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CONTRACEPTIVE CONTAINING 25 mg MEDROXYPROGESTERONE
ACETATE AND 5 mg ESTRADIOL-CYPIONATE:
EFFECTS ON CERVICAL MUCUS

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Delayed first injection of the once-a-month injectable contraceptive containing 25 mg medroxyprogesterone acetate and 5 mg estradiol-cypionate: effects on cervical mucus[☆]

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Abstract

The objectives of this study were to assess whether women who were administered the first injection of the once-a-month contraceptive containing estradiol cypionate and 25 mg depot-medroxyprogesterone acetate (MPA+E₂C) on Day 7 of their menstrual cycle (delayed injection) exhibit the same degree of cervical mucus changes as women who receive it on Day 5 of their menstrual cycle. This was a multicenter, randomized, controlled clinical trial. A total of 158 women, aged between 18 and 38 years (inclusive), who, were willing to use MPA+E₂C as their contraceptive method participated in the trial. Participants received a MPA+E₂C injection on Day 5 (control group, n = 41) or Day 7 (delayed-injection group, n = 117) of their menstrual cycle. Participants who received MPA+E₂C on Day 5 of their menstrual cycle (control group) exhibited fair or poor mucus quality and poor sperm penetration. Of those women who received MPA+E₂C on Day 7 of their menstrual cycle (delayed-injection group), 3 (3%) showed good mucus or good sperm penetration at some time point during follow-up. It is possible to conclude that the first injection of MPA+E₂C given on Day 7 of a menstrual cycle does not provide the same degree of inhibition of mucus quality and sperm penetration as that observed if it is administered on Day 5. However, the theoretical risk of pregnancy after receiving MPA+E₂C on Day 7 would be expected to be low. © 2002 Elsevier Science Inc. All rights reserved.

Keywords: Cyclofem; Contraception; Cervical mucus; Sperm penetration test

1. Introduction

The once-a-month injectable contraceptive containing 5 mg estradiol cypionate and 25 mg depot-medroxyprogesterone acetate (MPA+E₂C) (Cyclofem, Aplicaciones Farmacéuticas, Mexico, a registered trademark of The Con-

cept Foundation, Seattle, WA, USA, and Lunelle, Pharmacia, Peapack, NJ, USA) has been shown to be a highly effective and acceptable method [1,2].

Inhibition of ovulation is considered the primary mechanism of action. In a previous publication, the effects of MPA+E₂C on ovarian function were evaluated on two different regimens: first injection on the fifth or seventh day. The study concluded that although effective, the first injection of MPA+E₂C 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 [3].

However, in addition to ovulation inhibition, changes in cervical mucus may contribute to MPA+E₂C contraceptive efficacy, and, although it may not be the primary mecha-

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nism of action, it may be the first to be established. The effect on cervical mucus is considered of importance for the effectiveness of hormonal methods, especially with progestin-only methods, such as Norplant implants, progestin pills, and depot-medroxyprogesterone acetate (Depot-MPA), which is the same progestin compound in MPA+E₂C. Therefore, if cervical mucus and sperm penetration are highly impaired after the injection of MPA+E₂C on Day 7 of a menstrual cycle, the injection window for the first injection might be increased to the first 7 days of the cycle without an increased risk of pregnancy.

Increasing the window in which the first MPA+E₂C injection can be given to Day 7 of the menstrual cycle would provide greater access for women. This randomized, controlled trial assessed whether women who were administered MPA+E₂C on Day 7 of their menstrual cycle (delayed injection) exhibited the same indications of impaired fertility as women who were administered MPA+E₂C on Day 5 of their menstrual cycle. This article reports the changes in cervical mucus after the injection.

2. Materials and methods

2.1. 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, People's Republic of China (n = 40), between May 1998 and September 1999. Eligible women were between 18 and 38 years old (inclusive), had a normal medical history and physical examination, had not used hormonal contraception in the 4 months prior to entry to the study, and were not pregnant or breastfeeding. Participants were advised to use back-up contraception during the study. Written informed consent was obtained from women before enrollment and randomization. The study was approved by the Institutional Review Boards of the research sites, Family Health International and the World Health Organization (WHO).

