Progestogen-only contraceptive use among breastfeeding women: a systematic review.

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Progestogen-only contraceptive use among breastfeeding women: a systematic review

Sharon J. Phillips, Naomi K. Tepper, Nathalie Kapp, Kavita Nanda, Marleen Temmerman, Kathryn M. Curtis

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Abstract

Background: Postpartum women need effective contraception. Concerns have been raised that use of progestogen-only contraceptives (POCs) may affect breastfeeding performance and infant health outcomes.

Objectives: We investigated the clinical outcomes of breastfeeding duration, initiation of supplemental feeding and weaning, as well as infant outcomes including infant growth, health and development among breastfeeding women using POCs compared with breastfeeding women not using POCs.

Search strategy: We searched the PubMed database for all articles published from database inception through December 2014.

Selection criteria: We included primary research studies of breastfeeding women of any age or parity who received POCs, including progestogen-only pills, injectables, implants or hormonal intrauterine devices (IUDs). The main outcomes were breastfeeding performance (as measured by initiation, continuation, frequency and exclusivity of breastfeeding) and infant health (as measured by growth, development or adverse health effects).

Results: Forty-nine articles reporting on 47 different studies were identified that investigated the use of POCs in breastfeeding women and reported clinically relevant outcomes of infant growth, health or breastfeeding performance. Studies ranged from poor to fair methodological quality and generally failed to show negative effects of the use of POCs on breastfeeding outcomes or on infant growth or development. One randomized controlled trial (RCT) raises concerns that immediate insertion of the levonorgestrel IUD postpartum may be associated with poorer breastfeeding performance when compared with delayed insertion, although two other RCTs evaluating early etonogestrel implants compared with delayed initiation of implants or depot medroxyprogesterone acetate failed to find such an association.

Conclusion: The preponderance of evidence fails to demonstrate adverse breastfeeding outcomes or negative health outcomes in infants such as restricted growth, health problems or impaired development. Evidence newly added to this review was largely consistent with previous evidence.

Keywords: Lactation; Contraception; Progestogens; Breastfeeding

1. Introduction

The benefits of breastfeeding for both women and their infants are considerable [1–3]. The World Health Organization (WHO) recommends infants breastfeed exclusively during the first months of life [4]. Although women breastfeeding exclusively and on demand are unlikely to conceive before 6 weeks postpartum, many women discontinue fully breastfeeding before that time and are at risk of repeat pregnancy [5]. Because birth spacing has demonstrated health benefits for women and infants, early initiation of contraception in the postpartum period may improve outcomes.

Progestogen-only and progestosterone contraceptives have been in use for years; however, their dosages and formulations have changed over time. Methods available...
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<th>Author, year, source of support</th>
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<th>Outcomes, follow-up duration</th>
<th>Results</th>
<th>Strengths/weaknesses</th>
<th>Quality grading/key question</th>
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</thead>
<tbody>
<tr>
<td>Kamal, 1969 [30] Newly identified</td>
<td>Nonrandomized clinical trial Egypt N=120 PP women (data available on 50)</td>
<td>6–10 weeks PP: POP (0.5 mg lynestrenol) IUD+placebo 2 kinds of COCs, 1 combined injectable contraceptive (not reported here) Allocation not reported</td>
<td>BF performance (age of supplementation) Infant growth (growth curve, percent weight increase) Follow-up 32 weeks</td>
<td>BF outcomes –Average age of supplementation 11.2 weeks POP group, 15 weeks placebo (statistics not reported) Infant outcomes –No relation between growth curve and method used BF outcomes –Lactation initiation earlier (3 vs. 5 days) in POP than placebo group Infant outcomes –Greatest weight increase in POP-exposed infants BF outcomes –No BF supplementation reported up to 6 months in any groups Infant outcomes –After 3rd month, infant weight gain per month higher in all POC groups than in NH controls; weight gain in hormonal groups equivalent –No physical, mental or radiologic differences in infants between groups</td>
<td>Strengths –Double blinded Weaknesses –No statistical analysis reported for comparisons of interest –High, but not clearly reported, loss to follow-up –Number of participants/group not reported</td>
<td>Level II-1 Poor Key Question 1</td>
</tr>
<tr>
<td>Kamal, 1970 [43] Not stated</td>
<td>Nonrandomized clinical trial Egypt N=40 primiparous and multiparous women, ages 20–37 years</td>
<td>2 days PP: 10=placebo 10=POP (lynestrenol 500 mcg) 10=COC (results not presented) 10=ethinyl estradiol (results not presented)</td>
<td>BF performance (initiation of lactation) Infant growth (weight) Follow-up 14 days</td>
<td>BF outcomes –Lactation initiation earlier (3 vs. 5 days) in POP than placebo group Infant outcomes –Greatest weight increase in POP-exposed infants BF outcomes –No BF supplementation reported up to 6 months in any groups Infant outcomes –After 3rd month, infant weight gain per month higher in all POC groups than in NH controls; weight gain in hormonal groups equivalent –No physical, mental or radiologic differences in infants between groups</td>
<td>Weaknesses –Nonrandomized –Small sample size –Short follow-up –No statistical comparisons</td>
<td>Level II-1 Poor Key Question 1</td>
</tr>
<tr>
<td>Karim, 1971 [36] Not stated</td>
<td>Prospective cohort Egypt N=331 women after normal delivery</td>
<td>7 days PP: 68=NET-EN (200 mg) 51=DMPA (150 mg) 100=NH 42 days PP: 57=NET-EN 55=DMPA</td>
<td>BF performance (supplementation) Infant growth and health (weight, physical exam, dentition, mentality, walking, radiographs) Follow-up 18 months</td>
<td>BF outcomes –Mean lactation duration (presented as mean months with 95% CI) Infant outcomes –After 3rd month, infant weight gain per month higher in all POC groups than in NH controls; weight gain in hormonal groups equivalent –No physical, mental or radiologic differences in infants between groups</td>
<td>Weaknesses –Percent follow-up of infants not reported –No standardized techniques to measure health and specifics of health outcomes not reported</td>
<td>Level II-2, poor Key Questions 1 and 2</td>
</tr>
<tr>
<td>Guiloff et al., 1974 [37] Population council, Warner-Lambert Research Institute</td>
<td>Cohort Chile N=696 multiparous women, ages 16–40 years</td>
<td>1–2 days PP: 80=DMPA (250 mg im q 6 months) 30 days PP: 33=DMPA</td>
<td>BF performance (mean duration of lactation) Follow-up 12 months</td>
<td>BF outcomes –Mean lactation duration (presented as mean months with 95% CI) Infant outcomes –After 3rd month, infant weight gain per month higher in all POC groups than in NH controls; weight gain in hormonal groups equivalent –No physical, mental or radiologic differences in infants between groups</td>
<td>Weaknesses –Unclear if prospective or retrospective –Historical control –Historical recall</td>
<td>Level II-2 Poor Key Question 1</td>
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Table 1 (continued)

