The safety of subcutaneously administered depot medroxyprogesterone acetate (104 mg/0.65 mL): A systematic review

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Abstract

Context: Depot medroxyprogesterone acetate (DMPA), a progestogen-only contraceptive injectable, has traditionally been formulated as a crystalline suspension delivered intramuscularly (IM) at a dose of 150 mg/1.0 mL. A new, lower dose formulation of DMPA (104 mg/0.65 mL) has been developed for subcutaneous administration (SC). Given its increasing global availability and public health relevance, DMPA-SC was prioritized for inclusion as a new method referenced in the World Health Organization (WHO) Medical Eligibility Criteria for Contraceptive Use (MEC), 5th Edition.

Objective: This systematic review evaluated the published peer-reviewed literature regarding the safety of DMPA-SC among women with various characteristics or medical conditions. Results of this review informed the decision-making of a WHO Guideline Development Group in order to include recommendations on contraceptive eligibility within the revised MEC.

Methods: We searched PubMed and Cochrane Library databases to identify all relevant evidence published in peer-reviewed journals regarding the safety of DMPA-SC when used by women of reproductive age, particularly those with select characteristics or conditions specified in the MEC, from inception through June 2015. The quality of each individual study was assessed using the system for grading evidence developed by the United States Preventive Services Task Force.

Results: Fourteen studies met criteria for inclusion. Ten reported results relevant to DMPA users of varying age or with obesity, endometriosis or HIV; four compared the safety of DMPA-SC and DMPA-IM when used by general populations of healthy women. A randomized trial evaluating changes in bone mineral density among adult DMPA-SC and DMPA-IM users demonstrated no differences at 2 years of follow-up. Limited evidence reported no consistent differences in weight change or bleeding patterns according to age; however, adolescents (<18 years) were not included in any studies. Similar contraceptive efficacy, weight change, bleeding patterns and occurrence of other adverse effects among obese and nonobese DMPA-SC users were observed. Women with endometriosis using DMPA-SC over 6 months had minimal decreases in bone mineral density, weight gain, few serious adverse events and experienced improved pain symptoms. Women living with HIV tolerated injection of DMPA-SC with rare complications. DMPA-SC and DMPA-IM also show therapeutic equivalence and similar effects on weight gain, changes in bleeding patterns and reports of other adverse effects when these different delivery systems were used by general populations of women.

Conclusion: Evidence for use of DMPA-SC by women with select conditions and characteristics including age, obesity, endometriosis or HIV demonstrates that this method can generally be used safely in these contexts. Further, DMPA-SC and DMPA-IM appear to be therapeutically equivalent with similar safety profiles when used by healthy women.

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Keywords: Depot medroxyprogesterone; DMPA; Subcutaneous; Progestogen-only injectables; Safety

1. Introduction

Progestogen-only injectable contraception is highly effective, reversible and safe for most women [1]. Depot medroxyprogesterone acetate (DMPA), a progestogen-only contraceptive injectable available since 1960, has traditionally been formulated as a crystalline suspension delivered intramuscularly at a dose of 150 mg/1.0 mL at one of two
recommended sites: the upper arm or buttocks (DMPA-IM) [2]. A newer, lower-dose formulation of depot medroxyprogesterone allows for subcutaneous delivery (DMPA-SC). This alternative formulation reflects development based on a 16% weight/volume solution resulting in a final dose of 104 mg/0.65 mL that cannot be achieved solely by diluting the original DMPA-IM formulation [3]. Sites for administration of DMPA-SC include the abdomen and anterior thigh; however, subcutaneous administration in the upper arm may also provide sufficient contraceptive protection [4].

Absorption of medroxyprogesterone acetate (MPA) is immediate following injection of DMPA-SC, resulting in MPA levels greater than 0.2 ng/mL at 24 h, a conservative threshold considered sufficient for contraceptive protection. MPA levels peak at approximately 8 days post-injection and remain greater than 0.2 ng/mL through 91 days [3]. For women interested in continuing this method, re-dosing is recommended every three months, similar to DMPA-IM. Two large, noncomparative Phase 3 trials conducted across more than 100 sites in North and South America, Europe and Asia, including a total of nearly 2000 participants, demonstrated that DMPA-SC is highly efficacious, safe and acceptable to women [5].

The World Health Organization (WHO) convened meetings of its Guideline Development Group (GDG) during March 9–12, 2014, and September 24–25, 2014. The purpose of these meetings was to review, and where appropriate, revise specific evidence-based recommendations included in the WHO Medical Eligibility Criteria for Contraceptive Use (MEC) [6]. The GDG consisted of 62 multi-disciplinary experts from 25 countries. In order to consider eligibility for inclusion of DMPA-SC in the fifth edition of the MEC guidelines, we conducted a systematic review of the safety of DMPA-SC for use by women of reproductive age according to the medical characteristics and conditions specified in the document.

2. Materials and methods

We searched the PubMed database to identify all relevant evidence published in peer-reviewed journals in any language from inception through June 2015 regarding the safety of DMPA-SC in women of reproductive age. The following search strategy was used: (“contraceptive agents, female”[MeSH] AND (“injections”[MeSH] OR (“injections”[All Fields] OR “injection”[All Fields])) AND (subcutaneous[All Fields] OR (“sc”[All Fields]) OR SQ[All Fields])) OR (”dmpa”[All Fields] OR (depot[All Fields] AND (“medroxyprogesterone”[MeSH] OR “medroxyprogesterone”[All Fields])) OR (”medroxyprogesterone acetate”[MeSH] OR (“medroxyprogesterone”[All Fields] AND “acetate”[All Fields]) OR “medroxyprogesterone acetate”[All Fields] OR (“depo” [All Fields] AND “provera”[All Fields]) OR “depo provera”[All Fields]) AND (subcutaneous[All Fields] OR (“sc”[All Fields]) OR “SQ”[All Fields] OR “subQ” [All Fields])). We also searched the Cochrane Library database for any existing systematic reviews on the method using the search terms “depot medroxyprogesterone SC or SQ or subcutaneous.” Additionally, we hand-searched reference lists of identified articles for further citations of interest. We did not attempt to identify unpublished articles or abstracts from scientific conferences or contact any individual authors.

