

UC Irvine

UC Irvine Previously Published Works

Title

The potential for intramuscular depot medroxyprogesterone acetate as a self-bridging emergency contraceptive.

Permalink

<https://escholarship.org/uc/item/0482967j>

Authors

Schickler, Robyn

Crabtree-Sokol, Diana

Patel, Jasmine

et al.

Publication Date

2021

DOI

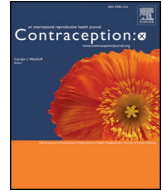
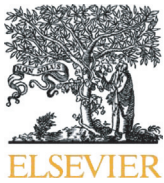
10.1016/j.conx.2020.100050

Copyright Information

This work is made available under the terms of a Creative Commons Attribution-NonCommercial-NoDerivatives License, available at

<https://creativecommons.org/licenses/by-nc-nd/4.0/>

Peer reviewed



The potential for intramuscular depot medroxyprogesterone acetate as a self-bridging emergency contraceptive[☆]



Robyn Schickler^{a,*}, Diana Crabtree-Sokol^a, Jasmine Patel^a, Nicole Bender^a,
Anita L. Nelson^{a,b}, Brian T. Nguyen^a

^a University of Southern California, Department of Obstetrics and Gynecology, Section of Family Planning, 2020 Zonal Ave Room 220, Los Angeles, CA, 90033, United States

^b Western University of Health Sciences, Department of Obstetrics and Gynecology, 1457 3rd St., Manhattan Beach, CA 90266-6335, United States

ARTICLE INFO

Article history:

Received 7 April 2020

Received in revised form 17 November 2020

Accepted 17 November 2020

Available online xxxx

Keywords:

Emergency contraception

Contraception

Birth control

Depot medroxyprogesterone acetate

Depo-Provera

ABSTRACT

Objective: To examine the rate of ovulatory disruption when intramuscular depot medroxyprogesterone acetate (DMPA) is administered across graded stages of dominant follicle development.

Study design: We assigned enrolled participants to one of three preassigned dominant follicle size groups: 12–14 mm, 15–17 mm and ≥ 18 mm. We followed dominant follicles via serial transvaginal ultrasound (TVUS) until the follicles reached their assigned size, at which time we administered DMPA. For 5 consecutive days thereafter, we followed the follicles via TVUS to observe follicle rupture and obtained serum luteinizing hormone (LH), estradiol, and progesterone concentrations. In the following 2 weeks, we collected serum progesterone concentrations twice weekly to detect possible ovulatory delay or dysfunction. We also collected serum medroxyprogesterone acetate (MPA) concentrations at 1 and 24 h after DMPA administration to examine against ovulatory outcomes.

Results: Twenty-six of 29 enrolled women completed the study. DMPA suppressed ovulation in 17/26 (65%) and caused ovulatory dysfunction in 1/26 (4%) participants. Larger follicles were more likely to rupture despite DMPA (12–14 mm: 0/10 (0%); 15–17 mm: 3/10 (30%); ≥ 18 mm: 6/6 (100%); $p < .01$). Pre-DMPA LH concentrations ranged from 13.8 to 93.7 IU/L (mean 49.0 IU/L) in cases of follicle rupture. We observed no cases of follicle rupture when DMPA was administered through cycle day 12. All 24-h MPA concentrations exceeded those needed for ovulation suppression.

Conclusion: DMPA suppressed and additionally disrupted ovulation in 65% and 4% of observed cycles, respectively. DMPA may provide effective emergency contraception as well as ongoing contraception if administered prior to an expected ovulation and specifically before the LH surge.

Implications: DMPA may be an alternative form of emergency contraception that can also self-bridge to ongoing contraception. As ovulation was not observed among any follicles when DMPA was given through cycle day 12, women who initiate DMPA up through cycle day 12 may not require backup contraception.

© 2020 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

1.1. The need for self-bridging emergency contraception

The increasing availability and uptake of oral levonorgestrel (LNG)-based emergency contraception (EC) over the last 2 decades has not decreased the rate of unintended pregnancy in the United States (US) [1,2]. While oral EC formulations containing LNG effectively disrupt ovulation when given prior to the luteinizing hormone (LH) surge, they do not provide ongoing contraception; women are advised to use a separate

method of contraception after using EC [2]. However, subsequent episodes of unprotected intercourse during the same cycle of EC use could result in unintended pregnancies [3,4].

As a result, “self-bridging” EC, a contraceptive that can both disrupt ovulation and provide ongoing contraception, may more effectively prevent unintended pregnancies. The only currently available method of self-bridging EC is the copper intrauterine device (IUD), which requires a trained provider and a readily available IUD at the time of patient need [5]. In addition, copper IUD users may experience heavier bleeding or more painful periods, negatively impacting the IUD’s acceptability and continuation [6,7]. Additional self-bridging EC methods are needed to expand the options available to women.

[☆] ClinicalTrials.gov Identifier: NCT03395756

* Corresponding author at: 2020 Zonal Ave #505, Los Angeles, CA 90033.

E-mail address: rschickler94@gmail.com (R. Schickler).

1.2. The potential use of depot medroxyprogesterone acetate

Depot medroxyprogesterone acetate (DMPA) is a contraceptive method that acts primarily by ovulation inhibition [8]; if able to prevent a dominant follicle from ovulating, DMPA may provide an additional method of self-bridging EC. Early pharmacokinetic and pharmacodynamic studies of DMPA suggested its potential for rapid-onset and lasting ovulation suppression. The serum metabolite of DMPA, medroxyprogesterone acetate (MPA), is detectable within 30 min of injection [8] and suppresses follicular activity within 24 h of administration when given within the first 5 days of the menstrual cycle [9]. MPA remains detectable and can suppress follicular activity for 120–270 days after injection [9,10] and may continue to suppress ovulation for up to 9 months following administration [9].

