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OPIOIDS (S YIP AND A KONOVA, SECTION EDITORS)

Advancing Preventive Interventions for Pregnant Women Who Are Opioid Using via the Integration of Addiction and Mental Health Research

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Abstract

Purpose of Review This review examines how research focused on treatment for opioid use in perinatal populations and preventive interventions for postpartum psychopathology have remained separate, despite significant overlap.

Recent Findings Guidelines for best practice in caring for pregnant women with opioid use disorder suggest the use of medication-assisted treatment with additional comprehensive care, including behavioral and mental health interventions. However, intervention research often mutually excludes these two populations, with studies of behavioral interventions for opioid use excluding women with psychopathology and research on preventive interventions for postpartum psychopathology excluding women who are substance using.

Summary There is a limited evidence-base to inform the selection of appropriate preventive interventions for pregnant women with opioid use disorder that can address opioid use and/or treatment adherence and concurrent mental health risks. We argue that it is critical to integrate research on pregnant women who are opioid using and preventive perinatal mental health interventions to catalyze pivotal change in how we address the opioid epidemic within this growing population.

Keywords Pregnancy · Opioid use disorder · Opioid use · Perinatal mental health · Postpartum mental health

Introduction

The devastating consequences of the opioid epidemic in the USA has been alarmingly documented in terms of the very high prevalence of opioid misuse, reaching 11.8 million adults in 2016 [1], and number of overdose deaths, estimated at 42,000 in 2016 [2]. Of utmost concern, the group with the greatest rise in opioid misuse includes women of childbearing age [3]. The consequences of opioid use disorder (OUD) [4] are more severe for women than men, including shorter length from opioid initiation to dependence (telescoping) [5, 6], more intense cravings [7], and greater resultant impairment [8, 9]. Risk factors for opioid misuse may not be equally weighted in men and women, with risk factors for women being more strongly linked to psychological distress [10, 11], interpersonal violence [12, 13], and childhood interpersonal trauma [10, 11, 14].

Particularly alarming is the impact of the opioid epidemic upon the next generation, highlighted by the increasing rate of pregnant women with OUD. From 1994 to 2014, the rate of women with OUD at the time of delivery increased 333% [15]. Opioid use during pregnancy can have substantial impact on mothers and infants, including neonatal opioid withdrawal (NOW), pregnancy and labor complications, and maternal death [16, 17]. Further, there are high rates of opioid misuse among young parents [18] and large numbers of children are estimated to live in families with a parent with OUD [19••]. Parental substance use significantly increases the likelihood of

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child maltreatment [20], child welfare involvement [21, 22], and poor behavioral and health outcomes for children [23, 24] .

Current research is heavily weighted towards neonatal, child, and birth/delivery outcomes, which are of critical importance. However, much less consideration has been placed on the impact of opioid use during pregnancy and postpartum on maternal mental health and well-being—constructs inexorably intertwined with infant outcomes and the intergenerational transmission of the effects of opioid use. We argue that a stronger focus on maternal mental health, specifically among pregnant women who are currently opioid using or receiving treatment for OUD (e.g., medication-assisted treatment; MAT) is a crucial component for addressing the opioid epidemic within this growing, but drastically under examined, population. The recent emphasis on maternal mental health during pregnancy and postpartum with regard to clinical guidelines [25•] and pharmaceuticals (e.g., brexanolone) [26] makes this an opportune moment to emphasize the importance of incorporating women who are opioid using into this growing movement towards greater maternal well-being during the prenatal and postpartum periods.

Relevance of Prenatal and Postpartum Neuroplasticity for Opioid Use and Mental Health

The prenatal and postpartum periods are times of heightened neuroplasticity, including volumetric and neurochemical changes in medial prefrontal, sub-cortical, and sensory brain regions [27•, 28–31]. Postpartum women demonstrate increased activation of brain regions implicated in reward circuitry, including ventral striatal (e.g., nucleus accumbens) and medial prefrontal brain regions, to images of their own infants [29, 31] and enhanced activation of brain regions involved in stress responding, such as the amygdala [27•, 28, 29, 31–34]. Stress reactivity peaks in the early postpartum period (4 to 6 weeks) [35, 36] and then gradually diminishes over the first 3 to 4 months after birth [36]. Neuroplasticity in reward and motivation circuits and stress reactivity during the postpartum period is thought to promote greater maternal responding [29–31, 37, 38] and responsive parenting behaviors [32, 39–41].

