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10.1080/13625187.2019.1569610.**Postpartum hormonal contraception use and incidence of postpartum depression: a systematic review****Angeline Ti** and

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Abstract**Purpose**—To evaluate the association between postpartum hormonal contraceptive use and postpartum depression.**Materials and methods**—We searched the literature through March 2018 on the association between postpartum hormonal contraception use and incident postpartum depression. We used the United States Preventive Services Task Force framework to assess study quality.**Results**—Of 167 articles identified, four met inclusion criteria. Two studies found no differences in rates of postpartum depression between women using postpartum depot medroxyprogesterone and those not using hormonal contraception; however, a study of women receiving injectable norethisterone enanthate immediately postpartum found a 2–3-fold increased risk of depression at six weeks, though not at three months. One study compared combined hormonal contraception, progestin-only pills (POPs), etonogestrel implants and levonorgestrel intrauterine devices (LNG-IUDs) with no hormonal contraception, and found a 35–44% decreased risk of postpartum depression with POPs and LNG-IUDs, a small increased risk of postpartum antidepressant use among women using the etonogestrel implant and vaginal ring, and a decreased risk of antidepressant use with POPs.**Conclusions**—Limited evidence found no consistent associations between hormonal contraceptive use and incidence of postpartum depression. Future research would be strengthened by using validated diagnostic measures, careful consideration of confounders, and ensuring adequate follow-up time.

Disclosures:

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Introduction

Perinatal depression is defined as a major depressive episode in the peripartum time period, including during pregnancy and in twelve months following delivery. It affects an estimated 12% of women globally [1], with peaks in incidence at 2 months and 6 months following delivery [2]. The strict diagnosis of postpartum depression is isolated to the time period of four weeks immediately postpartum [3]; however research and clinical guidelines generally consider the time when women are at risk for postpartum depression to range from delivery through three to twelve months postpartum [1, 4, 5]. Risk factors for postpartum depression include depression during or prior to pregnancy, life stress, traumatic or complicated birth experiences, and breastfeeding difficulties [4]. There are multiple options for treating postpartum depression, including different types of psychotherapy and antidepressant medications [6]. Uncontrolled postpartum depression can have negative impacts on the woman, her infant, and their families, including poor bonding, impaired infant development, and, rarely, suicide or infanticide [6]. Professional organizations, including the American College of Obstetricians and Gynecologists (ACOG), the National Institute for Health and Clinical Excellence (NICE), and the World Health Organization (WHO), recommend that all women should be screened for postpartum depression during postpartum visits using a validated screening tool, such as the Edinburgh Postnatal Depression Scale, the Patient Health Questionnaire 9 or the Beck Depression Inventory [4, 5, 7].

Postpartum contraception facilitates optimal birth spacing, which improves maternal and pediatric outcomes [8]. Short interpregnancy intervals are associated with negative birth and infant outcomes, including preterm birth, low birthweight and infants born small for gestational age, and increased risk for uterine rupture for women attempting a trial of labor following a cesarean section [9]. Postpartum contraception helps women control the timing of subsequent pregnancies to best meet their and their families' needs. ACOG, NICE and WHO also recommend that women receive contraceptive counseling and any desired contraceptive services during the postpartum time period [5, 7, 8]. Both the WHO and Centers for Disease Control and Prevention provide recommendations on the safety of initiating specific hormonal contraceptive methods in the postpartum period [10, 11]. Both the WHO and U. S. Medical Eligibility Criteria for Contraceptive Use recommendations consider progestin-only contraceptive methods to be generally safe for use any time in the postpartum period, while safe initiation of combined hormonal contraceptives may depend on the amount of time since delivery, presence of risk factors for venous thromboembolism, and breastfeeding status [10, 11].