No studies have examined the potential for DMPA to be used as a self-bridging method of EC. The only study exploring DMPA's ability to prevent a dominant follicle from continuing to ovulation gave DMPA 150 mg to 30 women between cycle days 8 and 13 [11]. We organized this study's ovulation data by follicle size and found that DMPA suppressed ovulation in one of three participants with a dominant follicle size of 12–14 mm and in one of three participants with a dominant follicle size of 15–16 mm [11]. Cycle length varies among women, and cycle day is an unreliable indicator of the periovulatory period. Dominant follicle size is a more reliable marker of the late follicular phase, immediately preceding ovulation [12]. Consequently, we examined DMPA's ability to disrupt ovulation based on its administration during graded stages of follicle development.

2. Methods

Our study design drew from procedures utilized by Croxatto et al. [13–15] to investigate the use of other contraceptive steroid hormone preparations for EC. We conducted this pilot study at the Women's Ambulatory Clinic at LAC + USC Medical Center from August 2018 through May 2019, following approval from the University of Southern California Institutional Review Board and registration on clinicaltrials.gov (Identifier: NCT03395756).

2.1. Screening, enrollment and randomization

We recruited healthy English- and Spanish-speaking volunteers from LAC + USC Medical Center, the Keck School of Medicine, the University of Southern California, and the surrounding community. We explained the risks and benefits of study participation in the woman's preferred language and obtained informed consent after we answered her questions. Eligible candidates included women between the ages of 18 and 39 years, with a body mass index (BMI) of 18–30 kg/m², with documented cyclic menses (interval 24–35 days) for 3 months prior to enrollment and who reported use of nonhormonal contraception. The women recruited reported satisfaction with their current nonhormonal contraception but were willing to receive DMPA specifically for this study. We excluded candidates with any contraindication to progestin-only contraception per the Centers for Disease Control and Prevention Medical Eligibility Criteria (e.g., Category 3 or 4 conditions), medications that could alter or be altered by the concurrent use of DMPA, noninjection hormonal contraceptive use in the month prior to recruitment, DMPA use in the 10 months prior to recruitment or history of allergic reaction to DMPA. Screening included a basic physical exam and measurements of height, weight, blood pressure, pulse rate and a serum midluteal progesterone concentration to document ovulatory status (> 3 ng/mL). After participants demonstrated enrollment eligibility, they were randomized to a follicle diameter size group: 12–14 mm, 15–17 mm and ≥ 18 mm; group assignments were contained in randomly sorted opaque envelopes that were chosen with the participant at the time of enrollment.

2.2. Study design

We administered a single dose of intramuscular DMPA 150 mg/mL into the deltoid muscle of each participant; we purchased the DMPA from the manufacturers Greenstone and Amphastar. The University of Southern California Medical Plaza Pharmacy stored and dispensed DMPA for each participant.

2.3. Study procedures

Randomized participants underwent the following procedures during the study cycle:

2.3.1. Ultrasonography

We followed each participant's dominant follicle for growth and rupture via transvaginal ultrasound (TVUS). We calculated the mean diameter of the dominant follicle from measurements of two perpendicular dimensions within the same plane. We began baseline follicular assessment on cycle day 8 via TVUS and repeated the assessment every 2–3 days until the dominant follicle was identified and reached its preassigned size. Once a participant's dominant follicle reached the assigned size, we administered DMPA. If the participant's dominant follicle surpassed its assigned group size, the participant entered the group that corresponded to that follicle size. Following DMPA administration, we measured the dominant follicle daily by TVUS for 5 days or fewer if the follicle ruptured earlier.

2.3.2. Blood sampling and hormonal assays

We collected serum concentrations of estradiol, LH and progesterone at the time of DMPA administration and daily for the following 5 days. In addition, to account for the possibility of giving DMPA after an LH surge in the ≥ 18-mm group, we started collecting serial serum LH concentrations once the dominant follicle reached 15 mm. To detect ovulations occurring after the 5-day DMPA follow-up window, we collected serum progesterone concentrations twice weekly for the next 2 weeks. We collected serum MPA concentrations at 1 and 24 h after DMPA administration to assess the relationship between MPA concentrations and ovulatory outcomes.

We measured progesterone and estradiol using radioimmunoassay following organic solvent extraction and Celite column partition chromatography. Interassay coefficients of variation (CVs) ranged from 8% to 12%. We measured LH using a chemiluminescent immunometric assay on the Immulite analyzer (Siemens Healthcare Diagnostics, Deerfield, IL, USA). The interassay CV was < 8%. MPA concentrations were measured in the Endocrine Technologies Core (ETC) at Oregon National Primate Research Center (ONPRC) with a Shimadzu Nexera-LCMS-8050 liquid chromatography–tandem triple quadrupole mass spectrometry platform (Shimadzu Scientific, Kyoto, Japan) using a previously published method [16]. Accuracy was 90.1%, with intra-assay CV at 3.2%. All samples were analyzed in a single assay; no interassay CV was calculated.

2.4. Outcomes definitions

We used the ultrasound and hormone-based criteria by Croxatto et al. [13–15] to define our ovulatory outcomes but modified the definition of ovulatory dysfunction more conservatively to avoid overestimating DMPA's ability to suppress ovulation:

- Follicular rupture: follicle ≥ 15 mm in diameter with sudden decrease in size by ≥ 50%.
- Ovulation: follicular rupture preceded 24–48 h by an LH surge (≥ 21 IU/L), followed by a serum progesterone > 3 ng/mL.
- Ovulation suppression:
 - Persistent enlarged follicle: follicle ≥ 15 mm persisting for at least 1 week without follicular rupture and without any progesterone > 3 ng/mL.

