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Review article

The relationship between progestin hormonal contraception and depression: a systematic review

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ABSTRACT

Objective: We performed a systematic review to look for an association between progestin-only contraception and depression.
Methods: We searched PubMed, Ovid and Web of Science for English-language articles including progestin-only contraception and depression from database inception to September 2016. We evaluated study quality with the procedures guiding reviews for the United States Preventive Services Task Force and the Cochrane Risk of Bias Tools. We included studies that evaluated progestin-only contraception and depression, focusing on externally validated depression measures. We excluded case studies, review articles and other psychiatric disorders.
Results: We identified 26 studies that met the inclusion criteria, including 5 randomized controlled trials, 11 cohort studies and 10 cross-sectional studies. We found minimal association between progestin-only methods and depression. No correlation with depression was found in five low-quality, high-risk-of-bias progestin subdermal implant studies and four out of five varying-quality and medium-risk-of-bias levonorgestrel intrauterine device studies. Three medroxyprogesterone acetate intramuscular injection trials with varying levels of quality and bias show no difference in depression. Two progestin-only contraceptive pill studies with varying levels of quality and bias indicate no increase in depression scores, while one good-quality, medium-bias study shows an association between progestin-only pills, the intrauterine device and depression.
Conclusion: Despite perceptions in the community of increased depression following the initiation of progestin contraceptives, the preponderance of evidence does not support an association based on validated measures (mostly level II-1 evidence, moderate quality, low risk of bias).

1. Introduction

Sexually active women of reproductive age who want to prevent pregnancy need reliable contraceptive options. Decisions about which method to choose may involve factors such as efficacy, medical problems, previous experiences with side effects or failures, or concerns about imperfect compliance. Due to the risks or side effects of estrogen, many women choose a hormonal contraceptive that is formulated only with progestin. Even with limited progestin exposure, concerns exist about side effects including weight gain, acne, mood changes and depression. Depression side effects of progestin contraception have been stressed in the lay press and are common patient concerns [1,2]. Depression is also a concern for women considering hormonal contraception due to female population prevalence. The major depression lifetime prevalence for US women is 7.4/100, twice that of men [3]. Concerns about progestin's influence on mood are based on clinical experience and basic science research [4,5].

Concerns about progestin-related depression effects also arise from early clinical data on depot medroxyprogesterone acetate (DMPA), which was approved for use as a long-acting contraceptive in 1992 by the Food and Drug Administration (FDA). The package labeling stated that women with depression should be observed carefully, and additional administration should not be performed if depression recurred. This concern was based on FDA clinical data showing that 1.5% of 4200 users reported depression and 0.5% discontinued their use of DMPA for this reason [6]. Since then, many studies have sought an answer to whether DMPA may cause depression.

The relationship between progestin-only contraceptives and depression remains unclear. This study aims to systematically review the medical literature regarding this relationship, additionally including generalized and postpartum depression, as well as adolescents.

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2. Methods

We conducted this systematic review using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [7]. Prior to conducting our literature review, we identified the following questions to guide our search:

1. Is there an association or causative link between progestin-only hormonal contraception and depression effects in human females?
2. Does the type of progestin or route of administration influence such an association?
3. Are there certain populations (such as adolescents, postpartum patients or women with a history of depression) in which this association exists?

2.1. Literature search

We searched PubMed, Ovid and Web of Science databases for English-language peer-reviewed articles published from database inception until September 2016 to identify studies examining depression effects of progestin contraceptives. We used PRISMA guidelines to report the data. PROSPERO Registration number is CRD42017059302. We used several combinations of search terms in order to address our three key questions (Appendix A). In addition to our electronic search, we cross-referenced review and other articles identified by our search, compared searches and discussed abstract presentations presented at national meetings over the past 10 years to find articles that may have been excluded based on publication bias due to null hypothesis findings or unfavorable results.

We searched clinical trials and abstracts with MESH terms and separate title and abstract searches with direction and assistance from a librarian. We excluded review articles, nonhuman studies, articles in languages other than English and case reports. We used search terms "progestin-only contraception," "medroxyprogesterone depression," "Levonorgestrel IUD," "levonorgestrel depression," "Subdermal rod," "etonogestrel depression," "norethindrone depression," "Progestin [AND] depression [AND] contraception," "progestin [AND] postpartum depression," "Contraception [AND] levonorgestrel [OR] medroxyprogesterone acetate [OR] [AND] mood." "Mood swings" and other psychiatric disorders were not the focus of this project, as they are mediated by different mechanisms, and were excluded. We reviewed studies for contraceptive method, population studied, measurements used and significance of effect. We compiled these data to look for patterns in response to similar medications and populations. We assessed each study and followed procedures guiding reviews for the United States Preventive Services Task Force and rated studies as "good," "fair" or "poor" [8]. We gave most weight to randomized controlled trials (RCT) and externally validated depression measures. Limited amounts of evidence from prospective trials led the authors to also consider observational studies. Had more trial and comparative cohort data existed, the review team would have focused on a higher level of evidence. The principal summary measure was risk of depression related to progestin-only contraception, using odds ratios (ORs) and difference in means as reported.