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<tr>
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<tr>
<td>Giner-Velasquez et al., 1976 [33]</td>
<td>RCT Mexico</td>
<td>≤ 14 h PP: 12=NET (350 mcg) 8=Placebo</td>
<td>BF performance (initiation) Infant growth (weight) Follow-up 14 days</td>
<td>of duration of lactation</td>
<td>Weaknesses: –Methods poorly described –Small sample size –Follow-up and exclusions not described</td>
<td>Level I, Poor</td>
</tr>
<tr>
<td>Zanartu et al., 1976 [31]</td>
<td>Prospective cohort CEBRE, University of Chile Medical School Newly identified</td>
<td>N=406 fully BF women using DMPA with at least 18 months follow-up, 173 controls</td>
<td>First 30 days PP: N=133 DMPA 30–90 days PP N=206 DMPA 30–90 days PP 91–180 days PP N=67 DMPA (DMPA 150 or 250–300 mg) N=173 no DMPA (and either received education about BF or no intervention)</td>
<td>BF performance (exclusive and partial lactation status at 3, 6, 12, 18 months) Follow-up 18 months</td>
<td>of duration of lactation</td>
<td>Weaknesses: –High percentage with follow-up (406/500 with at least 18 months follow-up) –Unclear if non-DMPA users were using other hormonal or NH contraceptives –No separate analysis by DMPA dose; minimal analysis by timing; no statistical analysis for indirect comparison –Wide range in timing of DMPA administration</td>
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<tr>
<td>Study</td>
<td>Design</td>
<td>Country</td>
<td>Sample size</td>
<td>Intervention</td>
<td>BF performance (duration)</td>
<td>BF outcomes</td>
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<tr>
<td>Zanartu et al., 1976</td>
<td>Nonrandomized</td>
<td>Chile</td>
<td>N=100</td>
<td>Chlormadione acetate 0.6 mg; NH (historical control; some inert IUD, some no method)</td>
<td>Follow-up 18 months</td>
<td>At 3 months: 98% Chlormadione still BF; 76% NH still BF</td>
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<td>[45] Ayerst</td>
<td>clinical trial</td>
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<td>Seth et al., 1977 [49]</td>
<td>Cohort</td>
<td>India</td>
<td>N=50</td>
<td>Implant (40 mg norethindrone acetate) (early)</td>
<td>BF at 8 months, supplementation rates</td>
<td>Still BF at 8 months: 80% NH, 56.6% early, 66.6% delayed, difference not significant</td>
</tr>
<tr>
<td>[49] WHO</td>
<td>Cohort</td>
<td></td>
<td></td>
<td>Implant (delayed)</td>
<td>Infant growth (weight)</td>
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<tr>
<td>Croxatto et al., 1982 [55]</td>
<td>Cohort</td>
<td>Chile</td>
<td>N=439</td>
<td>Progesterone pellets (100 mg)</td>
<td>BF performance (fully, partially or not BF at follow-up visits)</td>
<td>Fully BF: No significant difference between groups at 3, 6 or 9 months</td>
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<tr>
<td>[55] Population Council and</td>
<td>Cohort</td>
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<td>Placebo injectable</td>
<td>Infant growth (weight)</td>
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<td>Canadian International</td>
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<td>Cu T200 IUD</td>
<td>Infant health (reports of intercurrent illness)</td>
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<td>Development Research Center</td>
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<td>Follow-up 12 months</td>
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<tr>
<td>Dahlberg, 1982 [32]</td>
<td>Retrospective cohort</td>
<td>Thailand</td>
<td>Some time in 1st 9 months PP: 210=Some exposure to infant growth (weight)</td>
<td>Infant health (incidence of intercurrent illness)</td>
<td>Infant outcomes</td>
<td>Weight gain</td>
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<td>[32]</td>
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<th>Quality grading/key question</th>
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<tr>
<td><strong>Newly identified</strong></td>
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<td></td>
<td>$N=331$ infants born at Thai hospital between 1977 and 1979</td>
<td>DMPA 121=No exposure to DMPA</td>
<td>infectious diseases leading to clinic visits</td>
<td>No difference between groups at any time point in follow-up, regardless of length of exposure</td>
<td>presented with different amounts of DMPA exposure</td>
<td>Level I, Poor Key Question 1</td>
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<td>Health</td>
<td>Weaknesses: Data obtained solely through record review</td>
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<td>−Statistical analysis not reported</td>
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<td></td>
<td>−Analytical methods not clearly described</td>
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<td>−Timing of exposure to DMPA not clear</td>
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<td>−Wide variation in when DMPA was given PP</td>
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<td></td>
<td><strong>Weaknesses:</strong> Allocation concealment and randomization sequence ill-described</td>
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<td>−Mid-way through trial, added lower-dose IUD and changed allocation scheme</td>
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<td>−Copper IUD group younger and less parous</td>
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<td></td>
<td>−Illnesses not recorded or assessed systematically</td>
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<tr>
<td><strong>Heikkila and Luukkainen, 1982 [34]</strong></td>
<td>RCT (with change to protocol partway through trial) Finland</td>
<td>$N=110$ women</td>
<td>32–56 days PP: 30=LNG (10 mcg/day IUD) 40=LNG (30 mcg/day IUD) 40=Copper IUD</td>
<td>BF outcomes&lt;br&gt; BF continuation 75 days postinsertion: 79% in IUD group, 56% LNG 30 group, $p&lt;.05$ (results for LNG-10 not reported)&lt;br&gt; BF continuation 6 months postinsertion: no difference among 3 groups&lt;br&gt; Median duration of BF 141 days LNG-10; 154 days LNG-30; 197 days Cu-IUD (difference significant)&lt;br&gt; Mean duration: no significant difference</td>
<td>Weaknesses: Allocation concealment and randomization sequence ill-described&lt;br&gt; Mid-way through trial, added lower-dose IUD and changed allocation scheme&lt;br&gt; Copper IUD group younger and less parous&lt;br&gt; Illnesses not recorded or assessed systematically</td>
<td>Level I, Poor Key Question 1</td>
</tr>
<tr>
<td><strong>Population Council, US Agency for International Development, Ford Foundation</strong></td>
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<td>Infant growth (height, weight)&lt;br&gt; Infant development (time of walking, tooth eruption)&lt;br&gt; Infant health (infectious diseases)&lt;br&gt; Follow-up 12 months</td>
<td>No significant difference</td>
<td>Growth and development</td>
</tr>
<tr>
<td>Study</td>
<td>Cohort/Design</td>
<td>Methods/Outcomes</td>
<td>Findings/Weaknesses</td>
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<tr>
<td>West et al., 1983 [44]</td>
<td>Medical Research Council, Scotland</td>
<td>Cohort, N=227 healthy women, fully BF (data available on 203)</td>
<td>No differences between groups in respiratory/middle ear infections: BF outcomes: At 3 months: 62% POP, 62% NH still BF At 5 months: 51% POP, 53% NH still BF (statistics not reported) BF performance: No difference in BF status at 6 months between those initiated at 30 or 60 days PP and their contemporary controls; however, those who initiated at day 60 were more likely to supplement at month 6 than those initiating at day 30 (68% exclusive vs. 53% exclusive, statistics not reported) Infant outcomes: No difference between groups in height; weight different between groups but no</td>
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<td>Diaz et al., 1984 [54]</td>
<td>Instituto Bioquinoico, Beta, WHO, International Development Research Centre, Chile</td>
<td>Cohort, N=653 healthy women after normal pregnancy, 18–35 years</td>
<td>BF performance (exclusivity at 6 months and continuation) Infant growth (weight gain at 6 months) and health (how assessed not defined) Follow-up 6 months Weaknesses: – Follow-up by postal survey – No statistical analysis – Unclear when methods were initiated Strengths: – Clear description of methods and analysis Weaknesses: – Women lost to follow-up or discontinuing their method not reported – Statistical analyses not presented for outcomes of interest – No control for confounding – Unclear how infant health was assessed</td>
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<tr>
<td>Jimenez et al., 1984 [38]</td>
<td>Upjohn</td>
<td>Retrospective cohort — follow-up to unpublished primary study, Chile, N=270</td>
<td>BF outcomes: Median lactation duration: 21 months DMPA vs. 13 months NH (p&lt;.05) Infant outcomes: Growth No difference between groups in height; weight different between groups but no Weaknesses: – Primary study not published – Some outcomes relied on retrospective self-report – Groups dissimilar (mothers in DMPA group older, of higher parity)</td>
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</table>