We were interested in including direct evidence to answer the following question: Among reproductive age women with medical conditions or specific characteristics within the MEC, does the use of DMPA-SC increase the risk of adverse events or worsen the condition compared with nonuse of the method? We also searched for indirect evidence addressing whether healthy reproductive age users of DMPA-SC experienced any increased risk of adverse events compared to nonusers. Studies reporting comparisons from women using either no contraception or nonhormonal contraception were preferred; however, because examining whether the safety profile of DMPA-SC is similar to DMPA-IM, we also included studies where users of DMPA-IM formed the comparison group. Additionally, because assessing the safety among women with various conditions or characteristics who use the same form of contraception may be informative in addressing our review question, we also included studies simply reporting adverse outcomes among users of DMPA-SC, particularly to determine differences in safety according to age or obesity status.

2.1. Study selection

We reviewed titles and abstracts and the full article, when necessary, to identify studies for inclusion. Reference lists from identified articles and key review articles were hand-searched to locate any additional articles. Individual case reports and articles investigating other formulations of DMPA were excluded as were publications that reported on a subset of data published elsewhere in an already included larger analysis.

2.2. Study quality assessment

Evidence was summarized and systematically assessed using standard abstract forms [7] and the quality of each study was assessed using the system for evaluating evidence (Appendix A) developed by the United States Preventive Services Task Force (USPSTF) [8]. Table 1 summarizes the direct evidence from studies investigating DMPA-SC use in women with various medical conditions or characteristics and Table 2 summarizes indirect evidence from studies comparing DMPA-SC with use of DMPA-IM among healthy women. Studies were
abstracted by one author (M.D.) and verified by a second author (M.G.).

2.3. Data synthesis

We did not compute summary measures of associations due to heterogeneity of study designs, study populations, and outcome measures collected.

3. Results

Of the 296 articles identified by the search strategy, 14 satisfied the review inclusion criteria. Twelve articles presented results for seven studies investigating DMPA-SC use among women with four conditions or characteristics identified in the WHO MEC, including obesity [5,9–15], age [9–11] endometriosis [16–18] and HIV [19]. Four of these articles report on results from three multinational pivotal Phase 3 contraceptive trials, including results from two noncomparative trials of DMPA-SC users conducted at sites in North and South America, Europe, and Asia, and a randomized, evaluator-blinded trial comparing DMPA-SC and DMPA-IM users conducted in the United States, Canada, and Brazil [5,9–11]. Additional studies included four randomized-controlled trials [16–19] and four reports from a prospective cohort study [12–15]. As the occurrence of adverse events among women with medical conditions or characteristics using DMPA-SC is relevant for this review, two Phase 3 randomized-controlled noninferiority trials evaluating DMPA-SC use compared with leuprolide and one Phase 2 randomized controlled trial evaluating DMPA-SC compared with elagolix in the setting of endometriosis, were considered as noncomparative prospective studies for the purposes of this review [16,17].

Three articles provide indirect evidence derived from one of the Phase 3 trials comparing the safety of DMPA-SC and DMPA-IM formulations when used by general populations of healthy women [9,11,20]. In addition, an observational study conducted in Uganda and Senegal reporting safety outcomes among healthy past users of DMPA-IM who switched to DMPA-SC was included [21].

3.1. Obesity

3.1.1. Contraceptive efficacy

Two fair quality reports presented results on three Phase 3 contraceptive trials and described contraceptive efficacy among obese women using DMPA-SC [5,9]. These studies included sexually active adult women with a history of regular menstruation and excluded women with recent hormonal contraceptive use, known pregnancy or infertility or other medical contraindications for use. In the study by Kaunitz et al., approximately one in four of the entire study population (N=534) of had a BMI >30 kg/m²: DMPA-SC(n=65 of 266) and IM (n=69 of 268) [9]. No pregnancies were reported among any DMPA-SC or DMPA-IM users during the first year of follow-up. In Years 2 and 3, no women randomized to DMPA-SC experienced pregnancy during 3565 and 5241 woman-cycles of exposure, while the treatment-failure cumulative pregnancy rates among DMPA-IM users were reported as 0.75% (3442 woman-cycles of exposure) and 0.8% (5241 woman-cycles of exposure) respectively. In a pooled analysis of two noncomparative trials of nearly 2000 women by Jain et al. obese participants (BMI >30 kg/m²) accounted for 17.5% of the study sample in the Americas and 6.3% of the study sample in European and Asian sites combined. No pregnancies were reported during 1 year of follow-up, reflecting a total of 6227 injections and 16,023 woman-cycles of exposure [5]. In both studies, women underwent routine pregnancy testing at baseline and prior to each subsequent injection; additionally, the authors excluded cycles during which no intercourse or use of concurrent barrier contraception were reported to calculate contraceptive efficacy.