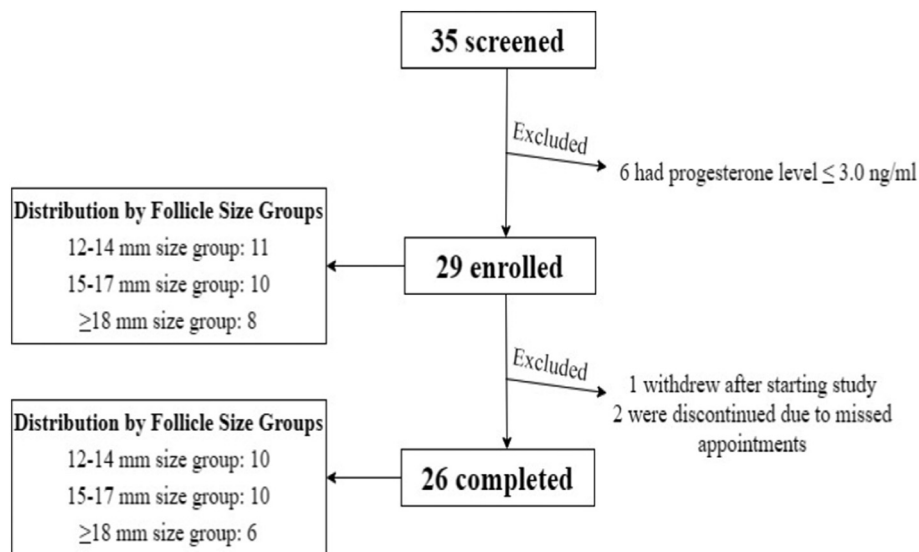


Fig. 1. Participant screening, enrollment and study completion.

- Luteinized unruptured follicle: persistent follicle associated with at least one progesterone concentration > 3 ng/mL.
- Follicular atresia: arrest in growth or decrease in size of a dominant follicle <15 mm without any progesterone > 3 ng/mL.
- Standard definition by Croxatto et al. for ovulatory dysfunction: follicular rupture not preceded by an LH peak or preceded by a blunted (<21 IU/L) LH peak OR without any progesterone > 3 ng/mL.
- Modified definition for ovulatory dysfunction used in this study: follicular rupture not preceded by an LH peak or preceded by a blunted (<21 IU/L) LH peak AND without any progesterone > 3 ng/mL.

2.5. Data analysis

All statistical analyses used STATA version 15.1. We used one-way analysis of variance testing to compare baseline demographic data between groups and descriptive statistics for assay results and ovulatory outcomes.

3. Results

Thirty-five women underwent screening: 29 had midluteal progesterone levels that were adequate for enrollment; 6 women had midluteal progesterone concentrations ≤3 ng/mL and were excluded. Of those enrolled, 2 participants were excluded due to missed appointments during pre-DMPA follicle evaluation, and 1 participant withdrew consent after enrollment and prior to receiving DMPA; all the remaining 26 women completed the study (Fig. 1).

3.1. Baseline characteristics

The 26 study-completing participants comprised three follicle size groups as follows: 12–14 mm (n = 10), 15–17 mm (n = 10) and ≥18 mm (n = 6).¹ After random group assignment, we moved three participants into different groups. We moved one participant from the 12–14-mm group into the 15–17-mm group due to a rapid increase in her follicle size and moved two participants from the ≥18-mm group to the 12–14-mm group to shorten the follicle screening period due to participant time constraints. Participants across groups shared similar baseline demographics (Table 1). The mean leading follicle diameters fell well within their respective group’s size range, without being skewed

¹ Of note, our initial intent was to include 10 participants in the ≥18-mm group. However, given consistent findings of ovulation on interim analysis, further recruitment was not expected to yield differing results.

by extreme values. Increasing baseline levels of estradiol correlated with increasing follicle size (r = 0.676; Table 2).

3.2. Ovulatory outcomes

DMPA suppressed ovulation in 17/26 (65%) of all cycles. We observed no ovulations when we administered DMPA at follicle size of less than 16 mm or through cycle day 12. Six of 10 unruptured follicles from the 12–14-mm group underwent follicular atresia; the remaining 4 were classified as persistently enlarged follicles. All 7 unruptured follicles from the 15–17-mm group remained persistently enlarged. Maximum estradiol concentrations in participants with unruptured follicles

Table 1 Baseline demographics of participants in each dominant follicle size group (groups based on the dominant follicle size at time of DMPA administration)

	12–14 mm n = 10 (%)	15–17 mm n = 10 (%)	≥18 mm n = 6 (%)
<i>Age</i>			
Mean ± SD (years)	22.4 ± 3.7	23.0 ± 4.3	23.0 ± 4.7
Range, years	18–29	18–33	18–31
<i>BMI</i>			
Mean ± SD (kg/m ²)	23.9 ± 2.9	21.0 ± 1.8	22.7 ± 4.7
Range, kg/m ²	18.0–28.6	18.2–24.1	18.3–29.7
<i>Cycle length</i>			
Mean ± SD (days)	30.5 ± 3.0	30.2 ± 1.9	31 ± 1.5
Range (days)	26–35	27–33	28–34
<i>Ethnicity</i>			
Hispanic	1 (10)	0	1 (17)
Non-Hispanic	9 (90)	10 (100)	5 (83)
<i>Race</i>			
White	4 (40)	5 (50)	4 (67)
Black	2 (20)	1 (10)	1 (17)
Asian	3 (30)	4 (40)	1 (17)
Native American	1 (10)	0	0
<i>Education</i>			
≤High school	0	0	0
Some college	7 (70)	5 (50)	3 (50)
College graduate	2 (20)	3 (30)	3 (50)
Graduate degree	1 (10)	1 (10)	0
Did not disclose	0	1 (10)	0

p values >.05 for all comparisons.

Table 2

Mean dominant follicle diameter and estradiol concentration at the time of DMPA administration for each dominant follicle size group (groups based on the dominant follicle size at time of DMPA administration)

	Dominant follicle size at time of DMPA administration		
	12–14 mm (n = 10)	15–17 mm (n = 10)	≥18 mm (n = 6)
Mean follicle diameter ± SD (mm)	13.0 ± 0.6	15.7 ± 0.6	19.0 ± 0.9
Range, mm	12.0–13.8	15.1–16.7	18.0–20.4
Mean estradiol concentration ± SD (pg/mL)	88.2 ± 45.5	168.3 ± 92.1	209.2 ± 61.9
Range, pg/mL	41.9–171	79.9–391	161–317

R (correlation coefficient) = 0.676, suggesting a positive linear relationship between mean dominant follicle size and mean estradiol concentration at time of DMPA administration.