Several studies have examined the influence of sex hormones and hormonal contraception on depressive symptoms in both healthy women and women with mental health diagnoses, based on hypotheses that exogenous estrogens and progestins influence mood-related neurotransmitters. However, results from these studies have been inconsistent and no clear conclusions have been reached [12, 13, 14, 15, 16]. Less work on this issue has been done among postpartum women [15], who may be at greater risk for depression due to their postpartum status [1]. Hormone fluctuations unique to the postpartum period, coupled with changes such as sleep deprivation, make this a distinct time period that warrants independent investigation. A recent analysis of adverse drug events reported to the US Food and Drug

Administration found elevated reporting odds ratios for postpartum depression with the use of certain hormonal contraceptives compared with the use of other drugs, and the authors concluded that this may indicate a possible “signal” that postpartum depression is more likely to be reported with the use of hormonal contraception [17]. The clinical relevance of these findings is unclear without further study. To better characterize the influence of hormonal contraception use during the postpartum period on the risk for subsequent identification of postpartum depression, this systematic review evaluated the published literature on the association between hormonal contraceptive use in the postpartum period and the incidence of postpartum depression. Specifically, we examined the research question: among postpartum women, do those using a hormonal contraceptive experience different rates of postpartum depression compared with those not using a hormonal contraceptive?

Materials and methods

We followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines in reporting this systematic review [18]. We developed a brief protocol to investigate our research question, including pre-specified inclusion criteria, search strategy and terms, and plan for assessing study quality, including risk of bias.

With the assistance of a librarian, we searched Medline, Embase, CINAHL, PsychINFO, the Cochrane Library, and [Clinicaltrials.gov](https://www.clinicaltrials.gov) for studies involving any form of hormonal contraception (combined hormonal contraceptives, progestin-only pills, injectable contraceptives, contraceptive implants and LNG-IUDs) and postpartum depression (see supplemental material for the specific search terms) from database inception through March 2018. We did not apply any language or publication date restrictions.

The first author conducted the initial study selection by reviewing titles and abstracts to determine which articles required full text review, and this was confirmed by the last author. Both authors then independently conducted the full text review to identify articles that met inclusion criteria. Disagreements were resolved by discussion and consensus. For each study that met inclusion criteria, data were extracted by the first author on: study design, location, timeframe of data collection, follow-up, study population, comparison group, outcome(s), results, and funding source, and the data extraction tables were reviewed by the last author.

We included studies of original research in the form of randomized controlled trials (RCTs), cohort and case-control studies of postpartum women using a specific form of hormonal contraception compared with postpartum women not using hormonal contraception. The exposure of interest was the method of hormonal contraception used postpartum, which included combined hormonal contraceptives (pills, patch, and ring), progestin-only pills, injectable contraceptives, contraceptive implants and levonorgestrel-containing intrauterine devices (LNG-IUDs). The comparison was no hormonal contraceptive use in the study period, which included women using non-hormonal methods such as sterilization, copper IUD, or barrier methods, as well as women using no contraception. The outcome of interest was the development of depression within the postpartum period, as identified by any clinical diagnosis of depression by a health care provider within the 12 months postpartum

or a score above a threshold for depression on a validated depression scale. Clinical diagnosis could be self-reported or assessed through the clinical record. Secondary outcomes included antidepressant use, suicidal ideation or suicide attempt, and hospitalization for depression. We excluded studies that included women with a pre-existing diagnosis of depression or who were receiving treatment for depression prior to or during pregnancy, as we were interested in examining the association between hormonal contraceptive use and incidence of depression in the postpartum period, rather than whether hormonal contraceptive use might impact existing mood disorders in the postpartum period.

To assess the overall quality of the evidence, we followed the framework developed by the United States Preventive Services Task Force [19], and assigned a quality rating (good, fair, poor) based on the evidence provided for each outcome by study. We assessed the risk of bias for individual outcomes within studies, study precision, and external validity. Components included in the risk of bias assessment differed by study design. For all studies, we assessed selection bias, reporting bias and performance bias. For RCTs, we also assessed detection bias, attrition bias and any other sources of biases relevant to the study. For cohort and case-control studies, we also assessed information bias and confounding. The quality of each study outcome was graded independently by each author and differences were resolved through discussion. Because of the heterogeneity of exposures and outcomes, we did not calculate summary measures of association.

