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# Safety and effectiveness of hormonal contraception for women who use opioids: A systematic review ☆,☆☆

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ABSTRACT

*Objective:* To systematically review the literature around the safety and effectiveness of hormonal contraception for women who use opioids. Our specific research questions are: 1) Among women who use opioids, do those who use hormonal contraception have increased adverse health events compared with those who do not use hormonal contraception? 2) Are there drug interactions between hormonal contraception and opioids that cause decreased effectiveness or increased toxicity from either drug?
*Methods:* We searched Medline, Embase, PsychInfo, CINAHL, the Cochrane Library, and clinicaltrials.gov through August 2018. We considered randomized controlled trials, cohort studies, and case-control studies, as well as pharmacokinetic and pharmacodynamic studies. We planned to use standard frameworks to assess risk of bias of included studies.
*Results:* The search identified 1852 articles. The full text of 66 articles was reviewed, and none met inclusion criteria.
*Conclusions:* Because we found no direct evidence on the safety and effectiveness of hormonal contraception for women who use opioids, we considered theoretical concerns. While women with OUD have a high prevalence of co-morbidities, such as viral hepatitis, generally women with medical conditions can safely use most contraceptive methods. When considering the pharmacokinetics and pharmacodynamics of hormonal contraception and opioids, there is little theoretical concern for interactions. Therefore, future research efforts could focus on improving access to the full range of contraceptive methods for women who use opioids, reducing unnecessary barriers to initiating and using contraception, while ensuring voluntary choice related to contraceptive use.



## 1. Introduction

Rates of unintended pregnancy among women with opioid use disorder (OUD) have been estimated in the United States (US) and elsewhere to be as high as 86% [1,2], substantially higher than 45% of pregnancies unintended in the general US population [3]. Untreated opioid addiction during pregnancy is associated with increased risks for poor fetal growth, placental abruption, preterm labor, fetal death, and neonatal abstinence syndrome [4,5].

Women with OUD use contraception at lower rates compared to the general population [6–10]. Coupled with high rates of unintended pregnancies, low rates of contraceptive use may indicate an unmet need for contraception. Recognizing this vulnerable intersection of reproductive health and substance use, the American College of Obstetricians and Gynecologists recommends that all patients be screened for substance use disorders [11]. Additionally, the American Society of Addiction Medicine recommends that all women seeking substance use disorder treatment should be screened for 12-month pregnancy intention at intake and offered referrals to comprehensive family planning services [12].

Despite these recommendations, providers might have concerns about the safety and effectiveness of hormonal contraception in women with OUD [13], which can act as a barrier to contraceptive access for these women. Providers may be concerned about whether women who use opioids have different health risks related to higher rates of comorbidities or behavioral risk factors

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that may influence the safety of hormonal contraception. Providers may also be concerned that drug interactions between opioids and hormonal contraception may affect safety or effectiveness.

The goal of this systematic review is to assess the safety and effectiveness of hormonal contraceptive methods among women who use opioids. Our specific research questions are:

- Among women who use opioids, do those who use hormonal contraception have increased adverse health events compared with those who do not use hormonal contraception?
- Are there drug interactions between hormonal contraception and opioids that cause decreased effectiveness or increased toxicity from either drug?

## 2. Methods

We created a protocol to investigate our research questions, and followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) reporting guidelines [14]. Briefly, we planned to include peer-reviewed primary research, including clinical trials, cohort studies, and case-control studies, as well as pharmacologic studies of interactions between opioids and hormonal contraception. Study populations included reproductive-aged women and adolescents using opioids, as well as women with a diagnosis of OUD.

The intervention of interest was any type of hormonal contraception, and the comparison was to those not using contraception or those using non-hormonal methods. The safety outcomes considered were adverse health events, including those directly related to side effects or toxicity of either the contraceptive method or the opioid, or worsening of OUD (e.g. relapse, withdrawal or overdose). The primary effectiveness outcome was pregnancy; secondary outcomes include pharmacokinetic and pharmacodynamic outcomes, such as drug levels and ovulatory function.

We searched Medline, Embase, PsychInfo, CINAHL, the Cochrane Library, and clinicaltrials.gov through August 2018 (Appendix A). Two authors (AT and KC) reviewed the search results by screening titles and abstracts to identify studies that required full text review. Uncertainty was resolved through discussion. We planned to extract relevant data from each study and to assess risk of bias using standard tools [15,16].