Brain regions implicated in maternal responding, specifically reward processing and stress reactivity, are also implicated in the neurocircuitry of addiction [42–44]. This overlap has led to a proposed reward-stress dysregulation model of maternal responding whereby the reward salience of infant related cues is decreased and stress reactivity to infant related cues is increased among postpartum women with addiction, leading to poorer maternal responding and less responsive parenting behaviors [44, 45]. Evidence in support of the reward-stress dysregulation model of maternal responding includes lower levels of engagement with infants [43] and dampened activation of reward circuitry, implicated in addiction, to infant stimuli among mothers using substances [46, 47]. In the context of the model, these findings have been interpreted as evidence of decreased reward sensitivity [48••] because infant stimuli consistently elicit activation of reward circuitry in postpartum women [29, 31].

Interestingly, reward processing and stress reactivity are also implicated in postpartum psychiatric disorders, particularly postpartum depression (PPD). Similar to postpartum women who are substance using, women with PPD demonstrate dampened brain activation of reward and motivation circuits to images of their own infants [49]. Additionally, they demonstrate decreased activation of prefrontal regions (e.g., medial prefrontal cortex) implicated in stress reactivity [50] to distress cues from their own infants [51]. Findings related to amygdala activation have been mixed, with some studies finding increased activation and others decreased activation in women with PPD [27•]. There is likely a U-shaped function for normative changes to amygdala activation during the postpartum period, with increased activation normative at certain periods (earlier postpartum) and decreased activation at others (later postpartum) [27•]. Therefore, altered activation of sub-cortical stress response regions may be dependent on the specific postpartum time period. In addition to altered functional recruitment of brain regions involved in stress responding, there is also altered functional connectivity within and between brain regions implicated in stress reactivity in women with PPD [52•]. The apparent overlap in the neural circuitry related to maternal substance use, including opioids, and PPD highlights the need to address these problems as interrelated from both a research and clinical perspective.

Limited Integration of Traditional Treatment for OUD During Pregnancy and Mental Health Treatment

The best practice guidelines recommend the use of MAT for treating pregnant individuals with OUD [53, 54••, 55]. Guidelines for MAT during pregnancy specify the use of methadone and, more recently, buprenorphine [53, 56]. Both medications have agonistic effects on opioid receptors and are FDA-approved for the prevention of opioid cravings and withdrawal symptoms among adults with OUD [57]. Among pregnant individuals, numerous health outcome studies have found methadone and buprenorphine to be effective and safe (for review, see [54••, 58]) when administered daily on a flexible dose schedule (i.e., 4–16 mg/day for buprenorphine or 60–120 mg/day for methadone) within a comprehensive care model [53]. Overall, both methadone and buprenorphine have been shown to be safer alternatives for infants than continued opioid use or medically supervised withdrawal [56].

Neonatal and maternal outcomes at or near the time of delivery are the primary health outcomes used to demonstrate the safety and efficacy of MAT during pregnancy. Neonatal outcomes typically include gestational age at birth, birth weight and length, head circumference, pre-term birth rates, NOW characteristics, and length of hospital/NICU stay [58–61].

When included, maternal outcomes are often secondary and focused on mode of delivery (e.g., Cesarean section vs. vaginal), use of anesthetics during delivery, drug use at time of delivery, MAT dosage at time of delivery, decision to breastfeed, and treatment retention [59–61]. A recent literature review conducted to inform national guidelines concluded methadone and buprenorphine to be effective when administered in the context of comprehensive care [54••]; however, no maternal outcomes related to mental health or well-being were reported.