2nd month PP: 128=DMPA (150 mg q 3 months) 142=NH
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<tr>
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</thead>
</table>
| Tankeyoon et al., 1984 [57] WHO | Prospective cohort with nested RCT Hungary Thailand N=341 experienced BF women, ages 20–35 years, parity 2–4, after healthy term delivery | 6 weeks PP (±3 days): 59=DMPA 111 = NH (barriers, sterilization, IUD) Pill-users (randomized): 85=POP 86=COC (results not reported here) | BF performance (use of complementary food, discontinuation due to perceived inadequate milk supply) Infant growth (weight, length, arm circumference) Follow-up 24 weeks | Health
1 death in control group (accidental), 0 in DMPA group Development No differences between groups in psychomotor development, milestones, health problems, infant height or physical exam | BF outcomes:
No differences in complementary feeding or discontinuation of BF between groups Infant outcomes No differences in mean weight or rate of growth between contraceptive groups | Level II-2, Poor Key Question 1 |
| Abdulla et al., 1985 [66] Rockefeller Foundation | Cohort Egypt N=20 healthy women after singleton, term delivery (mean age 29 years) | 30–39 days PP: 10=LNG implant 10=Barriers/ nothing | Infant health (occurrence of significant illnesses; serum IgA, IgG, IgM) Follow-up 6 months | Infant outcomes No infants had significant illnesses No significant differences between groups in infant serum immunoglobulins | Weaknesses:
--No adjustment of for possible confounders | Level II-2, Poor Key Question 1 |
| Shaaban et al., 1985 [50] Rockefeller Foundation | Cohort Egypt N=150 healthy, multiparous, BF-experienced women (mean age 29 years) after normal, term delivery | 30–42 days PP: 50=LNG implant 50=Cu T380 IUD 50=Barriers/ nothing | BF performance (frequency, supplementation) Infant growth (weight, length) Infant health (illness) Follow-up 6 months | Infant outcomes Growth Slower weight gain in Norplant group to 3 months (but >50% | Weaknesses:
--No adjustment of for possible confounders | Level II-2, Poor Key Question 1 |
<table>
<thead>
<tr>
<th>Study</th>
<th>Methodology</th>
<th>Country/Cohort</th>
<th>N</th>
<th>Intervention</th>
<th>BF Outcomes</th>
<th>Infant Outcomes</th>
<th>Weaknesses</th>
<th>Level</th>
<th>Key Question</th>
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<td>Shikary et al., 1986</td>
<td>Cohort</td>
<td>India</td>
<td>29</td>
<td>POP (LNG 30 mcg)</td>
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<td>Infant health (daily 4-h urine samples tested for FSH, LH, testosterone)</td>
<td>No significant differences in mean FSH, LH and testosterone area under the curve between the groups</td>
<td>II-2,</td>
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<td>WHO, Population</td>
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<td>N=29 women after term delivery of male infants, ages 20–35 years</td>
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<td>Follow-up 15 weeks</td>
<td>Small sample size with no power calculations</td>
<td>Fair</td>
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<tr>
<td>Council</td>
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<td>Short follow-up</td>
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<td>Zacharias et al., 1986</td>
<td>Prospective cohort</td>
<td>Chile</td>
<td>665</td>
<td>LAM, Cu T IUD (presumably NH)</td>
<td>BF performance (duration)</td>
<td>Infant outcomes</td>
<td>Measures for growth and development not provided</td>
<td>II-2,</td>
<td>Poor</td>
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<td>Upjohn, Ayerst</td>
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<td>N=665 women, after term deliveries</td>
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<td>Infant growth and development (not specified)</td>
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<td>Survival analysis techniques</td>
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<td>Follow-up of children to a median age of 4.5 years</td>
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<td>Statistical comparisons not performed</td>
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<td>No attempt to control analysis for confounders</td>
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<td>Infants with “signs of inadequate nutrition” discontinued from study and not reported on</td>
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<td>Affandi et al., 1986</td>
<td>Cohort</td>
<td>Indonesia</td>
<td>120</td>
<td>LNG implant</td>
<td>Infant growth (weight, length)</td>
<td>Infant outcomes</td>
<td>Measures for growth and development not provided</td>
<td>II-2,</td>
<td>Poor</td>
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<tr>
<td>Population Council</td>
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<td>N=120 women after term, healthy delivery, planning to breastfeed ≥6 months</td>
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<td>Follow-up 6 months</td>
<td>Infants in LNG group gained significantly more weight than the IUD group. No differences in length between groups (statistical comparisons, p values not provided)</td>
<td>Survival analysis techniques</td>
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<td>Baseline differences between groups</td>
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<td>Percent follow-up not reported</td>
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<tr>
<td>McCann et al., 1989</td>
<td>Cohort</td>
<td>Argentina</td>
<td>500</td>
<td>LNG (30 mcg)</td>
<td>BF performance (continuation, supplementation)</td>
<td>Infant growth (weight, length, head circumference,</td>
<td></td>
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</tr>
<tr>
<td>USAID, Family Health International, Wyeth</td>
<td>Cohort</td>
<td>N=500 healthy multiparous women, after term delivery</td>
<td></td>
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<td>BF outcomes</td>
<td>for LNG vs.</td>
<td>Survival analysis performed</td>
<td>II-2,</td>
<td>Poor</td>
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<td></td>
<td>Infant outcomes</td>
<td>Mediation of supplementation 5.4 for LNG vs.</td>
<td>Only enrolled older,</td>
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</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Author, year, source of support</th>
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<th>Results</th>
<th>Strengths/weaknesses</th>
<th>Quality grading/Key question</th>
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</thead>
<tbody>
<tr>
<td><strong>Shahin, 1991 [40]</strong></td>
<td><strong>Cohort, WHO, Population Council, Rockefeller Foundation</strong></td>
<td>5th to 7th week PP: 125E-EN implant, 125E-IUD</td>
<td>BF performance (supplementation, age of weaning, growth, age at weaning), BF outcomes (number of women supplementing, age of supplementation, age of weaning, growth, IMF, BMI, SFST)</td>
<td>No differences between groups in number of women supplementing at any time</td>
<td>Level II-2, Fair</td>
</tr>
<tr>
<td><strong>Mogali et al., 1991 [50]</strong></td>
<td><strong>Family Health International</strong></td>
<td>1 week PP: 250-Norgestrel 75 mcg, 250-NH methods (75% IUD)</td>
<td>BF outcomes: No differences in timing or type of supplementation</td>
<td>IUD users weaned earliest, followed by NH group and POC group. No differences in infant outcomes.</td>
<td>No statistical analyses not reported</td>
</tr>
<tr>
<td><strong>Shaaban, 1991 [40]</strong></td>
<td><strong>WHO, Population Council, Rockefeller Foundation</strong></td>
<td>5th to 7th week PP: 125E-EN implant</td>
<td>BF outcomes: No differences in timing or type of supplementation</td>
<td>Infant outcomes: No differences in growth, health</td>
<td>Level II-2, Poor</td>
</tr>
</tbody>
</table>

**Key Question 1**

- Statistical analyses not reported on all outcomes of interest.
- Infant health outcomes collected but not reported.
- High loss to follow-up (15% POC, 13% NH LTFU over 6 months).
- Baseline characteristics not described.
- Methodology poorly described.
- Statistical analyses not reported on survival analysis.
PVR and Cu-IUD, results not discussed here

Infant development (attainment of milestones)
Follow-up 12 months

Infant outcomes

Growth
No differences in infant growth

Development
No difference in attainment of milestones

Infant outcomes

Growth
Relative risk for score below −2Z on growth chart (no exposure as reference):
1.1 (0.9–1.2) lactational exposure only (no prenatal exposure);
1.2 (1.0–1.3, p < 0.05) any lactational exposure (including some with prenatal exposure); RR 1.1 (0.9–1.4) for any lactational exposure when adjusted for potential confounders

Strengths:
– Clear description of methodology
– Appropriate analytical methods

Weaknesses:
– Large differences between sites for BF performance and infant outcomes
– Percent lost to follow-up not reported

Level II-2, Poor

Key Question 1

Pardthaisong, 1992 [29]

Cohort
Ford Foundation
WHO
FHI

Thailand

N=3231 infants with varying levels of prenatal and lactational DMPA exposure/nonexposure

During lactation (any time, 77% initiated between months 1 and 3)
857=DMPA only during lactation (not pregnancy)
1215=DMPA during lactation, some also during pregnancy
1167=No DMPA

Infant growth (weight, height)
Length of follow-up for lactationally exposed infants unclear

Infant outcomes

Growth

Strengths:
– Clear description of methodology
– Appropriate analytical methods

Weaknesses:
– Baseline differences noted between DMPA users and nonusers
– Unclear length of follow-up
– Timing and amount of exposure to DMPA unclear
– Unexposed may have been using other hormonal methods

Level II-2, Fair

Key Question 1

WHO, 1994 [58,59]

Cohort
WHO

Egypt, Iran, Thailand, Kenya, Chile, Hungary

N=2466 married women, after term delivery and their infants

6–8 weeks PP:
475=POP (LNG or lynestrenol)
541=DMPA
121=NET-EN
453=LNG implant
876=NH (IUD, barriers, sterilization)

BF performance (frequency, duration exclusive BF)
Infant growth (weight, arm circumference, skinfold thickness)
Infant health (mortality)
Infant development (age passed standard developmental test)
Follow-up 12 months

BF outcomes:
Frequency and duration of BF differed between sites, but not between contraceptive groups within a site

Infant outcomes

Growth
One site had larger weight increase in NET-EN group (6, 12 months) and DMPA group (3 months) compared to NH group
Smaller increase in arm circumference at

Strengths:
– Large cohort, multicultural and multicenter
– Standardized assessment of development
– Confounders assessed and controlled for in analysis

Weaknesses:
– Large differences between sites for BF performance and infant outcomes
– Percent lost to follow-up not reported