## 3. Results

Our search identified 1852 unique articles that were screened by title and abstract, and full text as needed (Fig. 1). No articles met inclusion criteria. The majority of articles were excluded because of article type or study design, or because they did not include our study population with outcomes of interest.

## 4. Discussion

Despite the importance of this topic, we identified no evidence to answer our research questions. In the absence of direct evidence, we considered theoretical concerns about the use of hormonal contraception among women who use opioids to provide considerations for future research.

Women with OUD have a high prevalence of co-morbidities, and providers may be concerned that their family planning care may be more complex. For example, women with OUD are more likely to have viral hepatitis, HIV, depression and other mental health disorders, and to smoke [17,18]. However, most women, including those with medical conditions, can safely use most, if not all, contraceptive methods [19,20]. Routine assessments for

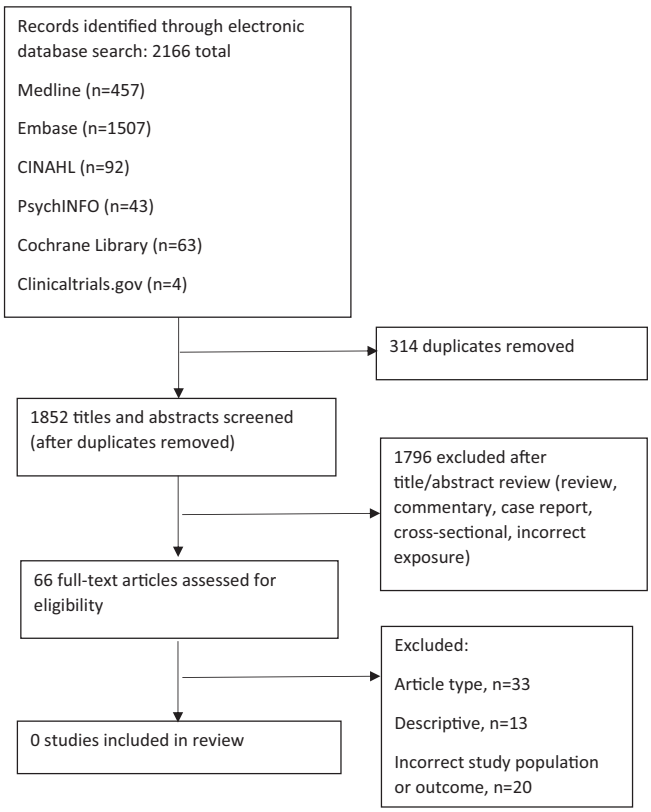


**Fig. 1.** PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart: flow diagram of study selection.

all contraceptive patients should include a review of their medical history [21], and guidelines such as the US Medical Eligibility Criteria for Contraceptive Use [19] can help providers safely provide contraception to women with medical conditions.

Providers may also be concerned about decreased contraceptive adherence for user-dependent contraceptive methods for women with OUD. A large cohort study of women in Massachusetts did not find an association between substance use disorder and contraceptive non-adherence [22]; however, a study of contraceptive adherence among female veterans found that those with dual diagnoses of a substance use disorder and another form of mental illness had increased odds of non-adherence when compared with women with neither diagnosis [23]. Contraceptive adherence is an issue for many women [24,25]: patient-centered counseling can help women find the method of contraception best suited to them [26], and certain strategies may improve adherence once a method is chosen [27]. Providers' concerns about adherence are not reasons to restrict or promote specific methods of contraception for women with OUD [28,29].

To consider potential interactions between opioids and hormonal contraception, we considered the pharmacologic activities of the more commonly used opioids, estrogens, and progestins by reviewing the pharmacokinetic and pharmacodynamics pathways separately, and evaluating potential areas of overlap. While the chemistry of illicitly manufactured opioids or the use of multiple illicit drugs concurrently may also affect pharmacologic activities, we are not aware of any evidence to evaluate the pharmacology of these issues.