Results

Our search identified 167 unique articles that were then screened by their title and abstract (Figure 1). The full texts of 21 articles were reviewed, and four met the inclusion criteria (Tables 1 and 2). The majority of articles were excluded because they did not address our question or were not primary studies. One was excluded because it did not use a validated scale to assess depression [20]. Another was excluded because it included both users of no contraception and users of combined oral contraceptives (COCs) as one comparison group [21]. In three of the included studies, women using injectable forms of contraception (either depot medroxyprogesterone acetate [DMPA] or norethisterone acetate [NET-EN]) were recruited from teaching hospitals or outpatient obstetric clinics in South Africa or the United States. The included fourth study used a large claims database of military personnel in the United States to examine a wide range of hormonal contraceptive types. All four included studies examined incidence of depression in the postpartum period and one study [22] also examined use of antidepressant medications. We did not identify any studies that looked at hospitalization for depression, suicidal ideation or suicide attempts.

Depression

For the outcome of depression, two RCTs [23, 24] and two retrospective cohort studies [22, 25] met inclusion criteria (Table 1). The studies included a total of 76,409 participants, with the majority (75,528) stemming from one study [22]. The remaining studies had sample sizes ranging from 180 to 247 participants. Two studies were conducted in the U.S. [22, 25], and the other two conducted in South Africa [23, 24]. One study assessed the risk of a diagnosis of depression in the postpartum period associated with various contraceptive

methods: COCs, the contraceptive vaginal ring, progestin-only pills, contraceptive implants, and LNG-IUDs [22]. Three studies examined the association of either depot medroxyprogesterone (DMPA) or injectable norethisterone enanthate (NET-EN) use in the postpartum period on scores on validated depression scales [23, 24, 25]. The comparison groups were generally women not using contraception or not using a hormonal method (e.g. using barriers, copper IUD or tubal ligation). Incidence of depression was assessed through diagnostic codes in one study [22] and through depression scales, including the Edinburgh Postnatal Depression Scale (EPDS) [25], EPDS and the Beck Depression Inventory (BDI-II) [24], and EPDS plus the Montgomery-Åsberg Depression Rating Scale (MADRS) [23] in the other three studies. Estimates of the overall incidence of depression in the study population varied, though tended to be lower in the study using diagnosis codes (Kaplan-Meier estimate of 5.0%, over 12 months) [22] and was as high as 14.1% using a diagnostic cutoff for major depression on a depression scale at 6 weeks postpartum [25]. For the outcome of depression, two studies were graded as fair quality [22, 23] and two were poor quality [24, 25].

Combined hormonal methods—Only one study examined combined hormonal methods, including two formulations of COCs and the vaginal ring [22]. This large retrospective cohort study of fair quality used claims data within the U.S. military health insurance program to compare women using hormonal contraception with those not using a hormonal method through 12 months postpartum, with mean follow-up of 8.9 months postpartum. Contraceptive use was assessed through pharmacy codes and incidence of depression through diagnostic codes. Women with any diagnostic codes for depression or antidepressant prescription in the 24 months prior to delivery were excluded from the analysis. Over 75,000 women were included in the analysis, and 5,797 of them used a combined hormonal method while 44,022 used no hormonal contraception. After adjustment for age, beneficiary category (e.g. military retiree, active duty service member, or family member) and rank of insurance sponsor (as proxies for socioeconomic status), no significant associations were observed between the use of ethinyl estradiol/norgestimate pills (adjusted hazard ratio [aHR] 0.89, 95% confidence interval [CI] 0.70–1.14), ethinyl estradiol/norethindrone pills (aHR 0.82, 95% CI 0.59–1.12), or the vaginal ring (aHR 1.09, 95% CI 0.80–1.50) and diagnosis of depression.

Injectables—Three studies examined the association between the use of injectable progestin contraception and postpartum depression. One poor quality RCT randomized 242 women in South Africa to immediate (within 48 hours of delivery) postpartum use of DMPA or copper IUD. Incidence of depression was measured through use of EPDS and BDI-II scores using validated thresholds for major and minor depression at 1 and 3 months postpartum [24]. While mean scores on both scales tended to be higher in DMPA users compared with copper IUD users, there were no significant differences in the proportions of women reaching the thresholds for major or minor depression using either scale at one or three months postpartum. A poor quality, retrospective cohort study of medical records from 247 women with postpartum visits at an outpatient clinic in the United States found no statistically significant association between the use of immediate (prior to hospital discharge) postpartum DMPA and major depression on the EPDS at the 6-week postpartum

