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Identifying The Risks and Benefits Of Buprenorphine-Naloxone Maintenance During Pregnancy: Unmet Needs and Challenges From A Critical Perspective

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Dear Editor,

Heroin use during pregnancy causes a broad range of negative consequences such as spontaneous abortion, intrauterine growth retardation (IUGR) and neonatal abstinence syndrome (NAS). Utilization of opioid agonist agents in the management of opioid-dependent pregnant women is associated with better maternal and neonatal outcomes compared to remaining untreated.[1] Abrupt opioid reduction and classical detoxification are not recommended in gestation due to the risk of fetal distress, central nervous system stress, stillbirth, and precipitating co-morbid maternal alcohol or sedative/hypnotic dependence led by an unsuccessful withdrawal management.[2] Buprenorphine, a partial opiate mu receptor agonist, has emerged as a novel and effective maintenance treatment alternative to methadone, particularly in pregnant women. Combination of buprenorphine and an opioid antagonist, naloxone, (B/N) has been the frequently preferred form by clinicians due to its lower misuse potential compared to buprenorphine alone.[3,4] In the literature, one can see that the studies rather focus on buprenorphine monotherapy during pregnancy; therefore, little is known about the safety and efficacy profile of the combined form in pregnant. We aimed to briefly present highlighted findings from the perspective of featured work on the management of opioid dependence during pregnancy and to discuss whether B/N could be employed in the mainstream opioid maintenance approach, as long as it further gets illuminated in terms of safety and efficacy with further research in pregnant women.

Opioid agonists are known to mitigate the risk of IUGR, placental abruption, fetal death, preterm labor, and meconium passage prior to delivery compared with continued heroin use.[5] Obviously, opioid agonist treatment per se is not without any risk. However, pregnant women are not recommended to be remained untreated, because of their prior benefits those considerably outweigh the risks. The most significant adverse effect of opioid agonists is fetal withdrawal (known as NAS). Chronic exposure to an opioid drug during pregnancy can result in the development of NAS which is a morbid entity characterized with a set of central and autonomic neurological symptoms including hyperirritability and seizures that appears hours to days following the delivery and frequently requires neonatal intensive care.[2] Unfortunately, related literature does not point out any opioid agonist with a prominent lower risk of NAS. However, a randomized, double-blind, controlled trial demonstrated the superiority of prenatal exposure to buprenorphine compared to methadone in terms of neonatal adverse effects. This study reported less severe prognosis in NAS, less neonatal treatment need for NAS, and shorter hospital stay duration in infants born to mothers under buprenorphine treatment during pregnancy.[6] B/N showed similar risk profile for the development of NAS compared to buprenorphine alone and B/N was found superior to methadone in terms of NAS risk during pregnancy.[7] Other side effects associated with opioid agonist treatment included alterations in fetal activity and heart rate, as well as IUGR.[2] Moderately strong evidence indicated a lower risk of preterm birth, IUGR, fetal heart rate with larger head circumference with buprenorphine compared to methadone and continued heroin use.[8] Aforementioned comparative clinical findings were undoubtedly invaluable and supported by iterative research; however, it is noteworthy to state that they were reported from studies performed with a short-term postnatal observational design.

Yet, a limited number of longitudinal observational studies of prenatal methadone or buprenorphine exposure have demonstrated conflicting results regarding infant's neurodevelopmental outcomes. On the other side, long-term consequences of prenatal opioid exposure could be interpreted from in vivo preclinical studies. Animal models showed that neurobehavioral deficits may occur even without overt developmental retardation when intrauterine opioid exposure existed.[2] Fetal exposure to opioids negatively affects the neuronal migration and neuronal survival in rat embryos and leads to an overall developmental inhibition in the central nervous system. Opioid exposure also alters opioid receptor density and distribution and leads to decreased dendrite length and branch numbers in the somatosensory cortex in fetus mice.[9] These findings allow us to argue that prenatal opioid exposure itself may be related more severe central nervous system maldevelopment that would clinically manifest within years after delivery. Thus, opioid substitution treatment with opioid μ partial agonists might be associated with a decreased risk of long-term neurodevelopmental abnormalities

compared to opioids, despite it is impossible to mention that these drugs are literally clean as a whistle when prenatally exposed.

Potential teratogenic effects of naloxone during pregnancy raised some concerns regarding B/N use in pregnant women.[2] Thus, buprenorphine monotherapy is recommended by some authors over its combination with naloxone, despite buprenorphine monotherapy is associated with increased risk of misuse.[2] Notably, we can speculate that this recommendation relies upon an insufficient body of work examining safety profile of naloxone. Mechanisms of attributed teratogenic properties of naloxone remain unclear due to lack of in vivo preclinical and clinical controlled studies in pregnant women; however, a limited number of studies reported that prenatal opioid antagonist exposure leads alterations in maternal luteinizing hormone levels which may cause fetal malformations.[10] It is also worth to mention that, there is no recommended dosing interval for buprenorphine during pregnancy in the current guidelines. Several studies including small numbers of pregnant women have revealed that daily buprenorphine doses at 6-12 mg resulted in with no undesirable delivery outcomes.[11] In the light of cumulative data provided from prospective studies, buprenorphine monotherapy offers additional, advantages in safety and tolerability such as fewer drug interactions and favorable side effect profile, despite patients initially claim higher dissatisfaction with buprenorphine compared to methadone.[5,12] Buprenorphine is expected to be the first-line treatment option in opioid addiction during pregnancy. However we believe that, the most commonly prescribed opioid maintenance agent, buprenorphine combined with naloxone, deserves more attention to be paid by researchers in terms of the understanding the efficacy, safety and tolerability profile.

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