3.1.2. Weight change

A fair quality report by Westhoff et al. presented results of a pooled analysis from three Phase 3 contraceptive trials regarding changes in weight among DMPA-SC users by BMI class and across DMPA-SC and DMPA-IM users [11]. While there were no significant differences reported in weight gain across BMI groups (≤25, >25 to ≤30, >30 kg/m²), all DMPA (SC and IM) users gained weight. The median change in body weight among users of DMPA-SC compared to DMPA-IM from enrolment though months 12, 24 and 36 were presented in a line graph; weight gain increased over time and was similar across users of the two methods. At month 36, the median weight change in the DMPA-SC group (n=65) was 4.5±8.5 kg and 5.8±8.7 kg in the DMPA-IM group (n=56).

Another small prospective cohort study evaluated weight change among five normal BMI (18.5–24.9 kg/m²), five obese (30.0–39.9 kg/m²), and five extremely obese (≥40 kg/m²) DMPA-SC users during 26 weeks of follow-up, or two injection cycles [13]. All women were noted to gain weight during the trial (mean range 0.62–2.59 kg). While normal BMI users gained more weight than obese or extremely obese women from baseline to 13 weeks and from 13 weeks to 26 weeks post-injection, the findings did not achieve statistical significance. Moreover, no difference in weight change by BMI class over the duration of the study period (baseline to week 26) was observed (p=.29).

3.1.3. Other adverse effects

Arias et al. described changes in bleeding patterns among obese and nonobese users of DMPA-SC and DMPA-IM included in three Phase 3 contraceptive trials [10]. All participants were asked to record daily bleeding patterns in a diary; data were analyzed according to 30-day intervals starting from the time of the first contraceptive injection
through follow-up. Nearly all women reported some bleeding in the first 30 days following the first injection (no figure reported), which was not unexpected as all women received their DMPA-SC injection within five days of the onset of their regular menstrual cycle. The majority (51%) of women reported 1–7 days of bleeding or spotting during this period in the noncomparative America trial. Bleeding and spotting gradually decreased over time; at 12 months, all studies noted that a majority of women experienced amenorrhea. When changes in bleeding patterns were assessed by BMI group (≤ 25, >25 to ≤ 30, >30 kg/m²), no consistent differences were apparent.

Four poor-quality reports from a small prospective cohort study evaluated a number of potential adverse effects of DMPA-SC use among five normal BMI (18.5–24.9 kg/m²), five obese (30.0–39.9 kg/m²), and five extremely obese (≥ 40 kg/m²) DMPA-SC users during 26 weeks of follow-up, or two injection cycles [12–15]. One reported serum measures of progesterone (P₄), estradiol (E₂) and medroxyprogesterone acetate (MPA) collected weekly, bi-weekly and monthly, as a means to quantify follicular development and ovulation among obese and nonobese DMPA-SC users [12]. Following the first week of injection, no users were observed to have a P₄ level ≥3 ng/mL. Median E₂ levels did not exceed 100 ng/mL for any BMI class. Though median medroxyprogesterone acetate (MPA) levels remained within a therapeutic contraceptive range for all BMI categories throughout the study period, these levels were noted to be lower in obese compared with normal BMI women. Another report of changes in serum androgen markers (total testosterone (T), total androstenedione (A), dehydroepiandrosterone sulfate (DHEAS), 3α-androstenediol glucuronide and sex hormone-binding globulin (SHBG)) measured at week 13 and week 26 during exposure to DMPA-SC described net decreases in all groups for total T, total A and SHBG with no change in the serum levels of other markers; no significant differences in the observed serum levels of any androgen markers were noted among BMI groups [13]. When a number of cardiometabolic risk markers measured at baseline and at 18 weeks were compared across BMI groups, no differences were noted except for the Disposition Index, a measure of β-cell compensation for insulin resistance, which decreased in obese women (~286) and increased in nonobese women (188.5) (p = .04) [14]. Finally, small decreases in mean bone mineral density (BMD) at the lumbar spine measured by Dual Energy X-ray Absorptiometry (DEXA) were noted at 18 weeks post-enrollment among all DMPA-SC-users (normal: −0.083, obese: −0.091, extremely obese: −0.112, p = .89), though no difference was reported across BMI groups [15]. All participants had normal BMD at baseline.

3.2. Age

3.2.1. Changes in bone mineral density

Kauzit et al. reported changes in bone mineral density during use of DMPA-SC in a Phase 3 clinical trial [9]. Adult women, aged 18–35 years, with normal measures of BMD at baseline were randomized to use of DMPA-SC (n = 266) or DMPA-IM (n = 268). All women experienced a decrease in BMD during use of DMPA through up to three years of study follow-up. At the end of year one, DMPA-SC users had less of a decrease in BMD compared to IM users at the lumbar spine (~2.4% vs. −3.4%, p = .021); however, no significant changes were noted at the hip. In years two and three, the median percent changes in BMD among DMPA-SC compared to DMPA-IM users were not statistically different. Six women discontinued DMPA at two years during the trial and underwent a repeat BMD assessment 1 year following discontinuation; it was not specified whether they used SC or IM formulations. Four of these women showed an increase in BMD at the hip and all five women with BMD measurements at the lumbar spine showed an increase. Two women in each group showed complete recovery of BMD back to baseline. Four fractures were noted among 3 DMPA-SC and 1 DMPA-IM users (foot, rib, ankle and wrist) and none were assessed to be due to osteoporosis.

3.2.2. Weight changes

Westhoff et al. reported on weight changes experienced by adult women of various age groups during exposure to DMPA-SC or DMPA-IM based on data from Phase 3 trials [11]. Though all women experienced weight gain during use of either method over time that was similar, there were no consistent differences in the distribution of weight change across age groups (<25, 25–35, >35 years). The authors note that there was a trend toward higher weight gains among women >35 years in the North/South American noncomparative Phase 3 trial (p = .076). However, in the DMPA-SC/IM Phase 3 trial including among women aged 18–35 years, weight gain was significantly higher among women <25 years using DMPA-SC compared to women ages 25 to 35 years at month 9 (p = .025) and 12 (p = .003).