Level II-2, Fair

Key Question 1
<table>
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<th>Quality grading/key question</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdel Aleem et al., 1996 [51]</td>
<td>Cohort</td>
<td>2nd PP month:</td>
<td>BF performance (frequency of BF, % BF at all and exclusively at different time periods)</td>
<td>BF outcomes</td>
<td>No significant differences between groups in BF frequency, continuation or exclusivity</td>
<td>Level II-2, Fair Key Question 1</td>
</tr>
<tr>
<td>South-to-South Cooperation in Reproductive Health</td>
<td>Egypt</td>
<td>120=Nomegestrol implant</td>
<td>Infant growth (weight, arm circumference, skinfold thickness)</td>
<td>Infant outcomes</td>
<td>Growth No differences in infant growth</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N=242 healthy, exclusively BF women and their term infants (mean age 26 years)</td>
<td>120=Cu-IUD</td>
<td>Infant health (frequency of diarrhea, fever, cough and mortality)</td>
<td>Health No significant differences in health.</td>
<td>7 infants died: 6 in implant group (4 gastroenteritis, 1 seizures, 1 pneumonia), 1 (gastroenteritis) in IUD group (not significant, p&gt;0.05)</td>
<td></td>
</tr>
<tr>
<td>Hannon et al., 1997 [41]</td>
<td>Cohort</td>
<td>At the time of hospital discharge:</td>
<td>BF performance (BF continuation and exclusivity)</td>
<td>Follow-up 16 weeks</td>
<td>No difference in duration of lactation (median 10.14 weeks for DMPA vs. 6.57 weeks in NH</td>
<td>Level II-2, Poor Key Question 1</td>
</tr>
<tr>
<td>National Institutes of Health and Thomas Wilson Sanatorium</td>
<td>USA</td>
<td>45=DMPA 150 mg</td>
<td></td>
<td></td>
<td>Strengths: Sample selection/methods clearly described</td>
<td></td>
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<tr>
<td></td>
<td>N=103 women consecutive, term deliveries with ability to follow-up by</td>
<td>52=NH (unspecified)</td>
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<td>Power calculations performed</td>
<td></td>
</tr>
</tbody>
</table>

**Results**
- Two sites for POP group (3 months and 3 and 12 months)
- Development: 247 comparisons; 32 showed significant differences: in 20, infants in progesterone-only groups passed tests at earlier ages, and in 12, they passed at later ages.
- Mortality: No significant differences within sites by method
- BF outcomes: No significant differences between groups in BF frequency, continuation or exclusivity
- Infant outcomes: Growth No differences in infant growth
- Health: No significant differences in health. 7 infants died: 6 in implant group (4 gastroenteritis, 1 seizures, 1 pneumonia), 1 (gastroenteritis) in IUD group (not significant, p>0.05)
- BF outcomes: No difference in duration of lactation (median 10.14 weeks for DMPA vs. 6.57 weeks in NH

**Strengths/Weaknesses**
- Assessment of infants was blinded to contraceptive group
- Power calculations presented
- Underpowered to look at infant health outcomes
- Percent follow-up not reported
- Baseline differences between groups

**Quality grading/key question**
- Level II-2, Fair Key Question 1
Diaz et al., 1997 [60]
WHO, Population council, CONRAD
Cohort with historical control
Chile
N = 662 cohabitating parous (1–3) women after term delivery, ages 18–38 years
57±3 days PP:
117=POP (lynestrenol)
187=PV/R
120=LNG implant
122=Copper IUD
236=NH (LAM)
BF performance (duration of any and exclusive BF)
BF outcomes
Infant growth (weight)
Follow-up 6 months
No difference in time to supplementation with formula
BF users, p=.19
No difference in mean and total duration of BF
Infant outcomes
No differences in growth between groups
Weaknesses:
- Limited duration of follow-up
- No infant outcomes
- Baseline differences between groups (DMPA younger, unmarried)
Level II-2, Fair
Key Question 1

Lawrie et al., 1998 [35]
Schering Ltd, Iris Ellen Hodges Trust of the University of the Witwatersrand, South African Medical Research Council, South African Institute for Medical Research
RCT
South Africa
N = 166 immediate PP women ages >19 years
<48 h PP:
85=NET-EN
84=Placebo
All women additionally used an NH method
BF performance (duration of any and exclusive BF)
BF outcomes
Maternal depression (not reported here)
No difference between groups in continuation rates at 6 or 12 weeks
Strengths:
- Clear description of methods
- Enrolled women regardless of past/current BF experience
Weaknesses:
- Small sample size
- BF outcomes were secondary
Level I, Fair
Key Question 1

Coutinho et al., 1999 [64]
Rockefeller Foundation
Prospective cohort
Brazil
N = 135 women, 18–35 years old after term health delivery planning to breastfeed for 6 months and their infants
6 weeks PP:
66=Elcometrine implant
69=Cu-IUD
BF performance (any BF at follow-up time points)
Infant growth (weight, arm circumference, skinfold thickness)
Infant development (age meeting standard milestones, using developmental tests)
Follow-up 12 months
BF outcomes
Higher rates in implant group (95–76%) vs. IUD (84–57%) at 3, 6 months (p<.05), no differences at 9, 12 months
Infant outcomes
Growth
No differences between groups
Development
No differences in age met developmental milestones
Strengths:
- Power calculation performed
- Standardized outcomes used and described
Weaknesses:
- No control for potential confounders
Level II-2, Fair
Key Question 1

Diaz et al., 1999 [28]
Population Council
Newly identified
Prospective cohort
Chile
N = 108 BF women planning to continue to breastfeed
57±3 days PP:
29=LNG implant
51=Cu-IUD
28=PV/R (results not reported here)
BF performance (any or exclusive BF up to 6 months, no milk supplementation at 12 months)
Infant growth (weight)
BF outcomes
Fully BF month 6: 93% LNG, 86% IUD (no difference);
Fully BF month 12:
Strengths:
- Clearly described methods
Weaknesses:
- BF/Infant outcomes
Level II-2, Fair
Key Question 1