The allocation sequence was computer generated by using a permuted block randomization scheme. 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 to 3 ratio according to sealed, opaque, sequentially numbered envelopes opened at screening/admission. Participants randomized to the control group established the level of cervical mucus quality and sperm penetration suppression assumed to be adequate for contraceptive protection. Participants randomized to the delayed-injection group were considered the study group. Participants, clinic staff, and study monitors were not masked to the assignment group. Statisticians and medical reviewers were masked during the trial.

Participants made up to seven clinic visits (screening,

Table 1
CMS components

Component	Range	Definition
Mucus volume	0–3	0 = 0 1 = 0.1 mL 2 = 0.2 mL 3 = 0.3 + mL
Consistency	0–3	0 = thick, highly viscous, premenstrual mucus 1 = mucus of intermediate viscosity 2 = mildly viscous mucus 3 = watery, minimally viscous, mid-cycle mucus
Ferning	0–3	0 = no crystallization 1 = atypical fern formation 2 = primary and secondary stem ferning 3 = tertiary and quaternary stem ferning
Spinnbarkeit	0–3	0 = <1 cm 1 = 1–4 cm 2 = 5–8 cm 3 = 9+ cm
Cellularity	0–3	0 = >20 cells/HPF or >1000 cells/mm ² 1 = 11–20 cells/HPF or 501–1000 cells/mm ² 2 = 1–10 cells/HPF or 1–500 cells/mm ² 3 = 0 cells

admission, and five follow-up visits at 1, 3, 5, 10, and 14 days post admission). The injection visit took place on Day 5 or 7 after the onset of the participant's menses. The first day of flow was designated Day 1. At each visit, blood samples were collected for estradiol levels, and cervical mucus was collected.

2.2. Outcome measures

Both cervical mucus and mucus penetration outcomes were examined in the analysis. From the cervical mucus samples, three variables were constructed: the cervical mucus score (CMS), the CMS scale, and the dichotomous variable good cervical mucus. Two mucus penetration outcomes were defined as mucus penetration test (MPT) scale and presence of permeable mucus.

2.2.1. CMS

We used a modified Insler scoring method to construct the CMS. The CMS ranged from 0–15 and was constructed by adding the five components listed in Table 1. The definitions of the components adhere to the guidelines established by WHO in the collection and scoring of cervical mucus [4].

2.2.2. CMS scale

Following a review of the literature on CMS and prior to analysis, the variable CMS scale was created from the CMS as follows:

- Poor: (0–5)
- fair: (6–10)
- Good: (11–15)

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Participants who were bleeding/spotting or who had too little mucus to collect during a visit were characterized as having poor cervical mucus.

2.2.3. Good cervical mucus

A dichotomous variable, good cervical mucus, was created and was defined as:

1 if cervical mucus scale is Good;

0 if cervical mucus scale is Poor or Fair;

2.2.4. MPT scale

An ordinal variable, MPT scale, was used to describe the presence and permeability of the cervical mucus based on the results of the MPT. This variable was defined, prior to analysis, as:

- A. No mucus: insufficient mucus to perform the test;
- B. No travel: mucus was obtained, but sperm did not travel the mucus column at all during the 60 min of the test;
- C. Some travel: sperm traveled along the mucus column, but did not reach the end;
- D. Traveled column: sperm reached the end of the mucus column within 60 min.

2.2.5. Presence of permeable mucus

From the MPT scale, a dichotomous variable, presence of permeable mucus, was constructed to reflect the ability of sperm to penetrate and travel the mucus column. This outcome was defined as:

0 Poor MPT—a lack of permeable mucus (MPT scale categories A and B);

1 Adequate MPT—the presence of permeable mucus (MPT scale categories C and D).

The primary comparisons were stratified Wilcoxon–Mann–Whitney tests, controlling for center, of the CMS scale on injection day and the maximum post-injection CMS scale. A stratified exact Cochran–Mantel–Haenszel test was used to compare the proportion of participants with good cervical mucus with the proportion of participants who ovulated. A chi-square test analogous to the Mantel–Haenszel test but appropriate for clustered data (e.g., repeated measurements taken from the same woman) was used to compare the CMS scale with the MPT scale, and a random effects logistic model was fit to assess the influence of CMS scale and other covariates on the presence of permeable mucus.