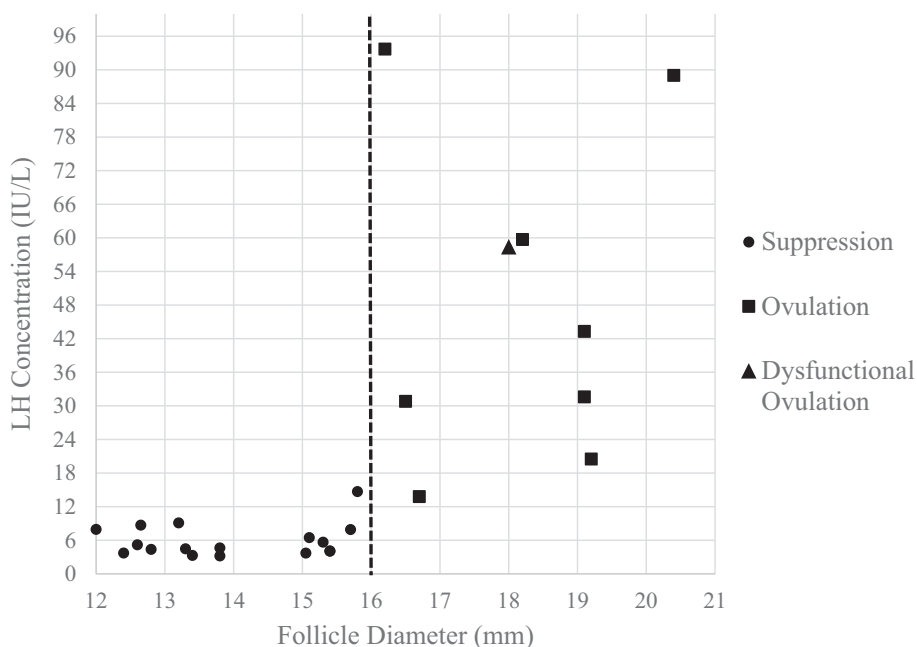


Fig. 2. Ovulatory outcomes according to leading follicle diameter and LH concentration at DMPA administration. The dotted line separates ovulations from nonovulations.

ranged from 70.3 to 318 pg/mL.

We observed ultrasound-defined follicle rupture in nine participants; the likelihood of rupture increased with follicle size (12–14 mm: 0/10, 15–17 mm: 3/10, ≥18 mm: 6/6). Follicle rupture occurred consistently among participants receiving DMPA at the time of an LH surge, except for one case in group B where follicle rupture occurred with LH 13.8 IU/mL prior to DMPA administration (Fig. 2). We classified this participant as having ovulated. We classified one case as ovulatory dysfunction following ultrasound-detected follicle rupture, which occurred in the ≥18-mm group; in this case, serum LH reached ≥21 IU/L and estradiol reached 174 pg/mL, but progesterone remained <3 ng/mL. Table 3a shows the results for the ovulatory outcomes based on our modified definition of ovulatory dysfunction. For comparison, Table 3b shows our results based on the standard definition of ovulatory dysfunction by Croxatto et al. [13–15]. During the 2-week follow-up period, maximum progesterone concentrations ranged from 3.31 to 12.8 ng/mL in cases of ovulation, while the maximum progesterone concentration in the case of ovulatory dysfunction was 0.964 ng/mL. All cases of follicle rupture occurred with dominant follicles at or beyond 16 mm, inclusive of the single case of ovulatory dysfunction (Fig. 3).

3.3. Serum MPA concentrations

Six participants did not provide 1-h serum MPA concentrations; however, all provided 24-h MPA concentrations. In all but two participants, serum MPA concentrations at both time intervals were above 0.2 ng/mL, the estimated threshold for contraceptive effect (Fig. 4)

[17]. The two MPA concentrations below the efficacy threshold were drawn at 1 h post-DMPA administration – one participant from the 15–17-mm group (BMI 24 kg/m²) had a persistently enlarged follicle; the other participant from the ≥18-mm group (BMI 29.7 kg/m²)

Table 3a

Outcomes of ruptured and unruptured dominant follicles during the 5 days following DMPA administration according to dominant follicle diameter at the time of DMPA administration using this study's conservative definitions of ovulation and ovulatory dysfunction^a

	12–14 mm n = 10 (%)	15–17 mm n = 10 (%)	≥18 mm n = 6 (%)
No follicular rupture	10 (100)	7 (70)	0 (0)
Follicular atresia ^b	6 (60)	–	–
Persistently enlarged follicle ^c	4 (40)	7 (100)	–
Luteinized unruptured follicle ^d	–	–	–
Follicular rupture	0	3(30)	6 (100)
Ovulation dysfunction ^e	–	–	1 (17)
Ovulation ^f	–	3 (100)	5 (83)

^a Ovulatory dysfunction is defined conservatively to avoid overestimation of DMPA's ability to disrupt ovulation.

^b Follicle <15 mm that arrests growth or decreases in size by <50%; progesterone remains ≤3 ng/mL.

^c Follicle ≥15 mm that persists for at least 1 week; progesterone remains ≤3 ng/mL.

^d Follicle ≥15 mm that persists for at least 1 week; progesterone rises to >3 ng/mL.

^e Follicle ≥15 mm that disappears or decreases in size by ≥50% not preceded by an LH surge; progesterone remains ≤3 ng/mL.

^f Follicle ≥15 mm that disappears or decreases in size by ≥50% preceded by an LH surge; progesterone rises to >3 ng/mL.

Table 3b

Outcomes of ruptured and unruptured dominant follicles during the 5 days following DMPA administration according to dominant follicle diameter at the time of DMPA administration using standard definitions of ovulation and ovulatory dysfunction, as used by Croxatto et al. [13–15]

	12–14 mm = 10 (%)	15–17 mm = 10 (%)	≥ 18 mm = 6 (%)
No follicular rupture	10 (100)	7 (70)	0 (0)
Follicular atresia ^a	6 (60)	–	–
Persistently enlarged follicle ^b	4 (40)	7 (100)	–
Luteinized unruptured follicle ^c	–	–	–
Follicular rupture	0	3 (30)	6 (100)
Ovulation dysfunction ^d	–	1 (33)	1 (17)
Ovulation ^e	–	2 (67)	5 (83)

^a Follicle < 15 mm that arrests growth or decreases in size by < 50%; progesterone remains ≤ 3 ng/mL.

^b Follicle ≥ 15 mm that persists for at least 1 week; progesterone remains ≤ 3 ng/mL.