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</tr>
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<tbody>
<tr>
<td>Bjarnadóttir et al., 2001 [46] Organon</td>
<td>Cohort Iceland N=83 multiparous women with prior experience BF, after term delivery, ages 18–40 years</td>
<td>28–56 days PP: 42=Desogestrel 75 mg 41=Cu 375 IUD</td>
<td>BF performance (any BF) Infant growth (length, weight, head circumference) Infant health (intercurrent illness, hospitalizations) Follow-up 2.5 years</td>
<td>Follow-up minimum 12 months 4% LNG, 10% IUD (no difference) Duration of lactation 15 months LNG, 14 months IUD (no difference) Infant outcomes Growth No difference between LNG and Cu-IUD groups at month 1, 6 or 12 BF outcomes No difference in BF continuation at cycle 4 (5–6 months PP), but at end cycle 7 (8–9 months PP), 78% in desogestrel compared with 59% in IUD group were still BF (statistics not reported) Infant outcomes Growth No difference Health Temporary breast enlargement in 2 infants, increased sweating in 1 infant in desogestrel group; no occurrences in IUD group. No other differences in health Infant outcomes Growth No differences Infant outcomes Growth No differences in weight or length at any time; mean head circumference change 1.42 cm (progestogen-only) vs. 1.19 (NH) at 10–13 weeks (p&lt;.05). No</td>
<td>were secondary –Length of follow-up unclear –Loss to follow-up not specified</td>
<td>Level II-2, Fair Key Question 1</td>
</tr>
<tr>
<td>Baheiraei et al., 2001 [68]</td>
<td>Prospective cohort Iran N=140 women, after healthy term delivery</td>
<td>6 weeks PP: 51=Progestogen-only (DMPA; POP) 89=NH (IUD, condom, sterilization)</td>
<td>Infant growth (weight, length, head circumference) Follow-up 26 weeks</td>
<td>Infant outcomes Growth No differences in weight or length at any time; mean head circumference change 1.42 cm (progestogen-only) vs. 1.19 (NH) at 10–13 weeks (p&lt;.05). No</td>
<td>Weaknesses: –Contraceptive use/ switching or formulations are not stated –Separate estimates for different methods not presented –Percent lost to follow-up not reported</td>
<td>Level II-2, Poor Key Question 1</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Country</td>
<td>Sample Size</td>
<td>Follow-Up</td>
<td>BF Outcomes</td>
<td>Infant Growth</td>
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<tr>
<td>Massai et al., 2001 [63]</td>
<td>Prospective</td>
<td>Chile</td>
<td>200</td>
<td>55–60 days</td>
<td>BF outcomes</td>
<td>Infant growth</td>
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<tr>
<td>US Agency for International Development/UN Population Fund</td>
<td>Cohort</td>
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<tr>
<td>Halderman and Nelson, 2002 [42]</td>
<td>Cohort</td>
<td>USA</td>
<td>319</td>
<td>6 weeks</td>
<td>BF outcomes</td>
<td>Infant growth</td>
</tr>
<tr>
<td>Schiappacasse et al., 2002 [62]</td>
<td>Prospective</td>
<td>Chile</td>
<td>442</td>
<td>6 years</td>
<td>BF outcomes</td>
<td>Infant growth</td>
</tr>
<tr>
<td>(Some data originally reported in Diaz 1985 [61] and as part of WHO 1994 [58,59])</td>
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<tr>
<td>Shaamash et al., 2005 [56] Schering</td>
<td>RCT Egypt N=320 women after term delivery</td>
<td>6–8 weeks PP: 163=LNG-IUD 157=Copper IUD</td>
<td>BF performance (duration, number of episodes/day, exclusivity) Infant growth (weight, length, skinfold thickness) and development (age passing standard developmental tests) Follow-up 1 year</td>
<td>Hospitalizations greater in LNG group (1% vs. 0.4%, p&lt;0.05) among BF infants; but higher in IUD group overall (1.7% vs. 0.6%) Rates for other illnesses similar; 1 death in Norplant group at 7 months for acute diarrhea and septicemia</td>
<td>generalizability</td>
<td>Level I, Fair Key Question 1</td>
</tr>
<tr>
<td>Taneepanichskul et al., 2006 [53] Reinprayoon et al., 2000 [52] Organon</td>
<td>Prospective cohort Thailand N=80 women after term deliveries, ages 18–40 years</td>
<td>28–56 days PP: 42=ETG implant 38=Copper IUD</td>
<td>BF performance (duration) Infant/child growth (length, weight) and development Infant health (intercurrent illness) Follow-up 3 years</td>
<td>BF outcomes Mean duration of BF: 421 days (Implant) vs. 423 days (IUD), NS Infant outcomes Growth (no statistical comparisons)</td>
<td>Strengths: –Randomized –Adequate allocation concealment –Sample size calculations –Standardized infant development tests Weaknesses: –Enrolment and exclusion criteria not stated –Intent-to-treat analysis and percent loss to follow-up not reported –Infant health outcomes collected but not reported</td>
<td>Level II-2, Fair Key Question 1</td>
</tr>
<tr>
<td>Study Authors and Year</td>
<td>Study Design and Country</td>
<td>Participants</td>
<td>Intervention</td>
<td>BF Outcomes</td>
<td>Infant Outcomes</td>
<td>Strengths</td>
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<tr>
<td>Brito et al., 2009 [20]</td>
<td>RCT (open label) Brazil RCT (open label) Brazil</td>
<td>40 women with BMI $&gt;$ 30, ages 18–35 years</td>
<td>Etonorgestrel implant (ETG) 6 weeks PP: 150 mg DMPA</td>
<td>No difference in exclusive BF between groups at 6 weeks or 12 weeks: (6 weeks 95% ETG, 85% DMPA; 12 weeks 95% ETG, 85% DMPA)</td>
<td>No difference in exclusive BF between groups at 6 weeks or 12 weeks: (6 weeks 95% ETG, 85% DMPA; 12 weeks 95% ETG, 85% DMPA)</td>
<td>Randomization methods appropriate</td>
</tr>
<tr>
<td>Chen et al., 2011 [22]</td>
<td>RCT (open label) United States RCT (open label) United States</td>
<td>96 women interested in PP IUD</td>
<td>LNG-IUD 6–8 weeks PP (delayed): 46=LNG-IUD</td>
<td>No difference in BF at 6 or 12 weeks</td>
<td>Differences at 6 weeks 12 weeks: (6 weeks 50% LNG-IUD, 80% DMPA; 12 weeks 50% LNG-IUD, 60% DMPA)</td>
<td>Randomization methods appropriate</td>
</tr>
</tbody>
</table>

No differences reported in adverse events or psychomotor development (60% infants in both groups had resp. disorders, and >30% in both groups had skin disorders) based on WHO recommendations for toxicology, not for BF or health outcomes.

Strengths:
- Randomization methods appropriate
- Allocation concealment appropriate
- Methods clearly described

Weaknesses:
- Short follow-up
- Small sample size with no power calculations

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<tr>
<td>Gurtcheff et al., 2011 [23] National Center for Research Resources Newly identified</td>
<td>RCT (open label) United States N=69 peripartum women desiring ETG implant</td>
<td>Insertion at 1–3 days PP: 35=ETG implant (early) 4–8 weeks PP 34=ETG implant (standard)</td>
<td>BF performance (time to lactogenesis stage II, lactation failure, formula supplementation) Follow-up 6 months</td>
<td>3/50 postplacental, 11/46 delayed p=.02 Exclusive BF at 6 months 1/50 postplacental, 6/46 delayed p=.05</td>
<td>prior to LNG-IUD placement --Short follow-up --Very low rates BF in both groups may limit generalizability</td>
<td>Level I, Fair Key Question 2</td>
</tr>
<tr>
<td>Costa et al., 2012 [26] FAPESP Newly identified</td>
<td>Cohort Brazil N=82 PP women</td>
<td>6 weeks PP: 28=POCs (DMPA, POP, LNG-IUD) 54=NH (Barrier, LAM, TL, Cu-IUD)</td>
<td>BF performance (exclusive and total BF duration) Follow-up 6 months</td>
<td>BF outcomes Mean time to lactogenesis stage II 64 h (early); 65 h (standard) Lactation failure 1/34 early, 0/35 standard, risk difference 0.03 (early vs. standard) Formula supplementation No difference between groups at 2 weeks, 4–8 weeks, 3 months or 6 months BF outcomes Exclusive: Mean duration 137 days NH, 113 days POC (p=.143) Total (any BF): 183 days NH, 183 days POC (p=.383)</td>
<td>Strengths: --Included primiparas --Clear description of methods Weaknesses: --No separate analysis of different POCs --BF outcomes were secondary outcomes</td>
<td>Level II-2, Fair Key Question 1</td>
</tr>
<tr>
<td>Espey et al., 2012 [21] ACOG contraceptive grant and University of New Mexico Newly identified</td>
<td>RCT (double blinded) US N=127 women ages 15–45 years, planning to BF and use oral contraceptives</td>
<td>2 weeks PP: 64=COC (0.35 mg ethinyl estradiol, 1 mg norethindrone) 65=POP (norethindrone 0.35 mg norethindrone)</td>
<td>BF performance (BF continuation at 8 weeks, 6 months; supplementation at 8 weeks) Infant growth (weight, length, head circumference) Follow-up 6 months for BF outcomes, 2 months for infant outcomes</td>
<td>BF outcomes: No difference in continuation at 8 weeks (64% COC, 63.5% POP) or over 6 months (survival analysis); no difference in supplementation at 8 weeks (percents not reported) Infant outcomes Growth: No difference through 8 weeks</td>
<td>Strengths: --Included primiparas --Randomization methods appropriate --Allocation concealment appropriate --Methods clearly described --Double-blinded --Minimal method switching --Loss to follow-up similar between groups Weaknesses --Small sample size</td>
<td>Level I, Fair Key Question 1</td>
</tr>
</tbody>
</table>
Matias et al., 2012 [16]
NIH, Fogarty Perú
International Center,
NICHD, UC Davis
Newly identified

Cohort

By 72 h
By 1 month PP:
19=DMPA
By 3 months PP:
41=DMPA
By 6 months PP:
45=DMPA

BF performance (exclusive BF at 3 months and 6 months PP)
Follow-up 6 months

BF outcomes: Women initiating DMPA after 72H PP had higher odds of exclusive BF at 3 months than those who initiated before 72 h or those who did not initiate at all (adjusted OR 6.1, CI 1.7–21.4 — unpublished data)

Multivariate model: DMPA use by 3 months associated with adjusted RR of exclusive BF at 3 months 1.35 (1.1–1.66)

Strengths:
--Clearly described methodology
--Appropriate analytic methods
Weaknesses:
--Unclear when within the time frame method was started
--Unclear what methods, if any, non-were used by non-DMPA users

Level II-2, Fair
Key Questions 1 and 2

Brownell et al., 2013 [25]
No funding
Newly identified

Cohort (retrospective)
US
N=183 women who initiated BF

BF performance (continuation)

BF outcomes: Median duration DMPA 30 days, no DMPA 41 days (HR 1.14, nonsignificant) Continuation at 2 week No difference between groups on survival curve (p=.24) Continuation at 6 weeks No difference

Strengths:
--Power analysis done (but post hoc)
--DMPA exposure verified through hospital records
--Survival analysis methodology
Weaknesses
--Few women in either group continued BF after

Level II-2, Fair
Key Question 1

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<tr>
<td>Singh et al., 2013 [24]</td>
<td>Brazil, PP: 40 multiparous women with prior BF experience</td>
<td>Doc 42 PP: 10 COC implant</td>
<td>BF performance (duration), number of episodes/day</td>
<td>No significant difference among groups in BF duration at 6 weeks or 3 or 6 months</td>
<td>Strengths: Frequent data collection, Clearly described methodology</td>
<td>Level II-2, Poor Key Question 1</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Infant growth (weight, length)</td>
<td>No significant difference in weight gain or length gain at any time point of follow-up</td>
<td>Weaknesses: Short duration follow-up (data not shown)</td>
<td></td>
</tr>
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</table>

**Abbreviations:** ACOG: American College of Obstetrics and Gynecology; BF: breastfeeding; CEBRE: Center for the Study of Reproductive Biology; FAPESP: Fundação de Amparo à Pesquisa do Estado de São Paulo; NE: non-hormonal; PP: postpartum; TL: tubal ligation;
include progestogen-only pills (POPs), progestogen and progesterone implants, injectables, progesterone rings and progesterone-releasing intrauterine devices (IUDs). They are highly effective when used as directed [6].