In addition to pharmacotherapy, best practice MAT guidelines for pregnancy recommend comprehensive care that includes adjunctive behavioral and mental health interventions [53, 56, 62]. Adjunctive behavioral interventions for OUD often address underlying processes that support continued opioid use and maintenance of pharmacotherapy, with some interventions also addressing mental health difficulties that sustain substance use [63, 64]. The behavioral interventions with the greatest support in reducing opioid use, increasing adherence to pharmacotherapy, and harm reduction in non-pregnant [63, 65] and pregnant [66] populations are contingency management (CM) and cognitive behavior therapy (CBT), which can include motivational interviewing (MI) techniques. There is growing evidence that behavioral interventions during pregnancy, as an adjunct to MAT, can also increase engagement in prenatal care [66, 67]. However, less than 40% of pregnant women receiving opioid pharmacotherapy had claims for behavioral health services in a recent trend analysis [62].

The recommended inclusion of not just behavioral interventions to support treatment retention and reduced substance use but also *mental health interventions* is of critical importance because of the high comorbidity in rates of opioid use and psychiatric disorders [68, 69]. Further, the presence of a psychiatric disorder significantly increases the rate of illicit substance use [68, 69], including specifically in populations of adults seeking MAT for OUD [70]. In women, comorbidity of OUD with mood and anxiety disorders is significantly more pronounced than men [69–71]. Psychiatric disorders overall occur at significantly higher rates among women than men using illicit substances [69].

Similar to research on MAT, outcomes for behavioral interventions for opioid use during pregnancy have traditionally focused on physical neonatal characteristics, NOW symptoms, delivery outcomes, treatment engagement, and substance use [66], with limited inclusion of maternal mental health outcomes. The limited research available suggests that behavioral interventions for OUD during pregnancy have the potential to reduce depressive symptoms postpartum [67]. However, psychiatric symptoms may be a barrier to pregnant women seeking MAT during pregnancy. For example, women who seek MAT for OUD during pregnancy and have higher levels of depression are more likely to withdraw from treatment than women with lower levels of depression [67]. On the other hand, up to 50% of RCTs for behavioral interventions for OUD during pregnancy exclude women with psychiatric disorders, symptoms, or distress, or who are suicidal [66]. Therefore, we have limited evidence speaking to the effectiveness of behavioral interventions for pregnant women with co-morbid OUD and psychiatric disorders *or* the impact of behavioral interventions during pregnancy for OUD on mental health outcomes.

Preventive Interventions for Postpartum Psychiatric Disorders Do Not Sufficiently Include Pregnant Women with OUD

Over the past decade, greater emphasis has been placed on the importance of prenatal and postpartum mental health due to our growing knowledge of the effects of prenatal and postpartum psychiatric disorders on women and their infants [52, 72, 73]. PPD is the condition that has received the greatest attention. In particular, the need for *preventive* interventions to reduce risk of PPD as opposed to responsive interventions once PPD symptoms onset has been increasingly recognized. The US Preventive Services Task Force (USPSTF) [25•] recently recommended all pregnant and postpartum women at-risk for prenatal or postpartum depression be referred for psychosocial intervention [25•]. Despite the urgent need for such preventive interventions, few have been validated with high quality studies and the pooled effect size of the interventions in higher quality studies is small [72•].

The increasing recognition of the importance of early identification of risk and preventive interventions for mental health disorders during pregnancy and postpartum suggests an opportunity to highlight and address maternal OUD from a similar perspective. However, interventions addressing maternal mental health in this early critical period have continued to be developed and validated separately from approaches to address maternal OUD or other forms of substance use. We argue that the continued separate development of these lines of research, and subsequently practice and policy, is detrimental to families in the greatest need. For example, the review of preventive interventions for PPD conducted by the USPSTF found that of the 17 studies deemed high quality RCTs, more than 50% excluded pregnant women who were using substances [72•]. Exclusion criteria adopted in psychosocial studies of *both* preventive interventions for opioid use and postpartum psychopathology perpetuate differentiating treatment for opioid use and risk for postpartum psychopathology in pregnant women, as opposed to integrating and/or augmenting these two critical needs for highly at-risk women and their infants.