2.2.6. Estradiol levels

Estradiol serum levels were measured by using direct enzyme immunoassay kits provided by the WHO Collaborating Center for Research and Reference Services in the Immunoassay of Hormones in Human Reproduction, London, UK. The interassay coefficient of variation for low (76 pg/mL), middle (128 pg/mL), and high (327 pg/mL) pools

were 34.5%, 19.2%, and 7.2%, respectively. One center did not participate in the joint quality control scheme. The interassay coefficient of variation for this center ranged from 4.2 to 8.1% and intra-assay from 4.0 to 7.0%.

3. Results

A total of 160 participants were randomized to initiate MPA+E₂C: 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 post randomization, but prior to MPA+E₂C injection. She did not receive the injection and was, therefore, excluded from the treated population. Another participant was excluded from the treated population because, based on a review of her ultrasound results and progesterone level (18.6 ng/mL) at admission, she was found to be in the mid-luteal phase of her cycle. Both of these participants were in the delayed-injection group. Thus, the treated population was composed 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 the average body mass index was 24. Complete characteristics of participants, progesterone levels, and ultrasound results have been described previously [3].

The delayed-injection group had better CMS scores at baseline than did the control group ($p = 0.006$). At injection, 25% of the delayed-injection group had fair to good CMS compared to only 5% with fair CMS and no woman with good CMS in the control group. This could be expected because the range of estradiol in the control group was 12–88 pg/mL, whereas the range in the delayed-injection group was 12–279 pg/mL. One day after the injection, 14% in the delayed-injection group still had fair to good CMS, whereas the percentage of participants in the control group with fair CMS remained the same, 5% (Table 2). By Day 3, the post-injection maximum CMS scores for the Q2 groups were very similar ($p = 0.69$).

In the absence of a contraceptive hormone, one would expect an association between good cervical mucus and impending ovulation. In this population, although 25% had fair to good CMS, there were few participants who ovulated, 3% [3]. Three of the four women who ovulated, did so within 24 h of their injection and had low progesterone (<6 ng/mL). The fourth woman who was classified as having ovulated had uncertain dating by ultrasound and low progesterone (<2.6 ng/mL; Table 3). Within the delayed-injection group, there was no significant association between ovulation and good cervical mucus ($p = 0.18$). Only one participant in the delayed-injection group ovulated and had good cervical mucus at the same time.

The listing in Table 3 presents the CMS and timing of ovulation for participants who were classified as having ovulated [3]. Both ovulation and incidence of good cervical mucus occurred early after injection, by the second follow-up visit, or Day 10 of the participant's cycle. The

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Table 2
Distribution of cervical mucus scores, by follow-up visit

Characterization	Injection*		Day 1		Day 3		Day 5		Day 10		Day 14	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Control group												
Missing	0	(—)	0	(—)	1	(2)	1	(2)	2	(5)	1	(2)
Poor (0–5)	39	(95)	39	(95)	38	(93)	38	(93)	36	(88)	39	(95)
Fair (6–10)	2	(5)	2	(5)	2	(5)	2	(5)	3	(7)	1	(2)
Good (11–15)	0	(—)	0	(—)	0	(—)	0	(—)	0	(—)	0	(—)
TOTAL	41	(100)	41	(100)	41	(100)	41	(100)	41	(100)	41	(100)
Delayed injection group												
Missing	0	(—)	4	(3)	5	(4)	5	(4)	4	(3)	4	(3)
Poor (0–5)	88	(75)	97	(83)	106	(91)	108	(92)	110	(94)	112	(96)
Fair (6–10)	26	(22)	13	(11)	5	(4)	4	(3)	3	(3)	1	(1)
Good (11–15)	3	(3)	3	(3)	1	(1)	0	(—)	0	(—)	0	(—)
TOTAL	117	(100)	117	(100)	117	(100)	117	(100)	117	(100)	117	(100)

* Percentages may not add up to 100% because of rounding. Participants with scanty mucus or with spotting/bleeding were characterized as having poor cervical mucus.

occurrence of early ovulation was noted and discussed in our previous paper reporting the ovarian activity [3].

