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Opioid substitution in pregnancy a narrative review: contemporary evidence for use of methadone and buprenorphine in pregnancy

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ABSTRACT

Illicit opioid use is a growing public health emergency and is associated with adverse medical and social outcomes. Opioid use in the pregnant population is increasing globally, and optimal management incorporates opioid substitution programs with improved concurrent engagement in medical care. The two main drugs used in opioid substitution programs are methadone and buprenorphine. Methadone has been used since the 1970s and provides treatment stability leading to improved engagement with obstetric services. Buprenorphine is a newer treatment, has greater dosing flexibility, and may be associated with fewer neonatal adverse effects. Direct comparisons of methadone and buprenorphine treatments are limited but suggest that buprenorphine is associated with less severe neonatal withdrawal; however, it is not universally well-tolerated and tends to be prescribed to less severely affected mothers. Given the lack of clear evidence to support one opioid substitution therapy over another, the principal aim of therapy should be to stabilize treatment and promote more comprehensive engagement with multidisciplinary services.

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Opioid use; methadone; buprenorphine; women's drug use; substance use

Introduction

There are approximately 62 million non-medical opioid users globally, with more than 11 million people injecting drugs in 2019 (United Nations, 2021). Opioid use in people of childbearing age and consequently in pregnancy is increasing and represents a growing public health challenge (Maeda et al., 2014).

Opioid dependence is associated with socioeconomic disadvantage, poly-substance use, and mental and physical comorbidities (Forray, 2016; Havens et al., 2009; Information Services Division Scotland, 2019; The Centre for Public Health Faculty of Health & Applied Social Science Liverpool John Moore's University, 2011). During pregnancy, continued opioid use is associated with obstetric and neonatal complications such as stillbirth, intrauterine growth restriction, placental abruption, preterm labor, prolonged hospital admission, maternal cardiac arrest, congenital defects, and fetal alcohol syndrome (Bell & Harvey-Dodds, 2008; Maeda et al., 2014). Furthermore, abrupt cessation of neonatal opioid exposure at birth can result in neonatal abstinence syndrome (NAS), characterized by autonomic, neurological, gastrointestinal, and respiratory system disturbances. A mother who has a neonate diagnosed with NAS has an 11–12-fold increased risk of death in the 10 years following delivery compared with a mother whose neonate does not have NAS (Guttmann et al., 2019). Opioid exposure *in utero* has been associated with developmental delay in childhood and an increased risk of addictions, criminal activity, and poor health in adulthood (Oei, 2018).

Maternal treatment with an opioid substitution regime during pregnancy has numerous advantages compared to ongoing illicit drug use. These include stopping the cycle of intoxication and withdrawal associated with illicit drug use, reducing the incidence of blood-borne virus infections, reducing criminal activity, and increasing engagement with healthcare services (European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), 2014; National Institute for Health and Clinical Excellence (2006); UK Department of Health (2017); Ward et al. (1994)). The two main drugs used for opioid substitution therapy are methadone and buprenorphine, with both recommended for use in pregnancy by international guidelines (US Department for Health and Human Services, 2018; National Institute for Health and Clinical Excellence, 2006; World Health Organisation, 2014). Studies comparing methadone and buprenorphine in pregnancy are complicated by differences in prescription practices (in cohort studies), and by small study sizes (in randomized control trials).

Mothers taking buprenorphine are more likely to be older, married, in employment, have a higher level of education and have a history of prescription rather than illicit opioids than those on methadone (Krans et al., 2016). This tendency to prescribe buprenorphine to mothers with less severe addictions may bias observational studies (Brogly et al., 2016). The paucity of high-quality evidence has led national guidelines to stress clinical equipoise regarding the optimal opioid replacement regime in pregnancy, stating that if a mother is stable on one medication, this

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should be continued (US Department for Health and Human Services, 2018; National Institute for Health and Clinical Excellence, 2021; World Health Organisation, 2014).

Maternal illicit opioid use has been identified as a research priority by the World Health Organization in 2014. During pregnancy, mothers are in frequent contact with their healthcare providers, making this a powerful 'teachable moment' for promoting positive behavioral change. This review appraises the evidence for both methadone and buprenorphine in pregnancy, with a focus on maternal, neonatal, and longer-term childhood outcomes.