The use of progestogen-only methods of contraception [progestogen-only contraceptives (POCs)] during the period of lactation has raised concerns for negative effects [7]. Progestogens could interfere with lactogenesis, especially immediately postpartum [8], and have been shown to be transferred to breast milk [9]. Animal data suggest that progesterone receptors are common in the developing rat forebrain [10]. It is therefore possible that POCs may affect infant health or development [11]. The large loading dose of progestogens found in the injectable depot medroxyprogesterone acetate (DMPA) has been particularly called into question [7].

This systematic review was conducted for the WHO’s Medical Eligibility Criteria for Contraceptive Use (MEC) [12] and examines the effects of POCs on outcomes such as breastfeeding performance and infant growth, development and health. It updates a previous review from 2010 [13].

2. Methods

We followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for the conduct of systematic reviews. [14]

2.1. Key questions

We identified two key questions of interest: (1) Among breastfeeding women and their infants, was the use of POCs associated with a difference in breastfeeding or infant outcomes, compared with nonuse of POCs? (2) Among breastfeeding women and their infants, was initiation of POCs before 6 weeks postpartum associated with a difference in breastfeeding or infant outcomes, compared initiation of POCs at 6 weeks or later?

2.2. Search strategy

We searched PubMed for relevant articles in all languages published or in press from database inception through December 15, 2014 (see Appendix I). We searched reference lists of relevant articles for additional citations of interest. We did not consider unpublished studies, abstracts or dissertations. We had previously contacted one author for clarification regarding allocation between treatment groups [15] and contacted another for clarification of method of analysis and measures of association of interest [16].

2.3. Study selection

We included primary reports of studies of breastfeeding women who received POCs (oral, injectable, implantable or hormonal IUDs), as well as progesterone pellets. Studies assessing progesterone vaginal rings (PVRs) [17] were excluded as they were reviewed separately [18]. The main outcomes were breastfeeding performance and infant health. Studies that reported solely on self-perceived ability to breastfeed (without any reporting on duration of breastfeeding), breastfeeding episodes, milk composition or milk quantity were excluded. Studies that did not specify when contraceptives were initiated were also excluded. Studies that compared use of POCs with use of another type of hormonal contraceptive were considered indirect evidence. We included trials, cohort and case–control studies and excluded cross-sectional and noncomparative studies.

2.4. Study quality assessment

Two authors assessed the quality of each study (SP and NT) using the United States Preventive Services Task Force evidence grading system [19].

2.5. Data synthesis

We used a standard data abstraction template to systematically assess and summarize the evidence. Because many studies and recommendations separate results by the use of contraception before and after 6 weeks postpartum, we structured this report similarly. Summary odds ratios were not calculated, given the heterogeneity of interventions, results and nonquantifiable outcomes reported.

3. Results

The literature search yielded 848 articles; 771 were excluded on title and abstract review and 28 were excluded after full-text review, leaving 49 reports meeting inclusion criteria. Since this review was last updated in 2008 [13], four new randomized controlled trials (RCTs) [20–23] and five new observational studies were published [16,24–27], and an additional five observational studies that were not included in the 2008 review were identified [28–32], for a total of eight reports of RCTs and 41 reports of nonrandomized clinical trials or observational studies for review (Table 1). These 49 articles reported on 47 different studies investigating the use of POCs in breastfeeding women and reported clinically relevant outcomes of infant growth, health or breastfeeding performance.

Results for Key Question One, then for Key Question Two, are presented by study design and by time of contraceptive initiation: less than 6 weeks or greater than or equal to 6 weeks postpartum. Newly identified studies are presented first, followed by a brief summary of findings from the previous review. Nonrandomized clinical trials are presented together with observational data.

3.1. Key Question One, initiation at less than 6 weeks postpartum: Lactation performance

3.1.1. Randomized clinical trials

Four RCTs [21,33–35] investigated POC initiation within 6 weeks postpartum. A new RCT provides indirect evidence:
this trial randomized 127 women planning to breastfeed to either POPs or combined oral contraceptives (COCs), started 2 weeks postpartum [21]. No difference was noted between groups in breastfeeding continuation or supplementation over 6 months.

Three RCTs were included in the previous review. In one, fewer levonorgestrel (LNG) IUD users were breastfeeding than copper (Cu) IUD users at 75 days; this difference disappeared at 6 months [34]. Mean duration of breastfeeding was similar. Another investigating the use of norethindrone compared with placebo found no difference between groups in breastfeeding initiation [33]. A third found no difference in breastfeeding outcomes over 12 weeks between women who received injectable norethisterone enanthate (NET-EN) or placebo [35].

3.1.2. Nonrandomized clinical trials and observational studies

3.1.2.1. Injectables. In 11 nonrandomized clinical trials and observational studies, four of which are newly included since the last review [16,25,27,31], progestogen-only injectables (POIs) (either DMPA or NET-EN) were initiated in the first 6 weeks postpartum; most of these found either no effect on breastfeeding outcomes or improved outcomes among DMPA users. In one new prospective cohort study, women initiated DMPA or a nonhormonal method postpartum; no difference in breastfeeding frequency or continuation was observed at 6 weeks or at 3 or 6 months [27]. A second prospective cohort study found that women who initiated DMPA after 72 h were more likely to exclusively breastfeed at 3 months than those who either did not initiate or initiated early [16]. No differences emerged in exclusive breastfeeding to 6 months for those who did not initiate DMPA compared with those who initiated by 3 or 6 months. A third retrospective cohort study found no significant differences in duration or continuation of breastfeeding through 6 weeks between women who initiated DMPA before 5 days postpartum compared with those who did not [25]. The fourth new study prospectively investigated the use of DMPA compared with use of other contraceptive methods [31]. Most of the women studied received DMPA within the first 3 months postpartum. Those who received DMPA were more likely to be fully breastfeeding at 3 and 6 months postpartum and were more likely to continue breastfeeding through 12 and 18 months. Of women who received DMPA in the first 3 months, 35% were still breastfeeding at 4 weeks [36]. Another found that mothers who received either DMPA or a nonhormonal method at hospital discharge had no differences in breastfeeding exclusivity, supplementation or duration [41]. Finally, when DMPA initiated at hospital discharge was compared with nonhormonal method use, no differences were found in breastfeeding at 2 or 6 weeks, although fewer DMPA users were breastfeeding at 4 weeks [42].

3.1.2.2. POPs. Eight observational studies assessed the use of POPs in the first 6 weeks postpartum; all were included in the previous review and found either no differences between POP users and nonusers or improved breastfeeding outcomes with POP use. In a nonrandomized trial, POP users initiated breastfeeding earlier than placebo users [43]. Other studies found no difference in breastfeeding duration for POP users compared with historical controls [37] or compared with nonhormonal users [39,44], while two found longer breastfeeding duration among POP users compared with historical controls [45] or IUD users [46]. Finally, two studies found less supplementation among POP users than nonhormonal users [47,48].

3.1.2.3. Implants. Five observational studies, all in the previous review, largely found no difference in outcomes when assessing the impact of implants in the first 6 weeks postpartum. Women using a norethindrone implant were more likely to supplement breastfeeding at 3 months than those using condoms, but no differences were noted at any other time through 6 months or in the mean duration of breastfeeding [49]. Two studies found no difference in supplementation comparing LNG implant with IUD users [40,50]; one of these also found no difference in breastfeeding duration [50]. Users of nomegestrol implants compared with IUD users similarly had no difference in time of weaning or breastfeeding rates through 12 months [51]. Finally, breastfeeding duration did not differ between users of an etonogestrel (ETG) implant compared with Cu-IUD users over 3 years [52,53].