3.2.3. Changes in bleeding patterns

Arias et al. reported no consistent differences in bleeding patterns across age groups (<25, 25–35, >35 years) among DMPA-SC users in Phase 3 trials [10]. In the noncomparative Americas trial (n = 722), women between the ages of 25–35 had higher rates of amenorrhea, while women aged <25 and >35 years reported more instances of bleeding and spotting (p < .05) at months 6, 9 and 12. In the SC/IM study, 73% of DMPA-SC users between 25 and 35 years reported amenorrhea at 12 months compared to 52.8% of women under age 25 using the method (p = .008); no differences were noted in bleeding patterns across groups at months 3, 6 or 9 in this sample.

3.3. Endometriosis

Two randomized controlled noninferiority trials were designed to assess DMPA-SC and leuprolide as treatment
for pain associated with endometriosis [16,17]. Another Phase 2 randomized, controlled trial investigated use of a GnRH antagonist, elagolix, compared with DMPA-SC [18]. All studies recruited reproductive-age women with a surgical diagnosis of endometriosis and persistent pain symptoms attributable to their condition prior to use of DMPA-SC. One hundred fifty-three women from sites in Europe, Asia, Latin America, or New Zealand and 136 DMPA-SC users from Canada and the United States contributed data to the reports lead by Crosignani and Schlaff. Carr et al. conducted their Phase 2 trial at 78 centers across the United States and randomized 84 women to DMPA-SC.

In these three fair quality studies, there were no significant changes to vital signs or standard laboratory assays. In addition, two trials noted minimal weight gain among DMPA-SC users; median changes in body weight were +0.70 and +0.95 kg at month six of treatment, and +0.9 kg and +1.30 kg at the end of the study period (18 months). These studies also reported that the median percent change in BMD at the hip (−0.3, −0.5) and lumbar spine (−1.1, −1.0) at Month 6 were minimal and BMD recovery at twelve months following discontinuation of DMPA-SC was observed. Carr et al. noted that mean percent decreases in bone mineral density after six months of use were minimal (spine: −0.99%; femur: −1.29%). Generally, all studies also reported a decrease in bleeding days over time. Many DMPA-SC users reported a variety of drug-related adverse events; however, serious adverse events were rare in all studies.

3.4. HIV

A randomized, cross-over study by Polis et al. was conducted to assess acceptability of SC versus IM administration of DMPA among clinically well women living with HIV who expressed interest in injectable contraception and attended community-based health clinics in Rakai, Uganda. Women were randomized to either receive DMPA-SC (n=179) or DMPA-IM (n=178) at enrollment and then received the alternative formulation 3 months later. Participants completed a pre-injection baseline questionnaire and post-injection questionnaires at baseline, 3 months and 6 months where they recorded adverse effects. In general, there were no differences in the report of any side effects overall in the first three months among DMPA-SC and DMPA-IM users; however, women in the SC group tended to report more fatigue (4.4% vs. 0%, p<.01). Few women reported “a lot” of skin irritation with their injection (0–5%), though more skin irritation was noted among DMPA-SC users at 3 and 6 months after enrollment. Women also reported more skin irritation associated with a recent injection of DMPA-SC compared to DMPA-IM received 3 months earlier (p<.01). Among women who received DMPA-SC at baseline and DMPA-IM at 3 months, more menstrual irregularity was noted at 6 months compared to those who received DMPA-IM at baseline and DMPA-SC at 3 months (10.9% vs. 4.4%, p=.03). Two deaths, one in each randomization group, were reported as unlikely to be due to DMPA exposure. Additionally, four pregnancies, two in each randomization group, were reported; all occurred between baseline and the 3-month follow-up visit. All women underwent baseline urine hCG pregnancy testing prior to DMPA administration.

3.5. Healthy women

Four articles compared various safety outcomes among healthy women using DMPA-SC and DMPA-IM [9,11,20,21]. Three report on evidence derived from a Phase 3 randomized, evaluator-blinded contraceptive trial comparing women, ages 18 to 35 years, who used DMPA-SC (n=266) or DMPA-IM (n=268) through up to 3 years of follow-up, described earlier in this review [9]. Among healthy women, DMPA-SC and DMPA-IM appear to be equivalently efficacious [9], associated with similar changes in bone mineral density during use that are unrelated to acute osteoporotic fracture [9], and mean weight gains (DMPA-SC: 4.5±8.5 kg, DMPA-IM: 5.8±8.7 kg 4.5 (mean ± SD) were not statistically different across methods through 36 months of follow-up [11].