Methods

We conducted a literature search without language restriction of published scientific articles on online databases (EMBASE, PubMed, Web of Science, Scopus, Open Gray, CINAHL, and the Cochrane Central Registry of Controlled Trials (CENTRAL)) from inception to April 2020. Eligible studies were full-text RCTs and observational cohort studies comparing methadone and buprenorphine and reporting maternal and or neonatal outcomes. Search terms were "pregnancy," "infant," "neonate," "opiate substitution treatment," "methadone," and "buprenorphine." Relevant articles were obtained, and the reference sections were reviewed to identify additional relevant literature. The population of interest was mothers receiving opioid substitution therapy in pregnancy. All obstetric, maternal, neonatal, and early childhood outcomes were considered. This article was prepared using the SARNA guidelines for quality assessment of narrative review articles (Baethge et al., 2019).

Methadone

Methadone is a full mu-opioid receptor agonist which has been used to treat opioid dependence in pregnancy since the 1970s (Finnegan et al., 1977). As its half-life is around 36–48 hours, it is generally administered once per day, in supervised clinics or in pharmacies, with 'take-home' doses generally limited to dates when the premises are closed or if compliance with treatment can be assured. Methadone remains a popular choice of opioid substitution due to its lower risk of neuropsychiatric toxicity, lack of active metabolites, minimal accumulation in renal failure, good bioavailability, and long duration of action. As methadone is bound to alpha-1-glycoprotein in the plasma, free concentrations of the drug can change at times of stress. Furthermore, drug-related liver enzyme induction (e.g., rifampicin), inhibition (e.g., omeprazole), and enzyme polymorphism may lead to altered methadone metabolism and necessitate changes to the drug dose (Brown et al., 2004; Garrido & Trocóniz, 1999; Holmquist, 2009).

A typical starting dose of methadone during pregnancy is between 10 and 20 mg per day, increasing to 60–120 mg per day with dose adjustments of 5–10 mg increments daily (British National Formulary, 2021a). As pregnancy progresses, methadone clearance increases and plasma concentrations reduce, resulting in the potential need for increased daily dose or split dosing throughout the day (American Society of Addiction Medicine, 2019).

Maternal outcomes

The risk-benefit profile of methadone has been widely studied in both obstetric and non-obstetric populations, with treatment retention found to be improved on flexible higher dose programs compared with fixed lower dose programs (National Institute for Health and Clinical Excellence, 2007). The advantages/benefits associated with methadone use include; stabilization of opioid levels and reduction in illicit drug use, improved HIV risk scores, reduced criminal activity, reduced mortality, and improved engagement with healthcare when compared to ongoing illicit opioid use (European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), 2014; Gaalema et al., 2012; Kandall et al., 1976; National Institute for Health and Clinical Excellence, 2006; UK Department of Health, 2017; Ward et al., 1994). Disadvantages of methadone include the risk of maternal respiratory depression, QT prolongation due to cardiac ion channel inhibition, drug interactions, and lifestyle restrictions reflecting the need for supervised intake (Ehret et al., 2006; Garrido & Trocóniz, 1999; White & Lopatko, 2007).

Birth outcomes

Methadone-exposed neonates generally have a lower birth weight than neonates born to non-opioid using mothers (approximately 279 g lighter) but greater birth weight than neonates born to heroin-using mothers (Hulse et al., 1997). Furthermore, methadone crosses the placenta affecting fetal heart rate, motor activity, and parasympathetic tone due to altered fetal neurodevelopment (Jansson et al., 2005, 2011; Walhovd et al., 2012; Wouldes et al., 2004). Such fetal neurobehavioral change does not necessarily imply longer-term impairment, and there is a lack of association between NAS severity and later developmental outcomes (Fucile et al., 2021).

NAS is common, with a reported incidence of 48–94% in offspring of mothers taking opioids (Osborn et al., 2010), and this risk increases with *in utero* co-exposure to other drugs (e.g., nicotine, benzodiazepines; Stover & Davis, 2015). Compared with neonates born to heroin-using mothers, neonates of mothers on opioid replacement programs have a later onset of NAS, lower peak NAS severity, and shorter length of hospital stay (Binder & Vavrinková, 2008; Stover & Davis, 2015). In a meta-analysis of 29 studies, methadone dose was not related to the incidence or severity of NAS. However, many studies were not blinded, and most did not control for other confounding factors (Cleary et al., 2010). Management of NAS includes close monitoring, supportive care, and reducing opioid regimes. Methadone is associated with lower neonatal mortality compared with heroin (relative risk 3.27 (95% CI 0.95–9.60) versus 1.75 (95% CI 0.60–4.59; Hulse et al., 1998), and advances in treatment have reduced short-term neonatal mortality to be comparable with offspring without withdrawal symptoms (Goel et al., 2011; Lisonkova et al., 2019; Rosen et al., 1988; Wachman et al., 2018).