visit compared with women not using birth control or who had a tubal ligation ($p=0.88$) [24]. A fair quality, placebo-controlled RCT of intramuscular NET-EN enrolled 180 postpartum women from a tertiary care hospital in South Africa. A single dose of NET-EN administered within 48 hours of delivery was significantly associated with scoring above the threshold for major or minor depression on the EPDS (relative risk (RR) = 3.04, $p=0.002$) and major or minor depression on MADRS (RR=2.56, $p=0.008$), but not major depression alone on MADRS (RR=2.13, $p=0.158$) at 6 weeks postpartum. This association was not observed at 3 months (major or minor depression on EDPS, RR=1.20, $p=0.573$; major depression on MADRS, RR 1.09, $p=0.895$; major or minor depression on MADRS, RR 1.03, $p=0.930$) [23].

Implant—One fair quality study assessed the association between progestin contraceptive implants and postpartum depression. The retrospective cohort study of U.S. military health insurance claims data included 2,730 implant users and 44,022 women using no hormonal contraception, and found no association between etonogestrel (ETG) implant use and diagnosis of postpartum depression during the 12 months after delivery (aHR 1.01, 95% CI 0.83–1.22) [22].

LNG-IUD—The only study to look at the LNG-IUD was the large retrospective cohort study of fair quality that used military health insurance claims data. Investigators reported a reduced risk of depression diagnosis among 3,096 LNG-IUD users compared with 44,022 women not using hormonal contraception (aHR 0.65, 95% CI 0.52–0.82) [22].

Anti-depressant use

In addition to a diagnosis of depression, the claims data analysis [22] also looked at antidepressant use as measured by filled prescriptions of any antidepressant during 12 months after delivery [26]. Overall, antidepressant were prescribed at an estimate rate of 7.8% (95% CI 7.6–8.0) during the postpartum period. For this outcome, we graded this study to be poor quality (Table 2). Investigators reported an elevated risk of antidepressant use in the postpartum period among postpartum women using the vaginal ring (aHR 1.45, 95% CI 1.16–1.8) and the ETG implant (aHR 1.22, 95% CI 1.06–1.41) compared with women not using hormonal contraception. This study also found a reduced risk of antidepressant use among women who used progestin-only pills as compared to women not using hormonal contraception (aHR 0.58, 95% CI 0.52–0.64). There were no significant associations between the use of ethinyl estradiol/norgestimate pills (aHR 1.02, 95% CI 0.85–1.22), ethinyl estradiol/norethindrone pills (aHR 0.88, 95% CI 0.69–1.13) or LNG-IUDs (aHR 1.01, 95% CI 0.87–1.18) and antidepressants.

Discussion

We identified four studies that examined the risk of postpartum depression among women using hormonal contraception in the postpartum time period. Of the four studies, three studies looked only at injectable contraceptives. These three studies used cutoffs on a validated scale to identify women with postpartum depression. One RCT and one retrospective cohort study found no differences in the rates of postpartum depression

between women using postpartum DMPA and those not using a hormonal contraceptive [24, 25]; however, an older RCT of women receiving a single dose of immediate postpartum NET-EN found a 2–3-fold increased risk of depression at six-weeks postpartum on two different depression scales, though differences were not observed at three months postpartum [23]. Only one study looked at the use of COCs, the contraceptive vaginal ring, progestin-only pills, the ETG implant and the LNG-IUD within the 12 months postpartum, and found a decreased risk of receiving a diagnosis of postpartum depression with progestin-only pills and the LNG-IUD, and no association with the other methods [22]. This same study found an increased risk of the postpartum use of antidepressants among women using the ETG implant and the vaginal ring, a decreased risk of postpartum antidepressant use among women using the progestin-only pill, and no association with those using the LNG-IUD or combined oral contraceptives.

Outside of the postpartum period, the association between hormonal contraception use and incidence of depression is also unclear. Three reviews were unable to draw firm conclusions from the evidence they evaluated [14, 15, 27]. Three recent large cohort studies found conflicting results, with two related studies finding an increased risk of depression and suicide among users of hormonal contraception [28, 29] and another finding decreased levels of depressive symptoms among women using hormonal contraception [30]. Among women who have depressive mood disorders, the very limited available evidence does not suggest worse outcomes for those who use hormonal contraception [13, 15].