In the primary report of the Phase 3 comparative trial results, treatment-emergent adverse events, or those that developed for the first time or were present and worsened in either intensity or frequency following treatment with DMPA SC or IM were recorded. At least one adverse event was reported among 81.4% of DMPA-SC users and 77.8% of DMPA-IM users; 54.4% and 56.0% of reported AEs were determined to be associated with the study drug. The most common drug-related event was weight gain (DMPA-SC: 12.2%, DMPA-IM: 14.3%) in both groups. Serious adverse events (SAE) were rare (DMPA-SC: 3.8%, DMPA-IM: 2.3%); and, with the exception of one unintended pregnancy in the DMPA-IM group, none of the reported SAEs were associated with study treatment. Among both DMPA-SC and DMPA-IM users, unpredictable bleeding and spotting decreased over time and amenorrhea increased. At the end of Year 1, 62.6% of DMPA-SC users and 61.1% of DMPA-IM users denied any bleeding or spotting; at the end of Year 2, 71.0% of DMPA-SC users and 80.0% of DMPA-IM users reported amenorrhea. The pattern of amenorrhea by 30-day month intervals among users of both methods demonstrated similar frequencies over time. It was also noted that there were more injection site reactions present in the SC compared to the IM group; however, the frequencies were not further specified; Jain et al. reported that 1.6% of SC users in the European/Asia trial and 9.7% of the SC users in the Americas trial experienced injection site reactions defined as the presence of pain, granuloma or atrophy [5].
Goldstein et al. performed a small secondary analysis of single site data from the trial to review changes in coagulation and inflammation markers among 14 women; four participants received DMPA-SC and ten participants received DMPA-IM. The investigators measured D-dimer, C-reactive protein (CRP), antithrombin (AT), factor VIIIc, activated partial thromboplastin time (aPTT) and aPTT plus activated protein C (APC) at baseline and 6 and 12 months. Decreases in D-dimer and aPTT were noted among all users, and no other alterations were noted among other measured markers. There were no differences across DMPA formulations.

Finally, a prospective, open-label observational study conducted in Uganda (n=120) and Senegal (n=242) invited healthy, reproductive age women currently using DMPA-IM to switch to DMPA-SC and then assessed several safety outcomes during 3 months following administration [21]. When asked to compare which injection caused more skin irritation, just over two thirds of women in Uganda (69.2%) and nearly half of the women in Senegal (43.0%) noted no difference; among those who noted a distinction, most women in both samples reported skin irritation more frequently with IM injection (19.2% and 44.6%, respectively). No serious adverse events related to DMPA-SC and no pregnancies were reported. Of the 34 adverse events (28 in Uganda; 6 in Senegal) noted among 25 participants, 10 were deemed attributable to DMPA-SC use. These were mild to moderate in severity; three were associated with skin irritation and the rest attributed to common side effects of DMPA, and all resolved without sequelae.

4. Discussion

Eight reports from three studies, including two Phase 3 trials and a small prospective cohort, of fair to poor quality suggest that the safety of DMPA-SC use among obese women is similar to nonobese women; and, obese users of DMPA-SC and DMPA-IM experience similar adverse effects [5,9–15]. Further, limited evidence from these Phase 3 trials also suggest that the safety of DMPA-SC use among subgroups of premenopausal adult women is also similar and that these women experience infrequent and comparable adverse effects when DMPA-SC and DMPA-IM are used in these populations; no studies reported on adverse outcomes among adolescents [9,11]. For the condition of endometriosis, three Level II-3 reports of fair quality presented prospective non-comparative descriptive data for women with the condition who used DMPA-SC [16–18]. There was no evidence that DMPA-SC contributed to a worsening of their condition or an increased frequency of any other serious adverse events. Of note, DMPA-SC also proved therapeutically beneficial in reducing signs and symptoms of endometriosis during use and for months following discontinuation in all studies, though this was not a primary outcome for this review. One Level-I randomized, cross-over study evaluated various adverse effects of DMPA-SC and DMPA-IM use among clinically well adult women living with HIV in Uganda [19]. Serious adverse events were rare and no different across treatment arms, and it was unlikely that any reported deaths were associated with exposure to DMPA. Generally, the findings from this study appear reassuring, but the authors did not comment on participants’ clinical status over time, which may have bearing on their susceptibility to and report of various adverse effects. Further, the study did not investigate critical health outcomes informing assessments for eligibility of women living with HIV and progestogen-only contraception, namely risks of HIV transmission or disease progression due to exposure to this new DMPA formulation, accounting for its assessment as poor quality.

Taken together, the existing evidence among healthy women suggests that DMPA-SC and DMPA-IM appear to be therapeutically equivalent. Additionally, the two formulations demonstrate similar effects on serum estradiol levels and high contraceptive efficacy [9]. Similar effects on weight gain, changes in bleeding patterns, and reports of other adverse effects have also been demonstrated. It appears that users of DMPA-SC may experience injection site reactions more frequently, but these are rare, typically mild to moderate in severity and generally resolve without further intervention [5,9,19].

The bulk of safety information identified for this review is derived from Phase 2 and 3 contraceptive trials, including two noncomparative prospective studies and one randomized trial comparing DMPA-SC and DMPA-IM, and three randomized, controlled trials providing prospective, non-comparative descriptive data among women with endometriosis using DMPA-SC [5,9,11,16–18,20]. While these studies do include women from study sites around the world, supporting generalizability of the results, both comparative and noncomparative studies had high dropout rates over time (>20%), possibly introducing bias. These studies and the reports generated from them received support (funding, statistical expertise, etc.) from the pharmaceutical company manufacturing DMPA-SC; this involvement could possibly introduce systematic bias into the review, as drug companies tend toward publishing only favorable results [22]. Additionally, a number of small studies with limited exposure to treatment with DMPA and short follow-up periods provided information on surrogate endpoints for disease that may not capture the true effect of DMPA-SC exposure on clinically relevant outcomes [12–15,20,23]. Given the limited scope of data we identified to inform assessments of safety among DMPA-SC users with the various characteristics or conditions of age, obesity status, endometriosis and HIV, determination of medical eligibility criteria for contraceptive safety required evaluating data obtained from studies of other contraceptives with similar mechanisms of action,
delivery systems or hormone formulations. It is reassuring that the evidence we identified comparing DMPA-SC and DMPA-IM demonstrated therapeutic equivalence of the formulations, suggesting that such comparisons may be well founded.