^c Follicle ≥ 15 mm that persists for at least 1 week; progesterone rises to > 3 ng/mL.

^d Follicle ≥ 15 mm that disappears or decreases in size by ≥ 50% not preceded by an LH surge OR without any progesterone rise to > 3 ng/mL.

^e Follicle ≥ 15 mm that disappears or decreases in size by ≥ 50% preceded by an LH surge; progesterone rises to > 3 ng/mL.

ovulated. Of the five participants considered to be overweight by BMI, four were in the 12–14-mm size group, all had 1-h MPA concentrations > 0.2 IU/L, and DMPA suppressed ovulation in all these participants. The fifth participant was in the ≥ 18-mm size group and is mentioned above. We found no statistically significant differences in the mean 1-h MPA concentration between follicle size groups or between participants with normal BMI and those with BMI > 24 kg/m².

4. Discussion

We report the first detailed pharmacokinetic and pharmacodynamic evaluation of DMPA given in the periovulatory period for emergency contraception. In this study, DMPA completely suppressed ovulation or caused ovulatory dysfunction in almost 70% of participants, a rate similar to that observed in similar studies using oral LNG (79%) [15]. For reference, Table 4 shows the proportion of ovulation suppression and dysfunction in similarly conducted studies of the Yuzpe regimen, oral LNG EC, and the Nestorone/ethinyl estradiol (NES/EE) vaginal ring [13–15].

We classified eight out of nine follicle ruptures as ovulations and one as ovulatory dysfunction. Notably, one of the cases we classified as ovulation did not necessarily fit the criteria in our definition for ovulation: “follicular rupture preceded 24–48 h by an LH surge (≥ 21 IU/L), followed by a

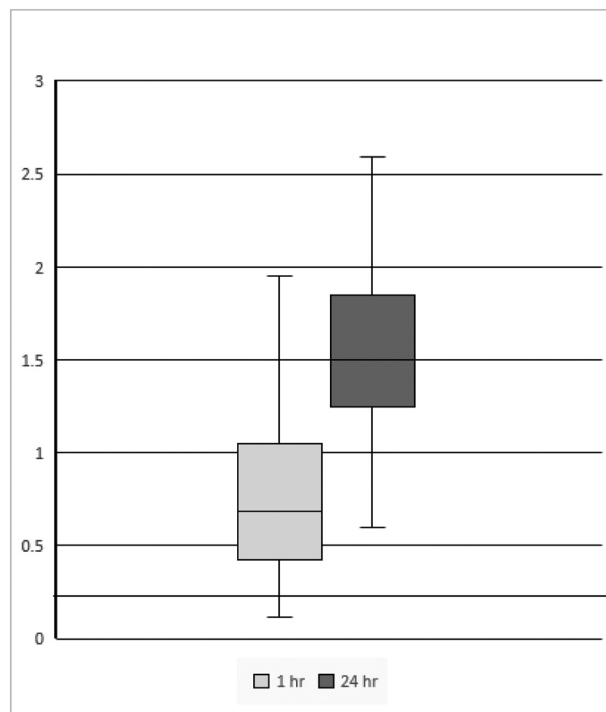


Fig. 4. Serum MPA levels at 1 and 24 h after DMPA administration (ng/mL). The dashed line at 0.2 ng/mL represents the estimated serum MPA level considered necessary for contraceptive effect [18].

serum progesterone > 3 ng/mL.” In this case, we observed follicle rupture on ultrasound and obtained a maximum progesterone of 4.11 ng/mL. However, we obtained a lower than expected LH concentration of 13.8 IU/L. The estradiol concentration at the time of DMPA administration was 240 pg/mL. Based on the combination of an elevated estradiol concentration on the first day of serum hormone assessments, ultrasound-identified follicle rupture and subsequent rise in progesterone to > 3 ng/mL, we surmise that the LH surge occurred prior to the time we started serum LH assessments. Based on the pulsatile nature of LH secretion, serial daily assessment is not as precise as more frequent assessments may be and is more likely to result in missing an LH surge. If we were to classify the above-mentioned case as an ovulatory dysfunction because of a lower than expected LH concentration, we believe we

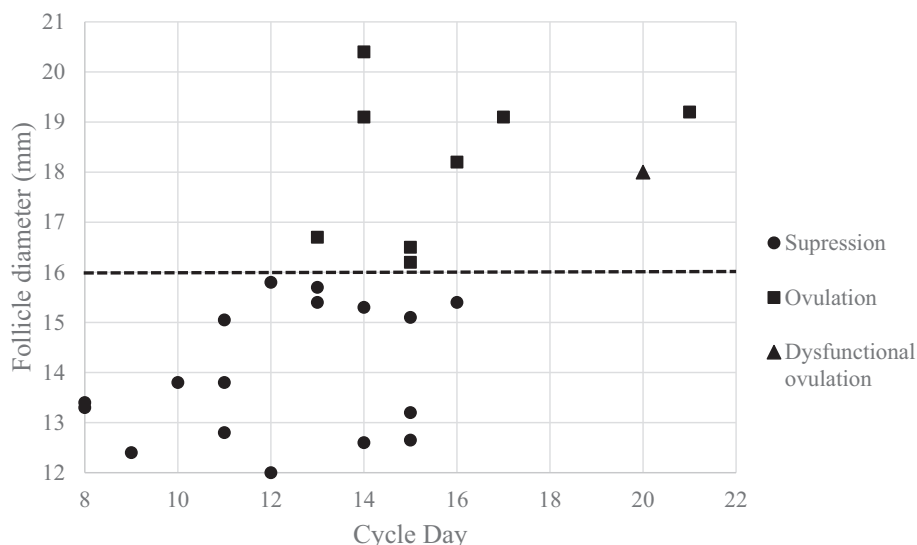


Fig. 3. Ovulatory outcomes according to follicle diameter and cycle day of DMPA administration. The dotted line separates the ovulations from nonovulations.