The elimination of estrogens, progestins, and common opioids is dependent on several mechanisms. These agents undergo first pass metabolism in the liver where they are broken down before reaching systemic circulation then elimination [30–33]. Two hepatic processes are significant in drug metabolism and interactions:

phase 1 metabolism via cytochrome P450 mono-oxygenase system enzymes (CYP450) and phase 2 metabolism via uridine diphosphate glucuronosyltransferase enzymes (UGT) [30–33]. Phase 1 metabolism via the CYP450 enzyme system accounts for approximately 50% of the elimination of all medications [34], and is more likely to contribute to clinically significant drug interactions than phase 2 metabolism [31,35,36]. If either hormonal contraception or opioids significantly modify metabolic pathways of the other agent, this could lead to decreased effectiveness, bothersome side effects, or toxicity.

Opioid agents are not known to alter CYP450 metabolism, although most are known substrates for CYP450 pathways (predominantly CYP3A4, CYP2B6, and CYP2D6) [30,35]. Thus, there is no theoretical concern for any of the opioid agents to significantly inhibit or induce hormonal contraceptive agents (estrogens or progestins) and alter the concentrations or effects of these agents. Additionally, progestins are not known to be inducers or inhibitors for the CYP450 enzyme system [37,38], and therefore present no theoretical concern in opioid metabolism.

Ethinyl estradiol (EE) is the form of estrogen used in combined hormonal contraception and has been reported as a weak inhibitor for select CYP450 isoforms [33]. Studies have demonstrated that EE may act as a weak inhibitor for CYP3A4, CYP2B6, CYP2C19, and CYP1A2 isoenzymes [33,39]. Since many prescription opioids, including buprenorphine, fentanyl, hydrocodone, meperidine, methadone, oxycodone, and tramadol, are substrates of these isoenzymes, there is theoretical concern for a decrease in opioid clearance and an increase in serum opioid concentrations with concurrent EE use [33,40]. This could potentially increase concentrations of opioids and lead to toxicity or overdose. However, only a single animal study from 1982 has demonstrated that EE may be a weak inhibitor of an opioid agent [41]. This study found rats who received meperidine (a CYP2C19 substrate) and high doses of estrogen (5 mg/kg/day) showed a 45% reduction in meperidine clearance, though typical doses of estrogen in modern contraceptives are much lower (~0.5 mg/kg/day).

Another potential pathway for interactions is related to EE's potential to induce UGT enzymes [33]. EE has been shown to increase the clearance of other medications which utilize glucuronidation for metabolism, including multiple benzodiazepines, lamotrigine, and propranolol, suggesting that EE enhances glucuronidation and the excretion of these drugs [33,42,43]. This is some theoretical concern because buprenorphine, codeine, hydromorphone, morphine, and oxymorphone are substrates for UGT enzymes [30,31].

This review identified no evidence describing the safety or effectiveness of hormonal contraception for women who use opioids, and areas of theoretical concern that we identified are limited to potential effects of EE on opioid metabolism. Pharmacologic studies of opioids and current EE-containing contraception can help assess these concerns. Similar to drug-drug interaction studies of hormonal contraception and other drugs such as antibiotics and antiretrovirals [44,45], studies could focus on both pharmacokinetic (i.e., opioid drug levels with and without concomitant use of combined hormonal contraceptives) and pharmacodynamic (e.g., opioid toxicity) outcomes.

Beyond addressing these theoretical concerns, it may be helpful for future research on this topic to identify effective implementation strategies for improving access to the full range of family planning services in a patient-centered, non-judgmental manner. Such research could focus on formative work to understand the values and preferences around family planning of women who use opioids, and the perspectives and concerns of health care providers and systems that care for these women. Additional research could focus on approaches for implementing existing evidence-based guidelines in the care of this patient population to reduce unnecessary barriers to initiating and using contraception, while ensuring voluntary choice and freedom from coercion related to contraception use. Implementation research on access to family planning among women living with HIV could be used as a model [46].

Women with OUD are interested in family planning services, but may experience a variety of barriers to care including cost, separation of services, and stigma [7,8,13]. Focused efforts to improve integration of care (e.g. providing family planning services on site within substance use treatment services) or strengthen referral systems appear to be desired by and acceptable to patients [13]. General best practices for family planning, such as following evidence-based guidelines on the safety of contraception for women with medical conditions, having access to same-day contraception or Quick Start, and eliminating unnecessary testing, can also reduce barriers and facilitate access [19,21,47]. Providing family planning care following principles of autonomy, reproductive justice and trauma-informed care is important for all, and given the societal context, especially important for women with OUD [48,49].

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.contraception.2019.08.006.

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