5. Conclusion

Following a review of the evidence in accord with WHO guideline development processes, the GDG determined that eligibility recommendations for progestogen-only injectables should not change with inclusion of DMPA-SC as a new method in this category, referenced in the WHO MEC, 5th Edition. No unique critical safety concerns for this formulation emerged for women with select characteristics or conditions using DMPA-SC or in comparison to DMPA-IM. WHO will continue to monitor the body of evidence informing these recommendations and will re-evaluate the recommendations, as needed, should new evidence necessitate reconsideration. Subsequent to the consultation, two new articles were published and included in this review [18,21]; the results from these studies offer additional supporting evidence and remain consistent with the updated recommendations.

In conclusion, women eligible to use DMPA have an option to choose the formulation and delivery route that matches their preferences without compromising safety.

Notably, DMPA-SC may offer important service delivery advantages over DMPA-IM. For example, several studies demonstrate that self-administration of DMPA-SC is feasible and associated with similar continuation and satisfaction rates as DMPA-IM [24–26].

Acknowledgments

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Table 1
DMPA-SC evidence in women with medical conditions.

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<td>Women, ages 18 to 49, with history of regular menstruation and desiring injectable contraception</td>
<td>Obesity</td>
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<td>North and South America, Europe, Asia</td>
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<td>Accounted for times of no intercourse and use of barrier contraception in calculation of efficacy</td>
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<td>Not powered to detect difference in contraceptive efficacy between methods or across BMI classes</td>
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<td>Failure reported for all weight/BMI classes combined</td>
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<td>High dropout rate; 43.6% (1062/2400) DMPA-SC users and 40.7% (109/268) DMPA-IM users completed 2 years’ treatment</td>
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<td></td>
<td>Not stated</td>
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<td>Multi-country design</td>
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<td>Accounted for times of no intercourse and use of barrier contraception in calculation of contraceptive efficacy</td>
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<td>High dropout over time</td>
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<td>Pfizer</td>
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<td>Multi-country design</td>
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<td>North and South America, Europe, Asia</td>
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<td>Height and weight measured at baseline and weight measured every 3 months during follow-up</td>
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<td>High dropout over time</td>
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<td>Anonymous donor United States</td>
<td>Up to 26 weeks (2 injections of DMPA SC 104) 7 month period; x (y) not stated</td>
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<td>Includes women of very high BMI</td>
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<td>Small sample size</td>
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<td>Short follow-up</td>
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<td>Measures biomarkers and not direct outcome</td>
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</table>
activity) and SHBG at baseline, week 13 and week 26. Net decreases in all groups for Total T, Total A and SHBG from baseline to week 26, no change in other markers. No significant differences in serum levels of any androgen markers between groups.

2. Changes in cardio-metabolic risk markers[14]
No significant differences in changes in risk markers between obese and normal weight groups, with the exception of Disposition Index (measure of B-cell compensation for insulin resistance) which decreased in obese women (-28%) and increased in non-obese women (18.8%) (p<0.4)

3. Changes in bone mineral density (BMD)[15]
At baseline, no differences in mean BMD of lumbar spine measured by DXA across groups. Noted small decreases in BMD across all groups with no significant differences between groups on repeat scan at 18 weeks after first injection (midway through injection #2). 4. FOLLICULAR DEVELOPMENT AND OVULATION[12]
No subject had P4 levels ≥ 3ng/mL after week one following injection. Median E2 levels never > 100 ng/mL among all BMI categories. Median MPA levels remained consistently above levels needed to suppress ovulation for all BMI categories at 12 weeks post-injection 1 and 14 weeks for injection 2; however, MPA levels in obese lower than normal BMI women.

### Table

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Population</th>
<th>Outcomes</th>
<th>Strengths</th>
<th>Weaknesses</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arias et al., 2006 [10]</td>
<td>Pfizer North and South America, Europe, Asia</td>
<td>Pooled analyses from two non-comparative Phase III trials[5] and RCT comparing IM and SC DMPA[9] 1 year, 2-3 years</td>
<td>Women, ages 18 to 49; with history of regular menstruation and desiring injectable contraception Excluded women with OC, implant or hormonal IUD use within previous 2 months and DMPA-IM within 10 months of enrolment, known pregnancy or infertility or medical contraindications</td>
<td>Normal vs. Overweight vs. Obese Adult women All DMPA-SC users</td>
<td>Outcome: Changes in bleeding patterns Nearly all women experienced some degree of bleeding across trials. Americas: 51% of women reported bleeding or spotting for 1 to 7 days in first 30 days after injection. Incidence of irregular bleeding or spotting decreased over time. Similar trends noted in Europe/Asia trial. Bleeding at 12 months Americas: 62% amenorrhea, 19% spotting Europe/Asia: 52% amenorrhea, 27% spotting</td>
<td>Strengths Multi-country design Weaknesses High dropout over time</td>
</tr>
<tr>
<td>Westhoff et al, 2007[11]</td>
<td>Pfizer North and South America, Europe, Asia</td>
<td>Pooled analyses from two non-comparative Phase III trials[5] and RCT comparing IM and SC DMPA [9] 1 year, 2-3 years</td>
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<td>Age Adult women DMPA-SC and DMPA-IM users</td>
<td>Outcome: Weight change Reports no consistent differences in the distribution of weight change across age group (&lt;25, &gt;25 to 35, &gt;35 years).</td>
<td>Strengths Multi-country design Weaknesses Height and weight measured at baseline and weight measured every 3 months during follow-up No non-POC comparison group</td>
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<tr>
<td>Kuunitz et al., 2009[9]</td>
<td>Pfizer United States, Canada, Brazil</td>
<td>Randomized, evaluator-blinded Phase III study 2-3 years April 2001 – Sept 2004</td>
<td>Women, ages 18 to 35 years, desiring injectable contraception with history of regular menstruation Excluded women with OC, implant or hormonal IUD use within previous 2 months and DMPA-IM within 10 months of enrolment, known pregnancy or infertility or medical contraindications</td>
<td>Age Adult women DMPA-SC vs. DMPA-IM users</td>
<td>Outcome: Changes in bone mineral density (BMD) Characteristic DMPA-SC DMPA-IM N=266 N=268 Age Mean ± SD 25.9±4.9 25.8±4.8 Range* 18.0-35.9 18.0-35.7 Decrease in total hip BMD of ≥ 5% from baseline DMPA-SC DMPA-IM Year 1 13/166 7.8% 20/162 12.3% Year 2 30/106 28.3% 34/103 33.7% Year 3 35/83 55.6% 28/84 51.9% Decrease in total lumbar spine BMD of ≥ 5% from baseline</td>
<td>Strengths Multi-country design Weaknesses High dropout rate over time</td>
</tr>
</tbody>
</table>
### Comparative Study on DMPA-SC and DMPA-IM