Table 4

Proportion of cycles with ovulation suppression compared to the proportion of cycles with both ovulation suppression and dysfunctional ovulation in studies of the Yuzpe regimen, LNG-EC, NES/EE ring as EC and DMPA as EC (this study)

Method	Proportion of cycles with ovulation suppression + dysfunction	Proportion of cycles with ovulation suppression	Proportion of cycles with ovulatory dysfunction
Yuzpe [14]	63%	43%	20%
LNG EC [15]	79%	44%	35%
NES/EE ring [13]	87%	56%	31%
DMPA (this study)	69%	65%	4%

would have overestimated DMPA's ability to disrupt ovulation.

Additionally, with respect to the case ovulatory dysfunction, we obtained an adequate LH concentration ≥ 21 IU/L in the setting of follicle rupture but found progesterone concentrations no higher than 0.964 ng/mL. Given the low progesterone concentration, we did not consider this case a true ovulation. Rather than strictly adhering to the aforementioned definitions, we individualized the analysis of these two cases, taking into account longitudinal follicle data and our data on estradiol and progesterone concentrations, as well as ultrasound findings.

Currently, DMPA product labeling recommends the use of backup contraception if DMPA is administered beyond the first 5 days of the menstrual cycle [18]; the Centers for Disease Control and Prevention recommend backup contraception if given after the first 7 days of menses [19]. However, as we did not observe any ovulations when we administered DMPA through cycle day 12, the 7-day period during which DMPA is given without the need for backup contraception could potentially be extended to 12 days if supported by confirmatory research.

Additionally, the standard in some family planning clinics is to use the *Quick Start* method when initiating or restarting DMPA, a practice shown to enhance adherence and result in very low pregnancy rates [20,21]. Published studies using the *Quick Start* method for DMPA give LNG EC to participants who have had unprotected intercourse in the 5 days prior to DMPA administration [20,22]. Our study shows that DMPA given alone as EC in the periovulatory period causes similar rates of ovulation suppression as LNG EC, which may suggest that taking LNG EC along with DMPA does not necessarily provide an added benefit. Certainly, we cannot make concrete conclusions based on our study of 26 participants, but such findings warrant larger and more inclusive studies to determine the need for LNG EC when using *Quick Start* DMPA administration.

Nevertheless, two concerns arise from using DMPA as EC or allowing later initiation through cycle day 12: (1) DMPA cannot be removed once administered due to its long half-life and continual secretion over time; (2) in addition, DMPA-induced amenorrhea could delay detection of an incidental pregnancy. Fortunately, DMPA exposure in utero has not been linked to any short- or long-term risks [18]. If DMPA were administered as EC or later in the cycle, we would recommend that the woman perform a urine pregnancy test 2 weeks after administration to avoid delaying the diagnosis of pregnancy. Additionally, prior to administering DMPA, clinicians with immediate access to ultrasound could scan the ovaries to check mean follicle size – if greater than 15 mm, DMPA may be more likely to fail, and the clinician may consider an alternative EC method, such as ulipristal.

We note that our results are generalizable primarily to healthy, young women with a normal, average BMI. We included very few overweight women (five total) and did not include any women with BMI ≥ 30 kg/m². Nevertheless, as oral LNG-EC is less effective in women with a BMI of ≥ 25 kg/m² [4,23], DMPA may provide a potentially better alternative given that the efficacy of DMPA as an ongoing method is not diminished among obese women [24]. Additionally, in our study, MPA reached concentrations considered necessary to inhibit ovulation by 1 h in all but two participants. One participant from the 15–17-mm group (BMI 24 kg/m²) had a persistently enlarged follicle; the other participant from the ≥ 18 -mm group (BMI 29.7 kg/m²) ovulated. MPA concentrations were not significantly different between participants with normal BMI and those with BMI ≥ 25 kg/m². Further, DMPA suppressed ovulation when administered prior to an LH surge, regardless of BMI or serum MPA concentration. Follicle size and LH concentration at time of method initiation may have a greater influence on ovulation suppression than BMI or MPA concentration. Future studies should additionally examine the effectiveness of DMPA for ovulation suppression among overweight and obese women. With 26 participants in this pilot study, our conclusions are limited by sample size. However, these encouraging findings suggest the value of future, more adequately powered studies to examine the use of DMPA as a self-bridging EC.

Acknowledgments

Funding: This work was supported by the Society of Family Planning [grant number SFPRF18].

We would like to acknowledge Angelica Mora, our research coordinator; Giana Cross, our medical student who worked on the research team; ETC at the ONPRC, supported by NIH Grant P51 OD011092 awarded to the ONPRC, for serum MPA analysis; and REDCap Online database software, used for data collection, supported by grants UL1TR001855 and UL1TR000130 from the National Center for Advancing Translational Science (NCATS) of the U.S. National Institutes of Health.

Declaration of competing interests

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Dr. Nelson receives grants from Agile Pharmaceutical, EvoFem, Merck and Sebela Pharmaceutical. She is on the Speakers Bureau for American Regent, TherapeuticsMD, Bayer HealthCare and Merck. She is also a consultant for and on the advisory board for AMAG, Agile Pharmaceutical, American Regent, Bayer HealthCare, Merck, Sebela

Pharmaceutical and TherapeuticsMD. The remaining authors have no relevant conflicts to disclose.

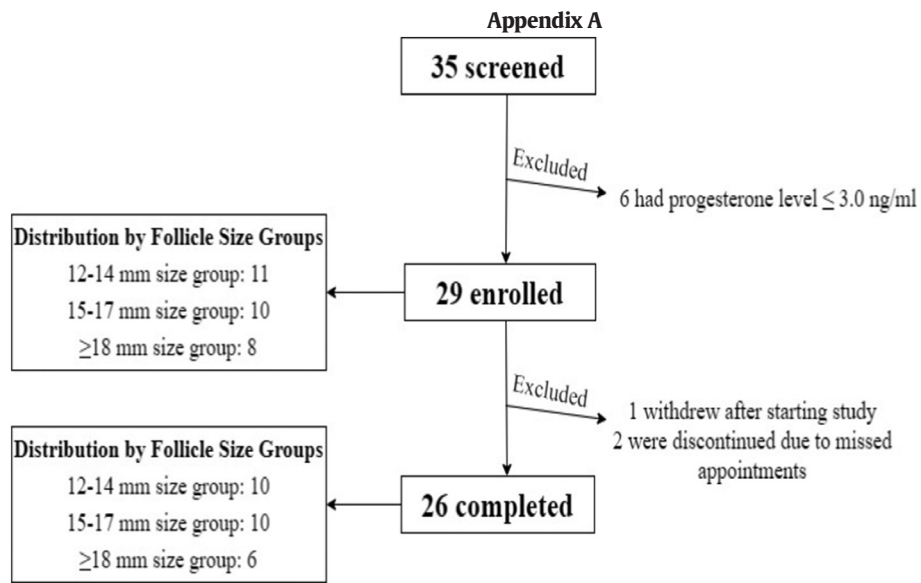


Fig. A1. Ovulatory outcomes according to maximum estradiol concentration in the 5 days following DMPA administration and follicle diameter at time of DMPA administration.