3.1.2.4. Multiple POCs. One study, included previously, assessed users of the LNG implant or POPs (analyzed together) and found no differences in breastfeeding initiation or exclusivity, although POC users were less likely to be breastfeeding than nonhormonal users at one of three time points [42].

3.1.2.5. Nor orally available progestogens. Progesterone, unlike progestogens, is not absorbable orally; therefore, use during breastfeeding is believed to be safe for a neonate. As it is absorbed by the mother, it could impact breastfeeding. Two studies examined the use of progesterone pellets in the first 6 weeks postpartum; both were included in the previous
review. Neither showed an impact on continuation of breastfeeding at 6 months [54] or at 6 and 12 months [55], compared with Cu-IUD use.

3.2. Initiation at ≥6 weeks postpartum: Lactation performance

One RCT and 13 observational studies (four newly identified [24,26,28,30]) evaluated the use of POCs initiated 6 weeks postpartum or more. None of these reported negative impacts on breastfeeding outcomes among POC users compared with nonusers, with the exception of one observational study that found that the average age of supplementation was younger among POP users compared with IUD users [30].

3.2.2. Observational studies

3.2.2.1. Injectables. Three observational studies (one new) were identified. The new study did not find supplementation among infants of mothers receiving injectables nor among those who received no method [36]. Among the studies included in the previous review, one found no difference between DMPA and nonhormonal users in breastfeeding discontinuation or initiation of complementary foods [57]. Another found no difference in breastfeeding duration within study sites between DMPA and NET-EN users, compared with nonhormonal method users, although differences were seen between sites [58,59].

3.2.2.2. POPs. Four studies (one new) assessed the impact of POPs on breastfeeding outcomes. In the new study, a nonrandomized trial [30], women used POPs, a Cu-IUD plus placebo pill or one of several combined hormonal methods. The average age of supplementation was lower in the POP group compared with the IUD group (11.2 vs. 15 weeks), although statistical comparisons were not reported. Among the studies included in the prior review, one found no difference in complementary feeding or breastfeeding continuation up to 24 weeks when comparing POP users with nonhormonal users [57]. Two others found no difference in breastfeeding duration between POP and nonhormonal users [58–60].

3.2.2.3. Implants and hormonal IUDs. Six studies, two of which are new, assessed the impact of implant or hormonal IUD use on breastfeeding outcomes; none found differences between groups. One new study assessed the effect of both the ETG implant and the LNG-IUD compared with Cu-IUD and found no differences between groups in mean duration of breastfeeding at 6 months [24]. The other new study included LNG implant and Cu-IUD users and found no difference in the percentage of fully breastfeeding at month 6 or 12 and no difference in breastfeeding duration [28].

In one of the previously reviewed studies, women who received a norethindrone implant were similar to condom users in supplementation and breastfeeding continuation to 8 months [49]. In three studies of women who initiated the LNG implant, similar duration of breastfeeding was seen among both hormonal and nonhormonal users [58–62].

3.2.2.4. Multiple progestogen-only methods. One new study assessed the impact of multiple POCs without presenting outcomes separately by method. This prospective cohort found no difference in duration of breastfeeding between users of POCs and nonhormonal methods over 6 months [26].

3.2.2.5. Nonorally available progestogens. Three studies, none new, assessed the impact of nonorally available progestogens (progesterone pellets and nesterone or elcometrine implants) on breastfeeding outcomes. In two of these, breastfeeding duration was similar between women using progesterone pellets [54] or a nesterone implant [63], compared with Cu-IUD. Elcometrine implant users had a higher rate of breastfeeding at 3 and 6 months and similar rates at 9–12 months compared with Cu-IUD users [64].

3.3. Initiation less than 6 weeks postpartum: Infant outcomes

Thirty-seven studies (four RCTs, 32 observational studies and one cohort study with a nested RCT) were identified, including many of the studies previously described. Although some studies found differences in growth, health or development at some individual time points, most demonstrated no adverse impact of POCs.

3.3.1. RCTs

Three trials were identified. One of these studies is new and provides indirect evidence; the other two were included in the previous review. In the new study, women initiated either POPs or COCs at 2 weeks postpartum; no differences emerged in infant weight, length or head circumference through 8 weeks [21]. In a study of POPs or placebo, no differences were reported for infant weight gain at 14 days [33]. Similarly, infants of LNG-IUD users had similar weight, height and health through 12 months compared with Cu-IUD users [34].

3.3.2. Observational studies

3.3.2.1. Injectables. Seven observational studies, three newly identified [27,29,32], assessed infant outcomes after initiation of POIs; all either found no detrimental effect or a protective effect of injectables on infant growth and health. A new cohort study of 250 women found no differences in infant growth or reports of illness up to 6 months when comparing users of DMPA initiated within 10 days postpartum with users of nonhormonal methods [27]. Another newly identified cohort study found no difference in infant weight gain up to 46 months between infants whose
mothers had been exposed to DMPA at various time points and those who did not receive DMPA prior to 9 months postpartum [32]. No significant differences were found between groups in infant infections, although a subgroup that received DMPA within 2 days postpartum had a 75% higher incidence than the other groups (statistics not reported). Another cohort study included infants who were exposed to DMPA during breastfeeding (but not during their mother’s pregnancy), during both pregnancy and breastfeeding or not at all [29]. Infants who were exposed only during breastfeeding were no more likely than the unexposed to have a height or weight over two standard deviations below the mean. Infants exposed to DMPA during breastfeeding (including those exposed during pregnancy) were more likely to have short stature; this difference was no longer significant after adjusting for socioeconomic factors and no effect on weight was seen. Follow-up period was unspecified.

The remaining four studies were included in the previous review. In one, infant weight gain was the same for NET-EN, DMPA and Cu-IUD users up to month 3, after which weight gain was greater in both the DMPA and NET-EN groups [36]. No physical, mental or radiological differences were seen through 18 months. Another study found no effect of maternal DMPA use on infant weight, development or health compared with nonhormonal method use through 3–6 years of follow-up [38]. One child death was reported in the nonhormonal group, and none was reported in the DMPA group. In another study, infants had no adverse effects with maternal NET-EN use through 30 months of age when compared with nonhormonal method use; specific outcomes were not provided [39]. The fourth study found no difference in growth or development among infants of NET-EN users compared with infants of Cu-IUD users over 12 months [40].

3.3.2.2. POPs. Six observational studies or nonrandomized trials, none new in this review, assessed infant outcomes associated with POP use; most found no adverse effects. In one study, infants of women using POPs had greater weight increase than placebo users at day 14 [43]. Another study found no difference in urinary FSH, LH or testosterone among male infants of POP users compared with users of no method at 4 weeks [65]. Another study found no adverse effects of POPs up to an average of 4.5 years of age, compared with infants of women who used the lactational amenorrhea method (LAM) or the IUD (presumably nonhormonal) [39]. Two studies found no growth differences between infants of mothers using POPs compared with nonhormonal users [47,48]; one of these also found no difference in hospitalizations [47], while the other found more frequent minor illnesses and greater mortality (3 vs. 0 deaths) among children of mothers who used nonhormonal methods [48]. Finally, infants of desogestrel users had temporary breast enlargement (2 infants) and perceived increased sweating (1 infant), compared with no adverse effects among infants of Cu-IUD users [46]. Follow-up through 2.5 years revealed no clinically relevant effects of desogestrel on the growth or health of the infants.

3.3.2.3. Implants. Eight studies that assessed the impact of implants were included, none of which is new; generally no adverse effects were reported. In one study, infant weight was no different between norethindrone implant and barrier method users [49]. Another found no health or serum immunoglobulin differences between infants of LNG implant and nonhormonal users [66] and another found no differences in mean FSH, LH or testosterone [65]. One study found slower weight gain in infants of LNG implant users up to 3 months, compared with Cu-IUD users. This difference disappeared at 4–6 months; however, length increased less among infants of LNG users compared with Cu-IUD users [50]. No differences in morbidity were reported. In another study, infant lengths did not differ and weight was greater among infants of LNG implant users [67], and in a third, no differences were found between implant users and nonhormonal users in growth or development [40]. A study of the nomegestrol implant compared with Cu-IUD found no difference in growth or health; greater infant mortality was seen in the implant group (six deaths from gastroenteritis, seizures and pneumonia, compared with one death from gastroenteritis in the Cu-IUD group) but was not statistically significant [51]. Finally, a study of ETG implants compared with the Cu-IUD found no differences in infant growth, adverse events, respiratory or skin disorders or developmental scores [52,53].

