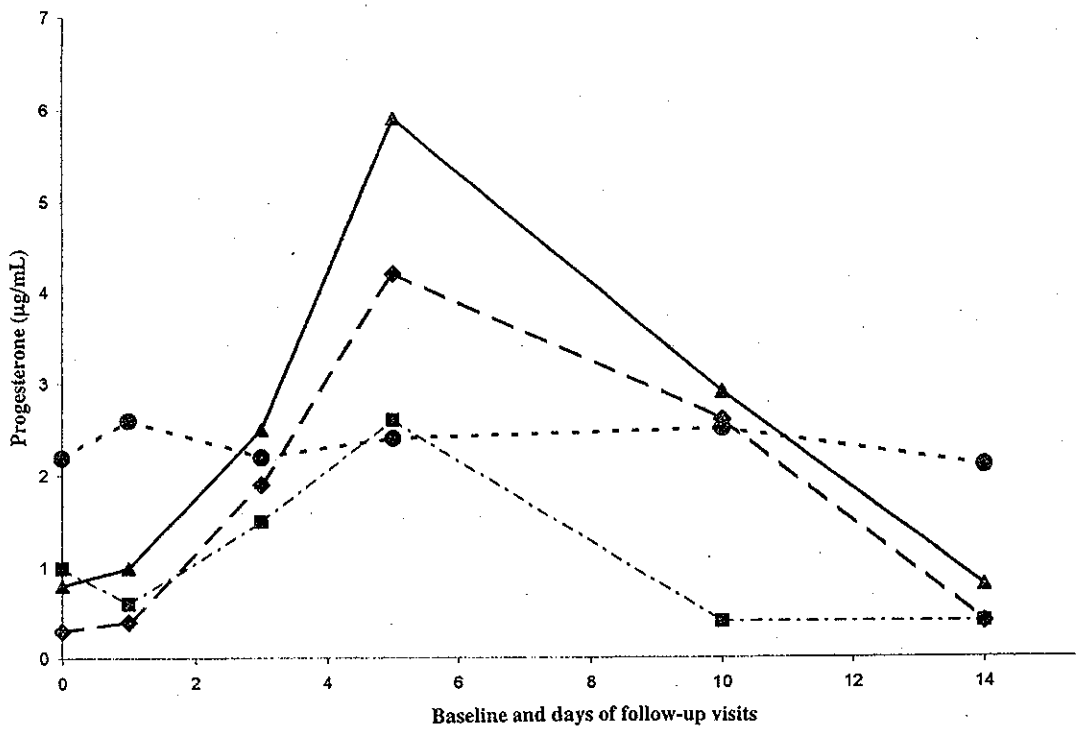
FIGURE 1

Progesterone levels in participants in categories 7 and 8. ♦ = participant 1; ■ = participant 2; ▲ = participant 3; and ● = participant 4.



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having ovulated. All three had abnormal cycles, having ovulated within 3 days of the DMPA+E_2C injection (day 10 of the cycle), and with low maximum serum progesterone levels (2.6, 4.2 and 5.9 ng/mL; Figure 1) but a sudden disappearance of an enlarging follicle (maximum size, 15.5–21 mm). One (1%) participant was categorized as having uncertain ovulation because she had slightly elevated progesterone levels (range, 2.1–2.6; Figure 1) but little ovarian activity (largest observed follicle size, 7 mm). Two participants (2%) were categorized with luteinized unruptured follicles, and nine (8%) had follicular disappearance without luteal activity.

TABLE 4

Number of percentage of women with ovulation or ovarian activity.