Commentary and Future Directions

While best practice guidelines [53, 56] speak strongly to the need to augment current MAT for OUD during pregnancy with comprehensive care that includes behavioral interventions *and* mental

health intervention, significant gaps in research place programs and institutions in the position of needing to make decisions about intervention implementation without a sufficient evidence-base that allows them to maximize both efficacious and efficient intervention delivery. This gap is fueled by a lack of evidence for whether existing interventions for maternal mental health could be effective for pregnant women with OUD in improving mental health and reducing future opioid use *and* evidence regarding how existing adjunctive behavioral interventions for women with OUD affect mental health. See Fig. 1. Multiple avenues of research have strong potential to increase evidence-based interventions targeting both opioid use and mental health as well as inform the development of policy supporting the comprehensive treatment of pregnant women with OUD.

At the most basic level, we have limited knowledge of the trajectory of mental health symptoms across pregnancy and postpartum in both women with and without OUD. Some studies have demonstrated a typical trajectory of depressive symptoms, across populations from different countries, with depressive symptoms typically increasing in the third trimester, peaking around 4 to 6 weeks postpartum, and then decreasing [52•, 74–77]. However, trajectories of mental health symptoms during pregnancy and the postpartum period in women with OUD have not been systematically studied. Prior research indicates that risk factors commonly co-occurring with OUD, such as a prior history of psychiatric disorders, trauma history, and prenatal stress, may significantly alter trajectories for prenatal and postpartum psychopathology [52•, 73]. Advancing our understanding of trajectories of mental health symptoms during pregnancy and postpartum among women with OUD has potential to reveal periods of heightened vulnerability, but also to shed light on times of particularly rapid change in symptomatology and other aspects of clinical presentation. Periods of rapid change would be suggestive of heightened plasticity, and thus potential opportunity for increased responsivity to intervention.

Another important direction for future research involves increasing our understanding of heterogeneity among pregnant and postpartum women with OUD. There has been a growing recognition of the importance of increasing our understanding of heterogeneity in psychiatry and other health disciplines, including unique etiologies and treatment needs despite similar behavioral or psychiatric presentations, as well as the occurrence of multiple symptom clusters or disorders within an individual [78]. Research addressing heterogeneity among pregnant and