The available evidence to answer our question is limited in both quantity and quality. The majority of this evidence comes from a single, large study of claims data among military personnel in the United States, and the remaining studies only provide data on injectable contraceptives. Of the four articles that met our inclusion criteria, we judged them to be either fair [22, 23] or poor [24, 25] quality. Of the cohort studies, one failed to adjust for any confounders [25] and the other missed some key potential confounders, including smoking status, pregnancy complications, breastfeeding status or difficulties, and prior history of postpartum depression [22]. Three of the studies followed women only to three months or less postpartum [23, 24, 25], which may not be enough time to observe the outcome. One RCT had a response rate of 25%, which raises concerns of significant selection bias and generalizability [24]. The external validity was also limited for three of the studies. The RCT that had a very low response rate was based in a teaching hospital in South Africa [23], which may limit the representativeness of their sample. The other RCT was also based in South Africa and had a low response rate (42%) and a very high rate of unplanned pregnancies (77%) [24]. One of the cohort studies used the U.S. military health insurance database [22], and while it likely represented a diverse cohort of families, it is unclear if findings from a military-involved population are generalizable to the general population. When considering the overall body of evidence, even though we only included studies using validated scales for postpartum depression, there was still significant heterogeneity in the scale used, the timing of the assessment, as well as the thresholds used for diagnosis within the same scale. All of these differences make it difficult to make comparisons across studies.

Additionally, the use of antidepressant prescription as a proxy for depression diagnosis or symptoms is questionable, especially within a military cohort that may have higher rates of

comorbid psychiatric conditions, such as acute- and post-traumatic stress disorders, anxiety disorders and chronic pain, which may also be treated with antidepressants. Even in general primary care settings, anywhere from one-third to nearly one-half of antidepressant prescriptions are for off-label use [31, 32]. These discrepancies may result in differential misclassification, for example, if those who are interested in using a hormonal contraceptive may also be more open to using antidepressants for off-label reasons or as treatment for a psychiatric condition, over non-pharmacologic alternatives.