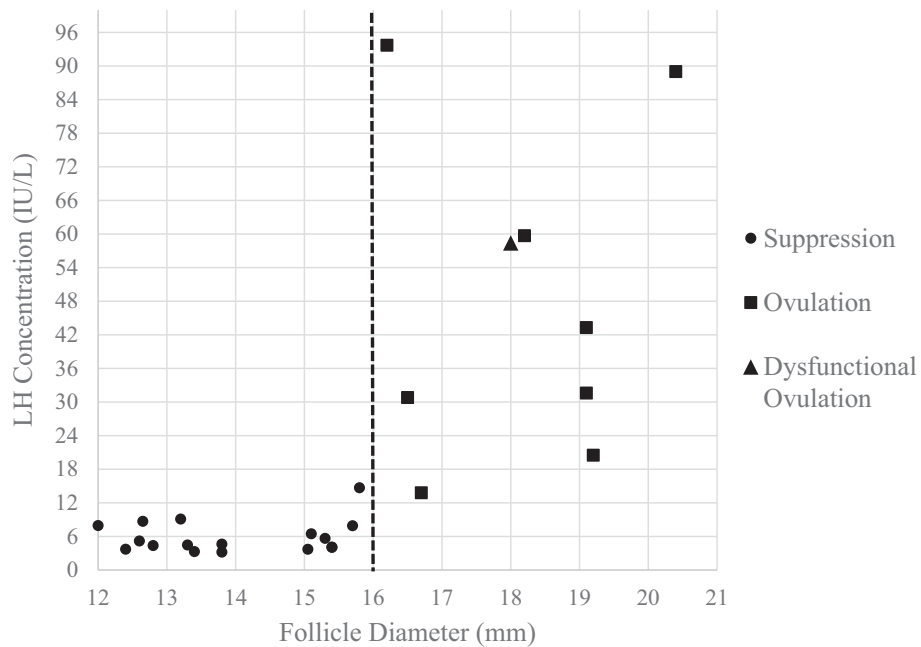


Fig. A2. Ovulatory outcomes according to maximum progesterone concentration during the 2-week follow-up period and follicle diameter.

Appendix B

Table B1

Follicle diameter and estradiol, LH and progesterone concentrations during the 5 days following DMPA administration, and progesterone levels during the 2-week follow-up period for cases of follicle rupture

		Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	2-Week follow-up				
Case ID												
B-04	Follicle size (mm)	16.2	Rupture	–	–	–	–					
	E2 level (pg/mL)	149	77.8	37.8	68.1	62.3	78					
	LH level (IU/L)	93.7	7.79	5.22	5.42	4.58	2.82					
	P level (ng/mL)	0.66	0.85	1.58	2.81	2.77	4.48	4.52	3.45	0.42	0.28	
B-05	Follicle size (mm)	16.7	17.8	Rupture	–	–	–					
	E2 level (pg/mL)	240	152	38.3	110	130	110					
	LH level (IU/L)	13.8	10	9.4	14.7	9.17	1.96					
	P level (ng/mL)	0.42	0.41	0.94	1.94	4.11	3.23	3.31	0.89	0.31	0.49	
B-06	Follicle size (mm)	16.5	18.8	13.8	Rupture	–	–					
	E2 level (pg/mL)	391	162	43.9	94.5	112	138					
	LH level (IU/L)	30.8	4.77	3.58	8.42	3.47	2.05					
	P level (ng/mL)	0.61	0.77	1.48	4.25	7.06	9.03	12.8	0.82	0.41	0.42	
C-01	Follicle size (mm)	18.2	Rupture	–	–	–	–					
	E2 level (pg/mL)	155	23.1	31.8	64.4	86.5	80					
	LH level (IU/L)	59.7	5.37	3.59	6.11	6.15	5.14					
	P level (ng/mL)	0.95	1.17	2.29	5.70	9.43	9.16	6.34	3.44	0.43	0.23	
C-02	Follicle size (mm)	20.4	Rupture	–	–	–	–					
	E2 level (pg/mL)	317	106	46.5	151	200	210					
	LH level (IU/L)	89	10.9	3.55	18.8	12.1	4.93					
	P level (ng/mL)	0.65	0.66	1.67	2.91	5.02	6.13	7.75	1.73	<0.20	<0.20	
C-04	Follicle size (mm)	18	Rupture	–	–	–	No					No
	E2 level (pg/mL)	174	92.1	67.6	53.7	71	Data					Data
	LH level (IU/L)	58.4	4.1	3.25	5.96	2.11						
	P level (ng/mL)	0.97	0.86	0.81	0.91	1.05		0.96	0.70	0.82		
C-05	Follicle size (mm)	19.1	18.2	Rupture	–	No	–					
	E2 level (pg/mL)	161	135	30.9	58.1	Data	71.2					
	LH level (IU/L)	31.6	15.5	6.25	13		6.04					
	P level (ng/mL)	0.468	0.567	1.17	1.88		3.67	5.13	4.95	0.40	0.271	
C-06	Follicle size (mm)	19.1	16.8	Rupture	–	–	–					
	E2 level (pg/mL)	241	45.2	50.2	93.9	98.9	89.9					
	LH level (IU/L)	43.3	2.97	2.57	8.72	11.3	4.99					
	P level (ng/mL)	1.32	1.99	2.58	5.42	6.83	9.11	6.17	2.47	0.42	0.28	
C-07	Follicle size (mm)	19.2	19.6	17.9	Rupture	–	–					
	E2 level (pg/mL)	207	286	75	114	109	163					
	LH level (IU/L)	20.5	12.3	12.5	14.1	12.1	9.97					
	P level (ng/mL)	0.28	0.29	0.62	1.79	2.72	3.93	4.57	4.30	0.27	<0.20	