At each follow-up visit, at least 60% of the participants in both groups had insufficient mucus for the MPT. Of the participants who had mucus, participants in the delayed-injection group had better MPT scores throughout follow-up. At injection and 24-h observation, more participants in the control group had insufficient mucus to perform the MPT than in the delayed-injection group. Throughout follow-up, both groups had approximately the same proportion of participants with MPT where the sperm did not travel along the mucus column at all (Table 4).

Most of the participants had both poor CMS and poor MPT. None of the participants had good CMS and poor MPT. No participant in the control group had good CMS and good MPT, but a small proportion of participants in the delayed-injection group did. More participants in the control group than in the delayed-injection group had poor CMS and poor MPT (Table 5). CMS outcomes and MPT outcomes were strongly associated with one another ($p < 0.001$).

On the basis of the results of the random effects model, a participant in the delayed-injection group was more likely to have a higher MPT outcome than was a participant in the

Table 3
Ovarian function and CMS results for participants who ovulated

Participant	Day of follow-up	Ovarian Function				Cervical Mucus Results						
		Progesterone	Estradiol	Follicle Size	Ovulated	Volume	Consistency	Ferning	Spinnbarkeit	Cellularity	Score	Category
1010	Injection	0.3	51	17		3	1	1	2	1	8	Fair
	24 hr	0.4	120	16.5	Yes	3	2	1	3	2	11	Good
	Day 3	1.9	90	8		1	0	1	0	0	2	Poor
	Day 14	0.4	28	0		1	0	0	1	0	2	Poor
2041	Injection	1	279	19.5		0	2	2	1	0	5	Poor
	24 hr	0.6	655	21	Yes	0	1	0	1	0	2	Poor
	Day 3	1.5	389	6.5		0	1	0	1	0	2	Poor
	Day 5	2.6	305	6		0	1	2	1	1	5	Poor
	Day 10	0.4	103	4		0	0	0	0	0	0	Poor
3008	Day 14	0.4	18	5		0	1	2	1	0	4	Poor
	Injection	2.2	51	6.5	Uncertain	1	2	0	1	0	4	Poor
	24 hr	2.6	172	7	Uncertain	1	3	2	2	0	8	Fair
	Day 3	2.2	206	6	Uncertain	1	2	2	1	0	6	Fair
	Day 5	2.4	178	5.5	Uncertain	1	2	1	1	0	5	Poor
3023	Day 10	2.5	130	5	Uncertain	1	2	2	1	0	6	Fair
	Day 14	2.1	74	4.5	Uncertain	1	0	0	1	0	2	Poor
	Injection	0.8	124	12.5		1	2	2	1	1	7	Fair
	24 hr	1	181	15.5	Yes	1	2	2	2	0	7	Fair
	Day 3	2.5	98	9		1	1	0	0	0	2	Poor
3023	Day 5	5.9	121	4		1	1	1	1	0	4	Poor
	Day 10	2.9	129	4		1	2	2	1	0	6	Fair
	Day 14	0.8	53	5		1	3	2	1	0	7	Fair

Table 4
Distribution of mucus penetration scale, by follow-up visit

Characterization	Injection		24 h		Day 3		Day 5		Day 10		Day 14	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Control group												
Missing	0	(—)	0	(—)	1	(2)	1	(2)	2	(5)	1	(2)
No mucus	39	(95)	36	(88)	29	(71)	35	(85)	34	(83)	38	(93)
No sperm travel	0	(—)	0	(—)	3	(7)	1	(2)	1	(2)	1	(2)
Some traveling	2	(5)	4	(10)	8	(20)	4	(10)	4	(10)	1	(2)
Traveled whole column	0	(—)	1	(2)	0	(—)	0	(—)	0	(—)	0	(—)
Delayed injection group												
Missing	0	(—)	4	(3)	5	(4)	5	(4)	4	(3)	4	(3)
No mucus	72	(62)	83	(71)	87	(74)	83	(71)	95	(81)	104	(89)
No sperm travel	5	(4)	4	(3)	4	(3)	2	(2)	3	(3)	1	(1)
Some traveling	33	(28)	22	(19)	18	(15)	24	(21)	14	(12)	8	(7)
Traveled whole column	7	(6)	4	(3)	3	(3)	3	(3)	1	(1)	0	(—)

control group, and CMS scale was a strong predictor of MPT outcome ($p < 0.0001$). The estimated odds ratio was 15 (95% CI = 6.73, 35.37). Results were similar when we controlled for day of follow-up since maximum estrogen level (data not shown).