The use of postpartum contraception remains an important intervention to reduce rapid repeat pregnancy and improve maternal and pediatric outcomes, while postpartum depression continues to be of significant public health concern. The studies included in this review also demonstrated relatively high rates of postpartum depression (5–14%), whether identified through diagnosis codes used in billing or through using cutoffs for major depression based on validated scales. Because we excluded studies of women with pre-existing mood disorders, these estimates likely underestimate the true burden of depression for all women in the postpartum period. This highlights the importance of patient education and routine screening for postpartum depression. Based on limited available evidence from two cohort studies and two RCTs of fair to poor quality, there is not a clear association between any specific forms of hormonal contraception and the development of postpartum depression; however, these findings should be interpreted with caution, given the paucity of high quality research. The lack of high quality studies on this topic precludes clear clinical implications based on the evidence. Further research including well-designed studies with sufficient follow-up (e.g. six months to one year), using a validated scale such as the EPDS or diagnoses based on billing codes from provider visits to evaluate the outcome of postpartum depression would advance the field. This information could better inform conversations between women and their providers in how to best choose a method of postpartum contraception, including in the immediate and early postpartum periods. Currently, women's health care providers can use evidence-based recommendations [10, 11] to provide patient-centered care in helping postpartum women choose and initiate contraception that is best suited to their needs and help manage side effects should they occur.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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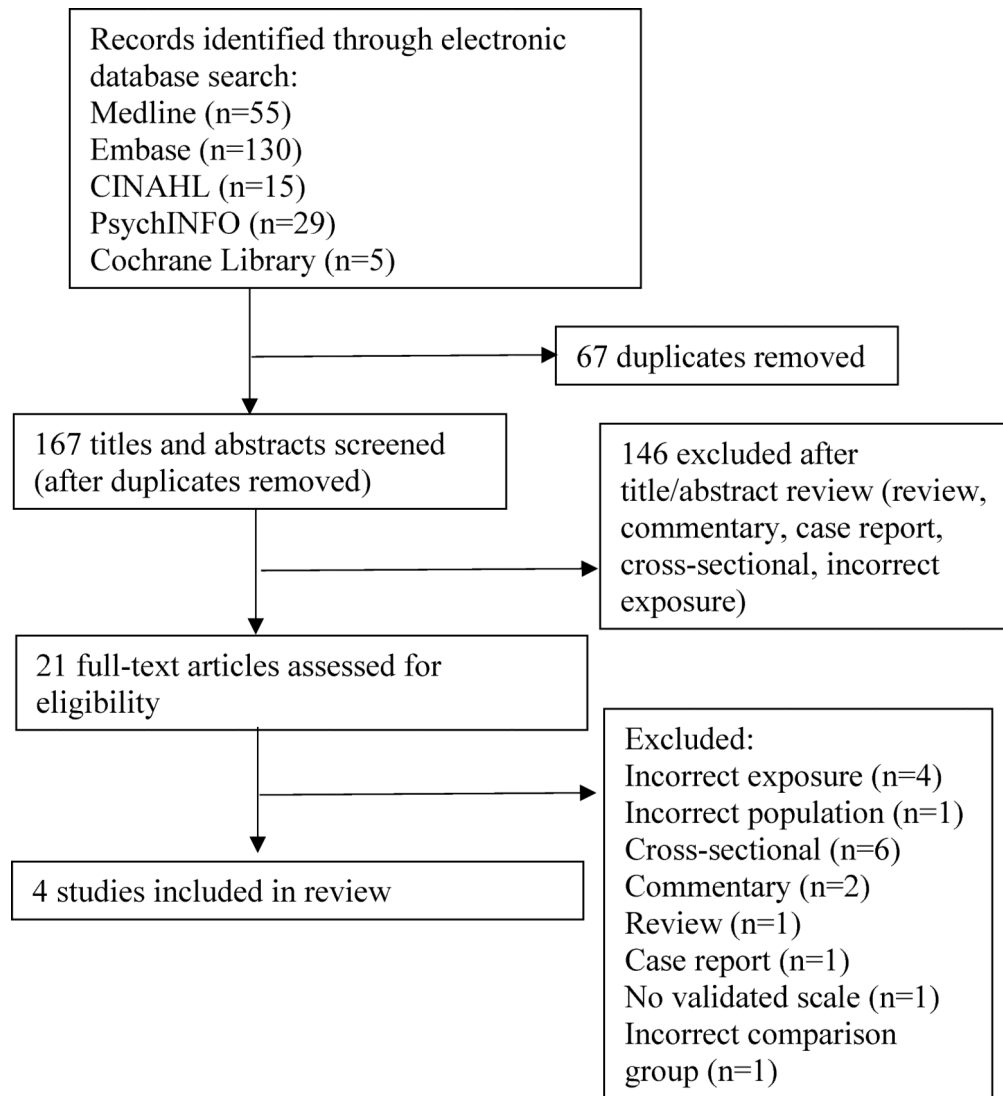


Figure 1.
PRISMA flowchart

Table 1.