We considered performing a meta-analysis, but this was inappropriate due to clinical and statistical heterogeneity of measures. We conducted a qualitative and narrative synthesis, highlighting effect consistency areas and findings from studies with the lowest risk of bias, identifying where data are lacking or insufficient to draw conclusions. We performed an assessment of bias using the Cochrane Risk of Bias Tools, rating articles with "low," "medium" or "high" risk of bias [9] (Tables 1A-7).

3. Results

3.1. Study selection

Our search used multiple title and abstract searches plus PubMed MESH search terms including "medroxyprogesterone depression" with 155 abstracts, "levonorgestrel depression" with 80 abstracts, "norethindrone depression" with 126 abstracts, "etonorgestrel depression" with 8 abstracts, "Progestin [AND] depression [AND] contraception" with 190 abstracts and "progestin [AND] postpartum depression" with 78 abstracts. This initially yielded 2305 citations and, once exclusion criteria were applied, yielded 696 abstracts. We identified 41 articles for possible inclusion after cross-referencing and further examining abstracts. All study authors reviewed the abstracts, and we excluded those ruled ineligible based on the above criteria. After careful review, the authors agreed on the inclusion of 26 articles that met all criteria (Fig. 1).

3.2. Depression association by type of contraceptive method

3.2.1. Injectable medroxyprogesterone acetate

Since the FDA warning on DMPA in 1992, providers have expressed concerns about whether this highly effective contraceptive method is associated with depression. No RCTs evaluating depression risk for DMPA users exist in the general population.

In a multicentered prospective study of 495 women starting DMPA [10], Westhoff et al. administered the Mental Health Inventory (MHI) at initiation and 1 year. Depression scores dropped in those continuing the medication, from 7.4 to 6.7 ($p=.03$), a statistically significant decrease. In addition, women with the highest depression scores at baseline improved, suggesting that DMPA does not make depression worse. This study did not compare DMPA users versus the general population.

Berenson et al. [11] recruited 608 US women ages 16–33 years old and allowed them to choose barrier methods of contraception, DMPA or combined oral contraceptive pills (COCP). The authors evaluated participants every 6 months for 2 years with a symptom checklist, Beck Depression Inventory (BDI), Zung Anxiety instrument and Positive and Negative Affect Scale (PANAS). While 355 people dropped out of the study, the DMPA patients had lower scores on the BDI, with no increased risk of depression [OR 1.08, 95% confidence interval (CI) 0.71–1.62] compared to the barrier method group. The reference group baseline depression rate from the self-reported symptom checklist was 34%, with an additional 31% in the nonhormonal group developing new-onset depression symptoms over 24 months, based on the checklist. BDI scores were 1.4 units lower for the DMPA group compared to the nonhormonal group at 24 months ($p<.05$). Although these studies were not randomized, large sample sizes and use of validated scales provide convincing evidence that DMPA does not increase the risk of depression.

Two prospective cohort studies both used the same validated scale, the Community Epidemiology Depression Scale (CESD), to assess mood. Civic et al. [12] evaluated 183 DMPA users and 274 nonusers at 6-month intervals for 3 years. In their study, significantly more women who discontinued DMPA had scores over 10 at 3 months indicating more depression symptoms (36.4%) before (OR=2.30, 95% CI 1.42–3.70) and after (OR=2.46, 95% CI 1.46–4.14) discontinuation compared to women who remained users (21.1%). The OR for developing depression symptoms (based on the CESD) in DMPA users was 1.44 (95% CI 1.00–2.07), and the OR for DMPA discontinuers was 1.60 (95% CI 1.03–2.48) compared with nonusers. Depression symptoms in nonusers were found to occur in 11.8%–17.5% of this population at the various study visits based on CESD scores. A smaller prospective cohort study by Westhoff et al. [13] looked at 80 DMPA users and 26 nonusers with the CESD 4 weeks after DMPA injection and immediately prior to the next injection. The full CESD was used with a range of 0–60, with scores over 16 suggesting clinical depression for adults and scores over 22 indicating depression in adolescents. The mean CESD score for nonusers was 14.4, while mean score for DMPA users was 15.6 (not significant). A total of 20%–41% of subjects were noted to have depression scores indicating increased risk of clinical depression during the study, including DMPA users and nonusers. In the Civic study, sample size was smaller, depression cutoff values were lower, the population was on average 5 years older, and discontinuation rate was higher, making

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