3.3.2.4. Nonorally available progestogens. Two studies reported no difference in infant growth or health comparing progesterone pellet users with placebo or Cu-IUD users [54,55].

3.4. Initiation at ≥ 6 weeks: Infant outcomes

Most of the studies described above also reported on infant outcomes. The majority found no significant differences between infants of POC users and nonhormonal method users, although differences in both directions were noted in some comparisons.

3.4.1. RCTs

Two RCTs (neither new) investigated the effect of POC initiation after 6 weeks postpartum. In both, no differences in infant growth or development were seen between users of the LNG-IUD compared with the Cu-IUD through 1 year [56] or between users of POPs or DMPA compared with nonhormonal method users through 24 weeks [57].

3.4.2. Observational studies

3.4.2.1. Injectables. Three observational studies (none new) assessed the impact of maternal use of POIs initiated at 6 weeks postpartum or later; none is new. One found increased weight gain among infants of DMPA and NET-EN
users compared with nonhormonal users and also found no physical, mental or radiological differences over 18 months [36]. Another similarly found no difference in mean weight between DMPA users and nonhormonal users through 24 months [57]. Another study showed more weight gain among infants of DMPA and NET-EN users at some time points (3 and 12 months) and no difference at others (6 and 9 months). The majority of comparisons in developmental tests were similar, although some tests favored nonhormonal methods and others favored DMPA or NET-EN [58,59].

3.4.2.2. POPs. Four studies, one new [30], assessed the impact of POPs. The new study found no difference in infant growth between those whose mothers used a POP compared with those whose mothers used an IUD plus placebo pill up to 32 weeks [30]. In the other three studies, one found smaller increase in arm circumference at two sites among infants of POP users compared with nonhormonal users but found no difference for other growth measures or for the majority of developmental test results [58,59]. The second found no differences in infant weight gain over 6 months when comparing infants of POP users with those of users of multiple other hormonal and nonhormonal methods [60]. The third found no difference in infant growth (length, weight, arm circumference) among infants of women using POPs compared with those using nonhormonal methods [57].

3.4.2.3. Implants/hormonal IUDs. Six studies, two new [24,28], assessed infants whose mothers initiated progesterone-only implants or hormonal IUDs. In one new study, women initiated the ETG implant or LNG-IUD 6 weeks postpartum; no difference was found in infant weight or height through 6 months, although infants in the implant group had less increase in tibial length than infants in the Cu-IUD group [24]. The other found no differences over 12 months in infant weight between users of the implant and users of the Cu-IUD initiated at 8 weeks [28].

The remaining four studies were included previously. In one, infants of women who used a norethindrone implant had no differences in weight gain compared with those who used nonhormonal implants [49]. Likewise infants of LNG implant users had similar growth and development compared with nonhormonal users, although a few differences were noted in some of the multiple developmental tests [58,59]. In two studies of LNG implant use compared with nonhormonal methods, no differences were noted between groups in infant weight gain [60,62], although in one of the studies, a higher incidence of respiratory infections and skin conditions was noted among infants whose mothers used an LNG implant [62]; more urologic and neurological conditions occurred among infants of Cu-IUD users.

3.4.2.4. Multiple progesterogen-only methods. One study (not new) included infants of mothers using various POCs and found that infant growth was generally the same between POC and nonhormonal users [68].

3.4.2.5. Nonorally available progestogens. Three studies reported on infant outcomes of mothers using nonorally available progestogens, none new. Infant growth was no different in users of nesterone pellets compared with nonhormonal methods [63]; neither infant growth nor health was different between users of progesterone pellets and users of nonhormonal methods [54]. Similarly, there was no difference in infant growth or development between infants of users of nesterone implants and Cu-IUD users [64].

3.5. Key Question Two: Early versus delayed initiation

In total, eight studies address the effect of initiation of POCs before 6 weeks postpartum compared with later initiation, of which five are new [16,20,22,23,32]. The majority found no effect on breastfeeding or infant outcomes, although one RCT found that more women continued breastfeeding at 6 months in the later initiation group [22] and another found more infections in infants of DMPA users [32].

3.5.1. Breastfeeding outcomes: RCTs and observational studies

Six of the studies assessed breastfeeding outcomes when POCs were initiated early or late postpartum (three RCTs, three observational). All three RCTs and one of the observational studies are new. One RCT compared women using ETG implants immediately postpartum versus DMPA initiated at 6 weeks [20]. No differences were seen between groups in the percentage of women exclusively breastfeeding at 6 or 12 weeks. Another RCT compared postplacental placement of LNG-IUD with delayed placement at 6–8 weeks and found no difference in breastfeeding initiation between groups or in breastfeeding continuation at 6–8 weeks; women in the delayed group were more likely to be breastfeeding at 6 months [22]. A final study compared women randomly assigned to the ETG implant either 1–3 days postpartum or at 4–8 weeks postpartum and found no significant difference in breastfeeding outcomes [23].

One new observational study found that women who initiated DMPA after 72 h postpartum were more likely to be breastfeeding at 3 months than those who initiated before 72 h or who did not use DMPA [16]. In the other observational studies, norethindrone implant initiated early compared with delayed was not associated with differences in supplementary feeding or continuation of breastfeeding [49], and women who initiated progesterone pellets later were more likely to be supplementing breastfeeding than those who initiated early [54].

3.5.2. Infant outcomes: Observational studies

No RCTs and four observational studies (one new [32]) were identified for infant outcomes. The new study found that women who received DMPA within 48 h postpartum reported a higher incidence of infectious diseases in their infants than those who initiated DMPA later or not at all [32].
4. Discussion

Overall, evidence from 49 articles reporting on 47 studies on use of POCs during breastfeeding is of poor to fair methodological quality. Of the 14 studies that were newly included in this review, four were older studies [29–32] of poor quality and one was published in 1999 and of fair quality [28]. None of these older studies showed any negative effect of use of POCs on breastfeeding or infant outcomes. Of the nine studies that were published since the last review, four were RCTs. One of the four trials suggested that early, compared with delayed, postpartum initiation of the LNG-IUD was associated with shorter breastfeeding duration and less breastfeeding exclusivity at 6 months [22]. However, two other RCTs found no differences [20,23]. The fourth new trial provides indirect evidence demonstrating no difference in outcomes between POPs compared with COCs [21]. Among the newly identified observational studies, findings were generally consistent with the observational studies in the previous review, with no adverse effects noted on breastfeeding or infant outcomes.

Exogenous administration of POCs could theoretically inhibit breastfeeding [69]; however, the evidence in this review does not generally support a negative impact on breastfeeding outcomes. Studies examining the initiation of POCs among postpartum women overall demonstrated no adverse effects on measures of breastfeeding success, such as duration of breastfeeding or time to supplementation, although a few reported differences in both positive and negative directions at individual time points. The preponderance of the evidence points toward no deleterious impact of POCs on breastfeeding success, although further study is warranted to examine the impact of immediate postpartum placement of the LNG-IUD.

Theoretical concerns also have been raised regarding the impact of exposure to progestogens on neonates, particularly in the first 6 weeks of life [7]. Studies identified in this review showed no consistent adverse effects of exposure to progestogens through breast milk on infant health outcomes such as growth, development and health through the first few years of life. We identified no data to inform a conclusion on longer-term effects and any such effects remain unknown.

The PVR was not addressed in this review. A recent review concluded that PVR use among breastfeeding women did not affect breastfeeding performance or infant growth during the first year postpartum [18].

Our ability to draw firm conclusions is limited as most studies are observational, have lacked clear definitions of breastfeeding patterns and failed to control for potential confounders [70]. Many did not provide information key to determining their quality and did not perform tests of significance. Some were not informative to our cutoff point of 6 weeks as participants initiated both before 6 weeks and after. Initiation before 6 weeks ranged from immediately postpartum to nearly 42 days.

In 2014, the WHO Expert Working Group reviewed this evidence to evaluate medical eligibility criteria for the use of POCs among breastfeeding women. All of the above-mentioned studies were reviewed with the exception of one, which was identified after the meeting and found no deleterious effects of POCs [27]. The findings of this systematic review were incorporated into the recent update of the MEC [71].

5. Conclusion

Consistent evidence by multiple measures of successful breastfeeding, largely from fair or poor quality observational studies, suggests that POCs, when used by lactating women, do not compromise a woman’s ability to breastfeed. Evidence that POCs do not adversely affect infant growth, health or development during the first year postpartum is generally consistent across observational and randomized studies. Further research is necessary to determine any effects on child health or development beyond the first year. Evidence newly added to this review is largely consistent with the previous evidence.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.contraception.2015.09.010.

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