Studies of women diagnosed with postpartum depression

Author, year, support, country	Study design, population, timeframe	Contraceptive use	Outcome	Results	Quality, strengths, weaknesses
Roberts, 2017, no funding, United States.	Retrospective cohort study, analysis of data from Military Health System Management Analysis and Reporting Tool. 75,528 women enrolled postpartum and followed for 12 months.	Norethindrone-only pills (n=19,883) LNG-IUD (n=3,096) ETG implant (n=2,730) EE/norgestimate pill (n=2,718) EE/norethindrone pill (n=1,675) EE/ETG ring (n=1,404) No hormonal contraception (n=44,022)	Depression diagnosis at encounter (ICD-9 code for postpartum depression, major depressive disorder, depressive type psychosis, depressive disorder NOS) during 12 months after delivery.	Norethindrone-only pills aHR 0.56 (CI 0.49–0.64) LNG-IUD aHR 0.65 (CI 0.52–0.82) ETG implant aHR 1.01 (CI 0.83–1.22) EE/norgestimate pill aHR 0.89 (CI 0.7–1.14) EE/norethindrone pill aHR 0.82 (CI 0.59–1.12) EE/ETG ring aHR 1.09 (CI 0.8–1.5)	Quality: fair (moderate risk of bias, good precision, fair external validity) Strengths: Large cohort using claims data within a relatively closed health care system, with adequate follow-up for outcome (12 months). Groups drawn from the same source population with consistent inclusion and exclusion criteria. Exposure and outcome assessed consistently throughout participants using clear diagnostic codes. Likely a diverse population (though no data presented), and likely adequate power given large sample size (though no power or effect size calculations provided). Excluded prior depression diagnosis or antidepressant use within 24 months prior to delivery. Weaknesses: Failed to adjust for key potential confounders (e.g. smoking, prior history of postpartum depression, birth complications, or breastfeeding problems). Military cohort with potential for higher rates of comorbid psychiatric conditions (e.g. post-traumatic stress disorder). Unique population with potentially limited generalizability.
Singata-Madiki, 2017; internal funding for study, manuscript prep funding from South African Medical Research Council; South Africa.	Single-blind RCT, enrolled postpartum women from two teaching hospitals. 242 women between 18–44, assessed at baseline (delivery), 1-month and 3-months postpartum.	DMPA within 48 hours of delivery (n=119) Cu-IUD (n=123) within 48 hours of delivery	Beck Depression Inventory (BDI-II), cut-off of 14 for minor depression and 29 for major Edinburgh Postnatal Depression Scale (EDPS), cut-off of 9 and 12 for minor and major depression	At 1 month: BDI 14, p=0.25 DMPA 34/111 (31%) Cu-IUD 27/117 (23%), BDI 29, p=–0.39 DMPA 11/111 (10%) Cu-IUD 7/117 (6%), EDPS 9, p=0.27 DMPA 27/111 (24%) Cu-IUD 21/117 (18%), EDPS 12, p=0.55 DMPA 13/111 (12%) Cu-IUD 10/117 (9%), At 3 months BDI 14, p=0.13 DMPA 30/113 (27%) Cu-IUD 23/117 (20%), BDI 29, p=0.05 DMPA 8/113 (7%) Cu-IUD 2/117 (2%), EDPS 9, p=0.63 DMPA 20/113 (18%) Cu-IUD 17/117 (15%), EDPS 12, p=0.93 DMPA 9/113 (8%) Cu-IUD 10/117 (9%).	Quality: poor (high risk of bias, fair precision, poor external validity) Strengths: Appropriate randomization and blinding. Minimal loss to follow-up. Used multiple validated scales to assess outcome in a consistent manner across participants. Weaknesses: Short follow-up time (3 months). Presence of baseline depressive symptoms. Baseline differences in disease severity among those with HIV (based on CD4 count) between groups not accounted for. Sample size and power calculation based on mean changes in scores, but not for changes in threshold diagnoses for minor or major depression. Limited external validity with low response rate (42%), and unclear if due to refusal or ineligibility. Very high unplanned pregnancy rates (77%) with potential impact on generalizability.

Author, year, support, country	Study design, population, timeframe	Contraceptive use	Outcome	Results	Quality, strengths, weaknesses
Tsai, 2010, funding not described, U.S.	Retrospective cohort study at outpatient obstetric clinic. 247 women who presented for 6-week postpartum visit.	Immediate (prior to discharge) postpartum DMPA (n=55) No birth control or tubal ligation (n=192)	EDPS score, cutoff of 13 as positive for depression, at 6 week postpartum visit	EDPS 13, p=0.88 DMPA 6/55 (10.9%) No hormonal contraception 27/192 (14.1%)	Overall quality: poor (high risk of bias, poor precision, fair external validity). Strengths: Selection procedures and outcome assessment consistent across all participants. Used a validated scale to assess outcome. Excluded women with a history of depression. Weaknesses: No adjustment for confounders, with significant age differences between groups. Insufficient follow-up period (6 weeks). No information on proportion of women who attend the six-week postpartum visit and how they differed from those who did not attend. Study not powered to detect differences in postpartum depression.
Lawrie, 1998, funded by research grants from Schering (Pty) Ltd, the Iris Eilen Hodges Trust of the University of the Witwatersrand, the South African Medical Research Council and the South African Institute for Medical Research, South Africa.	RCT, enrolled postpartum women from tertiary care hospital. 180 women aged 19 and older within 48 hours delivery of those interested in a non-hormonal method of contraception.	NET-EN 200 mg intramuscular injection (n=90) within 48 hours of delivery Placebo (1 ml normal saline) injection (n=90) within 48 hours of delivery	EDPS 0-30, >11 Montgomery-Asberg Depression Rating Scale (MADRS) 0-60, >9 minor and >18 major depression	6 week f/u MADRS > 18 (%), RR=2.130, p=0.158 NET-EN 11 (13.0) Placebo 5 (6.5) MADRS >9 (%), RR=2.556, p=0.008 NET-EN 35 (41.2) Placebo 18 (23.4) EPDS >11 (%), RR=3.035, p=0.002 NET-EN 39 (45.9) Placebo 20 (26.0) 3 month f/u MADRS > 18 (%), RR=1.091, p=0.895 NET-EN 8 (9.2) Placebo 7 (8.6) MADRS >9, RR=1.026, p=0.93 NET-EN 24 (27.6) Placebo 23 (36.4) EPDS >11 (%), RR=1.203, p=0.573 NET-EN 28 (32.2) Placebo 24 (29.6)	Overall quality: fair (moderate risk of bias, good precision, fair external validity). Strengths: Appropriate randomization and blinding. Analyzed by intention to treat. Appropriate adjustment for differences between groups. Weaknesses: Low response rate (<25%), with impact on external validity. Failed to meet intended sample size, however reached statistical significance for some outcomes.