	Ovulation (categories 7 and 8)		Ovarian activity (categories 3–8)	
	Control group	Delayed-injection group	Control group	Delayed-injection group
Center number	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Brazil	0/12 (—)	1/35 (3%)	0/12 (—)	6/35 (17%)
Chile	0/12 (—)	1/33 (3%)	0/12 (—)	9/33 (27%)
China	0/11 (—)	0/29 (—)	0/11 (—)	1/29 (3%)
Dominican Republic	0/6 (—)	2/20 (10%)	0/6 (—)	5/20 (25%)
Total	0/41 (—)	4/117 (3.4%)	0/41 (—)	21/117 (18%)
95% CI	(0, 8.6%)	(0.9%, 8.5)	(0, 8.6%)	(11.5%, 26.1%)
P values	0.32		0.001	

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Table 4 summarizes the postinjection frequency of ovulation (categories 7 and 8) and ovarian activity (categories 3–8). No participant in the control group was characterized as having either ovulation or ovarian activity (Table 4). In the delayed-injection group, four (3%, 95% confidence interval [CI] = 0.9%–8.5%) participants were characterized as having ovulation and 21 (18%, 95% CI = 11.5%–26.1%) as having ovarian activity. The proportion of participants characterized as showing ovarian activity in the delayed-injection group was significantly greater than that in the control group ($P = 0.001$). The proportion of participants characterized as having ovulation was not statistically significant compared with that in the control group ($P = 0.32$). The statistical results remained unchanged when the participant excluded on the basis of being midluteal at study entry was added (characterized as ovarian activity). Of note, no participants at the China center were characterized as having ovulation, and only 3% there were characterized as having ovarian activity.

A total of 24 adverse events, none of which were considered serious, occurred among 19 participants. Spotting and breast pain were the most frequently reported adverse events.

DISCUSSION

DMPA+E_2C administered on day 7 of the menstrual cycle did not inhibit ovarian activity as well as did administration on day 5. However, only a small percentage of women in the day 7 group ovulated, and those that did had abnormal cycles.

DMPA+E_2C administered on day 5 suppressed ovulatory activity, which is consistent with earlier studies of DMPA+E_2C (6). It is not surprising that DMPA+E_2C administered on day 7 of the menstrual cycle did not inhibit ovarian activity as well as in women administered DMPA+E_2C on day 5; follicular recruitment was more advanced at baseline. Why ovarian activity was not suppressed as well on day 7 as has been seen in studies of Depo-Provera is most likely due to the much lower dose of medroxyprogesterone acetate in DMPA+E_2C (25 mg, compared with 150 mg in Depo-Provera; (7).

Women who ovulated when administered DMPA+E_2C on day 7 of their menstrual cycle had abnormal cycles. These women ovulated earlier in the cycle (day 10) than in a normal ovulatory cycle (day 14) (8). This may be due to medroxyprogesterone acetate triggering ovulation in already-forming follicles, a phenomenon that has been observed previously (5, 7, 9). It may also be due to exogenous estrogen reaching preovulatory levels that trigger an LH surge and premature ovulation (8). Furthermore, the highest progesterone levels observed in the ovulating subjects (2.6–5.9 ng/mL) were lower than those observed in normal menstrual cycles (>10 ng/mL; see References (8, 10), and the duration of the progesterone rise was shorter. As further evidence of normal menstrual cycle disruption, other women presented with abnormal follicular development, such as luteinized, unruptured follicles.

Women in China had lower ovarian activity compared with the other sites. This finding is consistent with clinical trials of DMPA+E_2C in which higher rates of amenorrhea have been observed in Asian populations compared with in Western populations (1) and with other studies that have shown significant differences in medroxyprogesterone acetate pharmakinetics among different ethnic groups (11). In this study, the finding may also reflect the lower body mass index and older average age of the Chinese participants.

This study had a high completion rate and was conducted by experienced investigators in this field. It also had an adequate sample size for detecting equivalence between the day 5 and day 7 groups.

Women were recruited at clinics throughout South America and in China, yielding a diverse population for this study and making our findings more likely to be generalizable to a population of new DMPA+E_2C users.

It is difficult to extrapolate from these data what the likelihood of pregnancy is in women receiving DMPA+E_2C on day 7 of their cycle compared with those given DMPA+E_2C on day 5. However, because very few women ovulated and those that did had abnormal cycles, the probability of pregnancy is likely to be low in women receiving DMPA+E_2C on day 7 of their cycle, although slightly higher than on day 5.

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