Childhood outcomes

The effects of methadone on childhood development have not been investigated in large trials, with meta-analyses pooling opioid use (methadone, buprenorphine, or heroin) to achieve adequate sample sizes to assess the potential impact on a range of diverse developmental outcomes. These studies have shown impairments in multiple childhood outcome measures for opioid-exposed compared to non-opioid exposed offspring

(Andersen et al., 2020; Lee et al., 2020). The domains negatively associated with opioid exposure include cognitive scores (standardized mean difference, SMD: −0.77, 95% CI: −1.06 to −0.48); psychomotor scores (SMD: −0.52, 95% CI: −0.78 to −0.25); IQ (SMD: −0.76, 95% CI: −1.25 to −0.28); expressive language scores (SMD: −0.65, 95% CI: −0.97 to −0.34); and receptive language scores (SMD: −0.74, 95% CI: −1.12 to −0.3). A single-center study showed that methadone exposure is associated with a higher risk of abnormal visual assessment at 27 weeks of age (risk ratio (RR): 5.1, 95% CI: 1.3–20) when compared to matched non-drug exposed offspring (McGlone et al., 2014). The potential mechanism underlying this developmental delay has been investigated in animal studies, which show alterations in neurotransmitters across multiple systems as well as altered dendric length, synaptic plasticity, neuronal proliferation, and cholinergic function (McGlone et al., 2009; Ross et al., 2015).

Buprenorphine

Buprenorphine was licensed for use by the Federal Drug Administration (FDA) in the USA in 2002 and is a potent partial mu-receptor agonist, an opioid receptor-like-1 receptor (ORL-1) agonist with weak binding affinity, and a delta and kappa receptor antagonist with high binding affinity [Food and Drug administration (FDA), 2002]. The differential receptor activity of buprenorphine is favorable as it produces potent analgesia (meaning that doses can be given on alternate days), with a ceiling effect for respiratory depression and euphoria and a reduction in opioid-related side effects such as constipation, anxiety, respiratory depression, and addiction (Jones et al., 2012; White & Lopatko, 2007). Buprenorphine has a high first-pass metabolism, is most commonly administered via the sublingual or buccal routes, and may be co-administered combined with naloxone, to discourage intravenous injection. The starting dose for buprenorphine at a dose of between 0.8 and 4 mg per day increased up to 32 mg per day, with a typical range being 12–24 mg per day (British National Forumla, 2021).

Maternal outcomes

Despite its clear pharmacological advantages, the requirement to dissolve buprenorphine under the tongue for 10–15 mins may be poorly tolerated by some users and can impact treatment retention. Three randomized trials have investigated treatment retention rates (Fischer et al., 2006; Jones et al., 2005, 2010). The 223 mothers in these studies had a higher relative risk for drop-out on buprenorphine versus methadone (RR: 0.66, 95% CI: 0.37 to 1.20; Minozzi et al., 2020). This concern regarding retention on buprenorphine therapy was further supported by a meta-analysis of 1391 non-pregnant drug users, which showed higher treatment drop-outs (RR 0.83, 95% CI: 0.73 to 0.95) on buprenorphine compared to methadone (Mattick et al., 2008).

Birth outcomes

Three meta-analyses have compared the relationship between methadone and buprenorphine and neonatal outcomes (Brogly et al., 2014; Minozzi et al., 2020; Zedler et al., 2016). Each meta-analysis had a different approach to analysis. The study by Minozzi et al. (2020) included only RCTs (223 mothers), and found no statistically significant differences in the primary outcomes of NAS treatment, maternal retention on treatment, primary substance use, or adverse events. Birth weight was higher in the buprenorphine group, but the quality of the evidence was moderate to very low due to inconsistent outcomes, high drop-out rates, and small sample sizes. The authors concluded that "There is still a need for randomized controlled trials of adequate sample size comparing different maintenance treatments."

Two further meta-analyses by Zedler et al. in 2016 (including both RCTs and cohort studies), and Brogly et al. in 2014 (presenting the results adjusted for confounding factors in both RCTs and cohort studies) found greater gestation, larger head circumference, and lower risk of being pre-term with buprenorphine. These cohort studies increase the sample size of the comparison but could add biases due to lack of control for confounding factors. Overall, the effect sizes were attenuated, though still favored buprenorphine after adjustment for confounding (Brogly et al., 2014).