LNG-IUD = levonorgestrel intrauterine device. ETG = etonogestrel. EE = ethinyl estradiol. aHR= adjusted hazard ratio. CI = 95% confidence interval. ICD-9 = International Classification of Disease, Ninth revision. NOS=not otherwise specified. RCT = randomized controlled trial. DMPA = depot medroxyprogesterone acetate. Cu-IUD = copper intrauterine device. NET-EN=norethisterone ethanate. RR= relative risk.

Table 2.

Study of women receiving an antidepressant prescription in the postpartum period.

Author, year, support, country	Study design, population	Contraceptive use	Outcome	Results	Quality, strengths, weaknesses
Roberts, 2017, no funding, U.S.	Retrospective cohort study, analysis of data from Military Health System Management Analysis and Reporting Tool. 75,528 women enrolled postpartum and followed for 12 months.	Norethindrone-only pills (n=19,883) LNG-IUD (n=3,096) ETG implant (n=2,730) EE/norgestimate pill (n=2,718) EE/norethindrone pill (n=1,675) EE/ETG ring (n=1,404) No hormonal contraception (n=44,022)	Antidepressant use as identified by pharmacy record of filled prescription of an antidepressant defined using the American Hospital Formulary Service classification code 281604 during 12 months after delivery. Excluded tricyclic antidepressants and serotonin reuptake inhibitors typically prescribed for smoking cessation (Bupropion HCL formulated as Zyban®) or insomnia (Trazodone).	Norethindrone-only pills aHR 0.58 (0.52–0.64) LNG-IUD aHR 1.01 (0.87–1.18) ETG implant aHR 1.22 (1.06–1.41) EE/norgestimate pill aHR 1.02 (0.85–1.22) EE/norethindrone pill aHR 0.88 (0.69–1.13) EE/ETG ring aHR 1.45 (1.16–1.8)	Quality: poor (high risk of bias, good precision, fair external validity) Strengths: Large cohort using claims data within a relatively closed health care system, with adequate follow-up for outcome (12 months). Groups drawn from the same source population with consistent inclusion and exclusion criteria. Exposure and outcome assessed consistently throughout participants using clear diagnostic codes. Likely a diverse population (though no data presented), and likely adequate power given large sample size (though no power or effect size calculations provided). Excluded prior depression diagnosis or antidepressant use within 24 months prior to delivery. Weaknesses: Significant potential for misclassification of outcome. Failed to adjust for key potential confounders from analysis (e.g. smoking, prior history of postpartum depression, birth complications, or breastfeeding problems). Military cohort with potential for higher rates of comorbid psychiatric conditions (e.g. post-traumatic stress disorder). Unique population with potentially limited generalizability.

LNG-IUD = levonorgestrel intrauterine device. ETG = etonogestrel. EE = ethinyl estradiol. ICD-9 = International Classification of Disease, Ninth revision. NOS=not otherwise specified. aHR= adjusted hazard ratio. CI = 95% confidence interval.