4. Discussion

MPA+E₂C administered on Day 7 of the menstrual cycle did not impair mucus quality and sperm penetration as well as did administration on Day 5. However, only a small percentage of women in the Day 7 group had both good cervical mucus and permeable cervical mucus.

MPA+E₂C administered on Day 5 suppressed cervical mucus quality and sperm penetration as expected. In fact, injection on Day 5 did not allow mucus to become good. Mucus scores on the day of injection were all low and never reached a good score, showing that the injection was able to block any improvement in quality that typically happens during the menstrual cycle. On the other hand, when the injection was given on Day 7, good mucus has already

developed in 3% of the cases. The injection was able to prevent the remaining participants from developing mucus of good quality, but it took up to 5 days until all mucus was of poor or fair quality. The effect on cervical mucus of MPA+E₂C was similar to those observed in studies evaluating the influence of Depot-MPA on cervical mucus despite of the presence of estradiol cypionate on the compound [5]. Although assessment of the cervical mucus may be somewhat subjective, it has been traditionally used to evaluate the effect of hormonal methods.

Similar sperm penetration results were observed. In the control group, permeability of mucus was less on injection day and remained so throughout follow-up. In the delayed injection group, 34% of women had some sperm penetration on the day of injection; permeability progressively decreased during follow-up. There was a strong association between the mucus scores and the ability of sperm to penetrate the mucus, an expected finding.

An important observation was the lack of association between mucus quality and sperm penetration among women who ovulated. In the delayed-injection group, only three women ovulated, and another one had an uncertain

Table 5
Joint distribution of good cervical mucus scores (CMS) and good mucus penetration tests (MPT)

Visit	Control group								Delayed injection group							
	Poor CMS/ poor MPT		Poor CMS/ good MPT		Good CMS/ poor MPT		Good CMS/ good MPT		Poor CMS/ poor MPT		Poor CMS/ good MPT		Good CMS/ poor MPT		Good CMS/ good MPT	
	n	(%)*	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Injection	39	(95)	2	(5)	0	(—)	0	(—)	77	(66)	37	(32)	0	(—)	3	(3)
24 h	36	(88)	5	(12)	0	(—)	0	(—)	87	(74)	23	(20)	0	(—)	3	(3)
Day 3	32	(78)	8	(20)	0	(—)	0	(—)	91	(78)	20	(17)	0	(—)	1	(1)
Day 5	36	(88)	4	(10)	0	(—)	0	(—)	85	(73)	27	(23)	0	(—)	0	(—)
Day 10	35	(85)	4	(10)	0	(—)	0	(—)	98	(84)	15	(13)	0	(—)	0	(—)
Day 14	39	(95)	1	(2)	0	(—)	0	(—)	105	(90)	8	(7)	0	(—)	0	(—)

* Percentages include missing MPT and CMS that are not tabulated.

ovulation. However, of these four participants, only one had good mucus. Of the 117 women observed during this study, this would be the woman considered at risk of getting pregnant, a theoretical risk lower than 1%. Even in this case, ovulation and good mucus occurred very early in the cycle, before Day 10, earlier than in a normal ovulatory cycle (Day 14), and her progesterone level was abnormal (<2 ng/mL) [6]. This may be due to medroxyprogesterone acetate triggering premature ovulation in already forming follicles, a phenomenon that has been discussed elsewhere [3].

Suppression of normal ovarian activity is considered a primary mechanism of MPA+E₂C's contraceptive efficacy [7,8]. However, the data presented in this article show that the effect on the quality of cervical mucus and its sperm penetrability may also be an important part of its contraceptive effectiveness, as is the case with progestin-only methods, such as pills, implants, and Depot-MPA [5,9].

Our results show that ovulation combined with good cervical mucus is an infrequent event when injection of MPA+E₂C is delayed to Day 7, and theoretically the chance of pregnancy is low, although higher than on Day 5. Based on these results, the injection window could possibly be extended to Day 7. However, this study did not assess the risk of pregnancy, and women should be counseled of the possibly higher chance of getting pregnant during the first week following injection when adopting this procedure.

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