Childhood outcomes

Few studies have investigated the neurodevelopment of children exposed to buprenorphine, with those which have been undertaken primarily focusing on comparing buprenorphine to methadone. Following birth, offspring exposed to buprenorphine have fewer signs of stress, arousal, and excitability, compared to those exposed to methadone (Coyle et al., 2012). In a 3-year follow-up of the Jones et al. (2010) RCT, no differences were observed between opioid therapies for childhood development (cognition, language, sensory, and temperament), or maternal outcomes (parenting stress, home environment, and addiction severity), with the results of the development assessment for both groups within normal ranges (Kaltenbach et al., 2018). Furthermore, there were no differences in outcomes between offspring who had NAS and those who did not. This suggests that the type of opioid exposure *in utero* does not differentially affect development. Consistent with this when visual pathways were examined in a group of 30 offspring exposed to buprenorphine, no differences were observed between the buprenorphine group and the non-opioid exposed control group (Whitham et al., 2010).

Other treatments

Other opioid substitution regimes include buprenorphine-naloxone in combination, naltrexone, and oral morphine. A meta-analysis of 5 observational studies (1875 mothers) investigating the safety of buprenorphine-naloxone combination therapy compared to other opioid substitution regimes (Link et al., 2020) found a reduced risk of requiring treatment for NAS with buprenorphine-naloxone but no difference in other outcomes. Larger studies in the obstetric population are required to make definitive conclusions. Naltrexone, an opioid receptor antagonist, is rarely used, except in countries where methadone/buprenorphine are not prescribed (Krupitsky et al., 2010). A cohort study (n = 107) investigating naltrexone compared with methadone in the obstetric population found naltrexone to have a favorable profile in terms of birth weight, gestation, and Apgar score at oneminute (Hulse et al., 2004). This small study supports the idea that naltrexone may be a potential alternative to buprenorphine or methadone. Lack of

regulated programs in pregnancy, and high risk of default off-program may limit its use, as it does in the general population.

One small, randomized control trial (n = 48) investigated morphine compared to methadone, finding reduced benzodiazepine and additional opioid consumption in the morphine arm, though no other differences were observed (Fischer et al., 1999). The limitations of morphine for withdrawal therapy include difficulty in monitoring for additional illicit opioid use, lack of established treatment programs, and diversion risk.

Guidelines for the management of mothers with opioid addiction

Several national and international organizations provide guidelines on the treatment of opioid dependency in pregnancy. These include the National Institute for Health and Clinical Excellence, the American College of Obstetricians and Gynecologists (2017), the American Society of Addiction Medicine, and the World Health Organization. These guidelines provide valuable and freely available resources for managing opioid addiction during pregnancy. Key tenets of all guidelines include personalized and supportive treatment tailored to individual needs, use of opioid substitution therapies rather than withdrawal programs, encouragement of breastfeeding in those not using illicit drugs or without other contraindications, postpartum psychological support, and discussion surrounding ongoing contraception.

These guidelines provide a useful evidence base for the treatment of this complex condition. However, they are limited by low levels of evidence and a lack of studies specifically examining the obstetric population.

Summary

Opioid replacement therapy in pregnancy is preferable to ongoing illicit drug use, and when combined with specialist obstetric care, can improve birth outcomes. Both methadone and buprenorphine can be safely used in pregnancy, and there is some evidence that buprenorphine can improve neonatal outcomes. Differences are generally small, especially when adjusted for confounding factors, and maintaining stability on treatment regardless of the agent used, remains paramount. Further work is required to investigate the safety of different formulations of opioid replacement for longer-term childhood outcomes and how best to manage mothers who choose to abstain from opioids in pregnancy.

Treatment of opioid addiction during pregnancy is challenging and maintaining trust and engagement in services should remain the priority, irrespective of which drug treatment is used. Health professionals should be sensitive to mothers' physical, psychological, and social needs provide appropriate support and optimize good health practices. This review should reassure both mothers and healthcare professionals that there are two viable treatment options for this complex condition.

Disclosure statement

Drs Kinsella, Capel and Kearns report no conflicts of interest. Scott Nelson has participated in Advisory Boards and received consultancy or speakers' fees from Access Fertility, Beckman Coulter, Ferring, Finox, Merck, MSD, Roche Diagnostics, and The Fertility Partnership.

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