During both first and second years, observed median BMD decreases from baseline at hip and lumbar spine were smaller in SC group compared to IM group, finding significant at year 1, though not in years 2 and 3. BMD recovery at 12 months after discontinuation (N= 6)

**Hip:** 4/6 showed increase with 2 having full recovery

**Lumbar spine:** 5/5 showed increase in BMD, 2 with full recovery, however, no specification of IM vs. SC use

Four fracture AEs were reported among 3 DMPA-SC users and 1 DMPA-IM user at the foot, rib, ankle and wrist; no fracture was clinically assessed to be due to osteoporosis.

### Enrollment Criteria

**Endometriosis** DMPA-SC

- **Women, ages 18 to 49 years,** with laparoscopically diagnosed endometriosis and persistent pain symptoms
- **DMPPA-SC, n=104**

### Adverse Events

- **DMPPA-SC**
  - Any drug-related adverse event during treatment: 50.7%
  - Any serious adverse event: 3.9%

### Strengths

- Multi-country design
- Included women with surgically confirmed diagnosis
- Used validated measures to collect pain data
- Randomized sample of DMPPA users
- Weaknesses
  - No comparison group

### Comparative Study on DMPA-SC and DMPA-IM

During both first and second years, observed median BMD decreases from baseline at hip and lumbar spine were smaller in SC group compared to IM group, finding significant at year 1, though not in years 2 and 3. BMD recovery at 12 months after discontinuation (N= 6)

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- Randomized sample of DMPPA users
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  - High dropout rate during 6 month treatment period, 35.3% DMPA-SC
  - Among women who completed 6 month treatment period, only 58% of DMPA-SC users completed 12 month follow-up

### Comparative Study on DMPA-SC and DMPA-IM

During both first and second years, observed median BMD decreases from baseline at hip and lumbar spine were smaller in SC group compared to IM group, finding significant at year 1, though not in years 2 and 3. BMD recovery at 12 months after discontinuation (N= 6)

**Hip:** 4/6 showed increase with 2 having full recovery

**Lumbar spine:** 5/5 showed increase in BMD, 2 with full recovery, however, no specification of IM vs. SC use

Four fracture AEs were reported among 3 DMPA-SC users and 1 DMPA-IM user at the foot, rib, ankle and wrist; no fracture was clinically assessed to be due to osteoporosis.

### Enrollment Criteria

**Endometriosis** DMPA-SC

- **Women, ages 18 to 49 years,** with laparoscopically diagnosed endometriosis and persistent pain symptoms
- **DMPPA-SC, n=136**

### Adverse Events

- **DMPPA-SC**
  - Any drug-related adverse event during treatment: 50.7%
  - Any serious adverse event: 3.9%

### Strengths

- Multi-country design
- Included women with surgically confirmed diagnosis
- Used validated measures to collect pain data
- Randomized sample of DMPPA users
- Weaknesses
  - High dropout rate during 6 month treatment period, 35.3% DMPA-SC
  - Among women who completed 6 month treatment period, only 58% of DMPA-SC users completed 12 month follow-up

### Comparative Study on DMPA-SC and DMPA-IM

During both first and second years, observed median BMD decreases from baseline at hip and lumbar spine were smaller in SC group compared to IM group, finding significant at year 1, though not in years 2 and 3. BMD recovery at 12 months after discontinuation (N= 6)

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Four fracture AEs were reported among 3 DMPA-SC users and 1 DMPA-IM user at the foot, rib, ankle and wrist; no fracture was clinically assessed to be due to osteoporosis.

### Enrollment Criteria

**Endometriosis** DMPA-SC

- **Women, ages 18 to 49 years,** with laparoscopically diagnosed endometriosis and persistent pain symptoms
- **DMPPA-SC, n=136**