References

- [1] Daniels K, Jones J, Abma J. Use of emergency contraception among women aged 15–44: United States, 2006–2010. NCHS Data Brief [Internet]. 2013(112):1–8.
- [2] Crosignani PG. Emergency contraception. Widely available and effective but disappointing as a public health intervention: a review. Hum Reprod. 2015;30(4):751–60.
- [3] Wilcox AJ, Weinberg CR, Baird DD. Timing of sexual intercourse in relation to ovulation. Obstet Gynecol Surv. 1996;51(6):357–8.
- [4] Glasier A, Cameron ST, Bliithe D, Scherrer B, Mathe H, Levy D, et al. Can we identify women at risk of pregnancy despite using emergency contraception? Data from randomized trials of ulipristal acetate and levonorgestrel. Contraception. 2011;84(4):363–7.
- [5] Harper CC, Speidel JJ, Drey EA, Trussell J, Blum M, Darney PD. Copper intrauterine device for emergency contraception: clinical practice among contraceptive providers. Obstet Gynecol [Internet]. 2012;119(2 Pt 1):220–6.
- [6] Wu S, Godfrey EM, Wojdyla D, Dong J, Cong J, Wang C, et al. Copper T380A intrauterine device for emergency contraception: a prospective, multicentre, cohort clinical trial. BJOG An Int J Obstet Gynaecol. 2010;117(10):1205–10.
- [7] Rowe P, Farley T, Peregoudov A, Piaggio G, Boccard S, Landoulsi S, et al. Safety and efficacy of a 52 mg levonorgestrel-medicated intrauterine device: a seven year randomized comparative study with the TCu380A. Contraception [Internet]. 2016;93(6):498–506.
- [8] Mishell DR. Pharmacokinetics of depot medroxyprogesterone acetate contraception. J Reprod Med. 1996;41(5 Suppl):381–90.
- [9] Ortiz A, Hiroi M, Stanczyk FZ, Goebelsmann U, Mishell DR. Serum medroxyprogesterone acetate (MPA) concentrations and ovarian function following intramuscular injection of depo-MPA. J Clin Endocrinol Metab. 1977;44(1):32–9.
- [10] Fotherby K, Koetsawang S, Mathrubuthan M. Pharmacokinetic study of different doses of Depo Provera. Contraception. 1980;22(5):527–36.
- [11] Petta CA, Faúndes A, Dunson TR, Ramos M, DeLucio M, Faúndes D, et al. Timing of onset of contraceptive effectiveness in depo-provera users. II. Effects on ovarian function. Fertil Steril. 1998;70(5):817–20.
- [12] Hamilton Carl. JCM; Evers, Johannes LH; Tan, Frans ES; Hoogland HJ. The reliability of ovulation prediction by a single ultrasonographic follicle measurement. Hum Reprod. 1987;2(2):103–7.
- [13] Croxatto HB, Brache V, Massai R, Alvarez F, Forcelledo ML, Pavez M, et al. Feasibility study of Nestorone®-ethinylestradiol vaginal contraceptive ring for emergency contraception. Contraception. 2006;73(1):46–52.
- [14] Croxatto HB, Fuentealba B, Brache V, Salvatierra AM, Alvarez F, Massai R, et al. Effects of the Yuzpe regimen, given during the follicular phase, on ovarian function. Contraception. 2002;65(2):121–8.
- [15] Croxatto HB, Brache V, Pavez M, Cochón L, Forcelledo ML, Alvarez F, et al. Pituitary-ovarian function following the standard levonorgestrel emergency contraceptive dose or a single 0.75-mg dose given on the days preceding ovulation. Contraception. 2004;70(6):442–50.
- [16] Blue SW, Winchell AJ, Kaucher AV, Lieberman RA, Gilles CT, Pyra MN, et al. Simultaneous quantitation of multiple contraceptive hormones in human serum by LC-MS/MS. Contraception. 2018;97(4):363–9.
- [17] Jain J, Dutton C, Nicosia A, Wajszczuk C, Bode FR, Mishell DR. Pharmacokinetics, ovulation suppression and return to ovulation following a lower dose subcutaneous formulation of Depo-Provera®. Contraception. 2004;70(1):11–8.
- [18] Pharmacia and Upjohn Company LLC. DEPO-PROVERA—medroxyprogesterone acetate injection, suspension [Internet]. 2017.
- [19] Curtis KM, Jatlaoui TC, Tepper NK, Zapata LB, Horton LG, Jamieson DJ, et al. U.S. selected practice recommendations for contraceptive use, 2016. MMWR Recomm Reports [Internet]. 2016;65(4):1–66.
- [20] Rickert VI, Tiezzi L, Lipshutz J, León J, Vaughan RD, Westhoff C. Depo Now: preventing unintended pregnancies among adolescents and young adults. J Adolesc Health. 2007;40(1):22–8.
- [21] Nelson AL, Katz T. Initiation and continuation rates seen in 2-year experience with same day injections of DMPA. Contraception. 2007;75(2):84–7.
- [22] Kohn JE, Simons HR, Della Badia L, Draper E, Morfesis J, Talmont E, et al. Increased 1-year continuation of DMPA among women randomized to self-administration: results from a randomized controlled trial at Planned Parenthood. Contraception. 2018;97(3):198–204.

- [23] Kapp N, Abitbol JL, Mathé H, Scherrer B, Guillard H, Gainer E, et al. Effect of body weight and BMI on the efficacy of levonorgestrel emergency contraception. *Contraception*. 2015;91(2):97–104.
- [24] Segall-Gutierrez P, Taylor DS, Liu X, Stanzcyk F, Azen S, Mishell DR. Follicular development and ovulation in extremely obese women receiving depo-medroxyprogesterone acetate subcutaneously. *Contraception*. 2010;81(6):487–95.