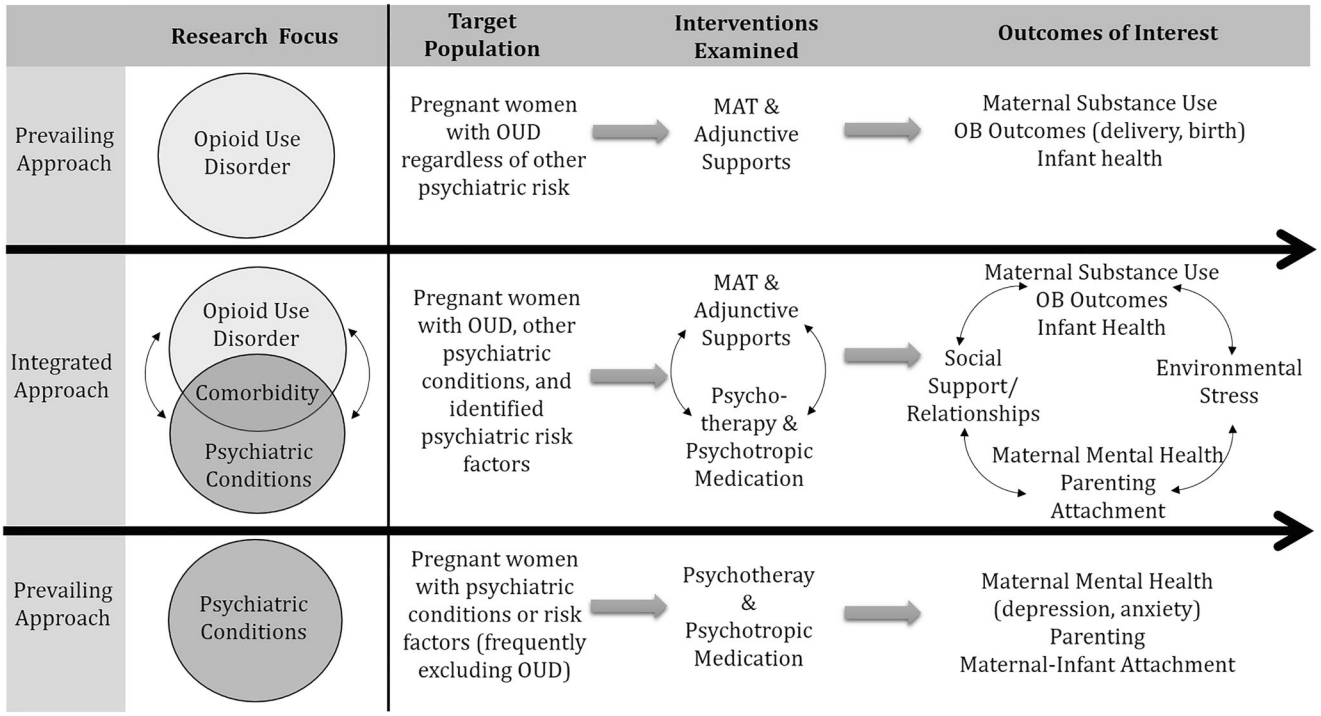

Fig. 1 Prevailing separate lines of research into opioid use and other psychiatric conditions during pregnancy versus an integrated approach. Prevailing approaches contribute to parallel lines of research into opioid use disorder (OUD) versus other psychiatric conditions and risk factors during pregnancy, missing the critical intersection. An integrated approach to both basic and intervention research has potential to advance understanding of the overlap and reciprocal connections between OUD, existing psychiatric conditions, and risk factors for postpartum psychiatric conditions (e.g., history of depression and trauma). Such an approach also draws attention to important questions regarding how treatments for psychiatric conditions during pregnancy (psychotherapy and psychotropic medications) may work for women with OUD, and/or interact with treatments targeting OUD (e.g., medication-assisted treatment (MAT)). Finally, the integrated approach lends towards conceptualizing outcomes at multiple levels and considering associations between them

postpartum women with OUD, particularly considering co-occurring mental health symptoms, underlying cognitive phenotypes, and neurobiological functioning, will be critical for advancing our understanding of pathways of risk and resilience. Given the prevalence of comorbidity between OUD and psychiatric symptoms/disorders, there will likely be overlapping and distinct pathways contributing to the development of OUD and mental health difficulties. Further, identification of subgroups among women with OUD may reveal unique combinations of environmental risk factors, trauma history, cognitive and emotional regulation skills, stress reactivity, and reward processing, which have significant implications for targeting intervention.

Intervention research can both benefit from and drive forward these avenues of more basic research to advance understanding of the unique opportunities and challenges of pregnancy and the postpartum period among women with OUD. Intervention research, and particularly involving randomization of individuals to conditions (e.g., randomized controlled trial [RCT]), can shed light on mechanisms underlying positive or negative forms of adaptation for mothers during these periods. This is particularly true of intervention research including in-depth characterization of cognitive, emotional, and reward processing, and examining neurobiological indicators. While outcome markers may be detectable by behavioral measures (e.g., cognitive, affective, functioning) or clinical measures (e.g., symptoms, disorders), neurobiological markers of treatment response may provide a unique window for examining aspects of treatment response critical for driving change in behavior and clinical symptomatology. Adaptive intervention designs, such as sequential, multiple assignment, randomized trials (SMART) [79], which allow for several decision points and tailoring based on individual responding (or nonresponding) will likely be particularly important for advancing our understanding of intervention efficacy and mechanisms of change [24••]. Such an approach would allow for testing varying levels and types of interventions to best support individuals within the heterogeneous population of women with OUD during pregnancy and postpartum.

Conclusion

There is an urgent need to better understand and support pregnant and postpartum women with OUD. Weaving together basic research, intervention and implementation science will be necessary to provide a more solid foundation of knowledge upon which to build efforts in this area. Targeting resources towards this population holds promise for supporting mothers and infants, and preventing intergenerational transmission of the negative sequelae of the current opioid epidemic.

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Compliance with Ethical Guidelines

Conflict of Interest The authors declare that they have no conflicts of interest.

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