### Adverse Events

- **DMPPA-SC**
  - Any drug-related adverse event during treatment: 50.7%
  - Any serious adverse event: 3.9%
| Carr et al., 2014 [18] Neurocrine Biosciences, BC, Synacth and Evofem United States | Randomized, double-blind, controlled trial As we are only interested in adverse events among women with endometriosis using DMPA-SC, and not in comparative therapeutic effects, we considered this a non-comparative prospective study December 2006 to November 2008 24 week treatment period with 24 week post-treatment observation | Women, ages 18 to 49 with laparoscopically diagnosed endometriosis and persistent pain symptoms DMPA-SC, n=84 | Endometriosis DMPA-SC No clinically relevant changes in laboratory safety parameters, vital sign measurements or ECG readings noted. Mean % change in BMD among DMPA-SC users at week 24 Spine -0.99% (-1.61 to -0.37) Femur 1.29% (-1.80 to -0.77) Mean percentage of days with any bleeding during treatment: 30.4% + 2.4% Most common adverse events among DMPA-SC users Headache 17.9% Nausea 15.5% Nasopharyngitis 10.7% Upper respiratory infection 11.9% Mood swings 11.9% No deaths occurred in the study period; 6 SAEs among DMPA-SC users deemed unrelated to use. No pregnancies occurred among users of DMPA-SC. | Strengths Multi-country design Included women with surgically confirmed diagnosis Randomized sample of DMPA users Weaknesses High dropout rate during treatment period, 60% (51/84) |
| Polis et al., 2013 [19] Society of Family Planning, Bill and Melinda Gates Institute for Population and Reproductive Health, Dr. Ronald Gray, Pfizer Uganda | RCT cross-over study 6 months April 2012 – March 2013 | Clinically well women living with HIV, ages 18 to 45, interested in injectable contraception recruited from community-based health clinics | HIV DMPA-SC vs. DMPA-IM Serious adverse events 2 deaths: one in each randomization group 1: febrile illness of unknown etiology, possibly immune reconstitution inflammatory syndrome after ART initiation 1: severe anemia, possibly due to zidovudine or malaria 4 pregnancies reported; 2 in each randomization group, all occurring between baseline and 3 mo visit, no comment on concurrent ART use Skin irritation Most women reported little or no skin irritation with IM and SC injection (95 -100%); however, more skin irritation was noted among DMPA-SC users (p < 0.01 at 3 and 6 months). Other adverse effects No significant differences in report of any side effect overall in last 3 months among women who received SC and IM at enrolment. No differences in menstrual irregularity, more days bleeding than before DMPA initiation, heavier bleeding, no bleeding, dizziness, headaches, decreased wetness during sex, or decreased libido. Women in the SC group reported more fatigue than IM group (4.4% vs. 0%, p < 0.01) At 6 months, women who received baseline SC/3-m IM reported more menstrual irregularity compared to women who received baseline IM/5-m SC (10.9% vs. 4.4%, p =0-03); no other differences noted. | Strengths First study to evaluate DMPA-SC among women living with HIV Weaknesses No non-HIV comparison group Not powered to detect differences in serious adverse events Unclear whether pregnancies due to method failure, possible ART interactions, or result of undetected early pregnancy at time of initial injection Did not report on participants clinical status over time and relation to report of adverse effects |
Table 2
Criteria for grading the internal validity of individual studies.

<table>
<thead>
<tr>
<th>Study design</th>
<th>Criteria</th>
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<tr>
<td>Systematic reviews</td>
<td>• Comprehensiveness of sources/search strategy used</td>
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<td>• Standard appraisal of included studies</td>
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<td>• Validity of conclusions</td>
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<td>• Recency and relevance</td>
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<td>Case–control studies</td>
<td>• Accurate ascertainment of cases</td>
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<td>• Nonbiased selection of cases/controls with exclusion criteria applied equally to both</td>
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<td>• Response rate</td>
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<td>• Diagnostic testing procedures applied equally to each group</td>
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<td>• Appropriate attention to potential confounding variables</td>
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<td>RCTs and cohort studies</td>
<td>• Initial assembly of comparable groups:</td>
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<td>• For RCTs: adequate randomization, including concealment and whether potential confounders were distributed equally among groups</td>
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<td>• For cohort studies: consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts</td>
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<td>• Maintenance of comparable groups (includes attrition, crossovers, adherence, contamination)</td>
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<td>• Important differential loss to follow-up or overall high loss to follow-up</td>
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<td>• Measurements: equal, reliable, and valid (includes masking of outcome assessment)</td>
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<td>• Clear definition of interventions</td>
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<td>• All important outcomes considered</td>
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<td>• Analysis: adjustment for potential confounders for cohort studies, or intention-to-treat analysis for RCTs</td>
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<td>Diagnostic accuracy studies</td>
<td>• Screening test relevant, available for primary care, adequately described</td>
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<td>• Study uses a credible reference standard, performed regardless of test results</td>
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<td>• Reference standard interpreted independently of screening test</td>
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<td>• Handles indeterminate results in a reasonable manner</td>
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<td>• Spectrum of patients included in study</td>
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<td>• Sample size</td>
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<td>• Administration of reliable screening test</td>
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<tr>
<td>Author, Date, Location</td>
<td>Study Design and Follow-up</td>
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<tr>
<td>Kermiti et al., 2009[9] Pfizer United States, Canada, Brazil</td>
<td>Randomized, evaluator-blinded Phase III trial 2-3 years April 2003 – Sept 2004</td>
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<tr>
<td>Goldstein et al., 2007[20] University of Vermont College of Medicine United States</td>
<td>Secondary analysis of single site data from RCT[9] 1 year</td>
</tr>
<tr>
<td>Westhoff et al., 2007[11] Pfizer North and South America, Europe, Asia</td>
<td>Pooled analyses from two non-comparative Phase III trials[5] and RCT comparing IM and SC DMPA [9] 1 year, 2-3 years</td>
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<tr>
<td>Burke et al., 2014 [21] USAID Senegal, Uganda</td>
<td>Prospective, open-label observational study July 2012- November 2012</td>
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Appendix A. Quality Assessment

Individual study: Each study was first given a rating based on the study design (Table 1). Each study was also given a rating of poor, fair, or good based on the criteria for grading the internal validity of a study (Table 2). A good study meets all criteria for that study design, a fair study does not meet all criteria but is judged to have no fatal flaw, and a poor study contains a fatal flaw. Also, the type of evidence was either identified as being direct (the evidence was based on data directly addressing the question) or indirect (the evidence was extrapolated from other relevant data).

References