Medically Assisted Withdrawal (Detoxification): Considering the Mother-Infant Dyad

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Recommendations for opioid agonist pharmacotherapy and against medically assisted withdrawal were based upon early reports that associated withdrawal with maternal relapse and fetal demise. Data from recent case series have called these recommendations into question. Although these data do not support an association between medically assisted withdrawal and fetal demise, relapse remains a significant clinical concern with reported rates ranging from 17% to 96% (average 48%). Given the high loss to follow-up in these studies, the actual relapse rate is likely even greater. Furthermore, while medically assisted withdrawal is being proposed as a public health strategy to reduce neonatal abstinence syndrome (NAS), current data do not support a reduction in NAS with medically assisted withdrawal relative to opioid agonist pharmacotherapy. Overall, the data do not support either benefit of medically assisted withdrawal or equivalence to opioid agonist pharmacotherapy for the maternal-newborn dyad. Medically assisted withdrawal increases the risk of maternal relapse and poor treatment engagement and does not improve newborn health. Treatment of chronic maternal disease, including opioid agonist disorder, should be directed toward optimal long-term outcome.

Key Words: fetus, neonatal abstinence syndrome, neonate, opioid use disorder, pregnancy

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For over 50 years medically assisted withdrawal (''detoxification'') has generally been considered insufficient for the treatment of opioid use disorder (OUD) (Duvall et al., 1963; Hunt and Odoroff, 1962). This conclusion was reaffirmed in WHO 2014 and ASAM 2015 guidelines based in part on methadone and buprenorphine having better rates of treatment retention and less risk of overdose than medically assisted withdrawal. Medically assisted withdrawal should be utilized only as a first step along a treatment continuum (Center for Substance Abuse Treatment, 2006). Unfortunately, the medical community often conflates medically assisted withdrawal with treatment. This confusion leads to a chronic illness inappropriately being treated with an acute approach, and often sets the patient up for failure.

The optimal treatment for pregnant women with OUD remains unclear. The decades-old standard of care outlining opioid agonist pharmacotherapy, based on fetal concerns, has recently come under question in several case series (Stewart et al., 2013; Bell et al., 2016).

The goal of this commentary is to review the pros and cons of medically assisted withdrawal during pregnancy on several key maternal-fetal health factors and consider what research is needed to move our understanding of treatment effectiveness forward.

SAFETY OF MEDICALLY ASSISTED WITHDRAWAL DURING PREGNANCY: FETAL DEMISE

Opioid agonist utilization during pregnancy arose from a concern for fetal safety. During the 1960s heroin epidemic, case series highlighted stillbirths among women who injected heroin. Each series described repeated admissions for medically assisted withdrawal followed by relapse followed by fetal demise (Rementeria and Nunag, 1973). These clinical observations were bolstered by biochemical evidence of fetal stress (increased amniotic fluid catecholamines) during maternal withdrawal (Zuspan et al., 1975). Methadone pharmacotherapy improved prenatal care attendance and was thought to prevent fetal stress and stillbirth associated with repeated episodes of withdrawal. Subsequently, methadone pharmacotherapy rather than medically assisted withdrawal was recommended in the absence of rigorous clinical trials.

Over the past two decades approximately 500 patients have been documented to undertake medically assisted withdrawal during all trimesters of pregnancy (Dashe et al., 1988; Luty et al., 2003; Stewart et al., 2013; Bell et al., 2016). Most recent studies included ancillary services that were absent in the earlier literature, including counseling and residential treatment. No fetal losses attributed to medically assisted withdrawal were observed, although monitoring protocols were inconsistent across the series. Collective results suggest

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that fetal safety alone should not be a barrier to offering women medically assisted withdrawal during pregnancy.

The main limitation in the existing data relates to study design and limited fetal safety assessment. Stewart et al. (2013) examined presence or absence of illicit substances in a cohort of newborns. Limitations included: 20% of women who attempted detoxification left treatment, 20% were treated with methadone maintenance, 13% had preterm birth, 20% had growth restriction, 75% of infants born to mothers who left treatment were exposed to illicit substances, and 40% of infants required treatment for NAS. Loss to follow-up is common in the recent literature. Of the 101 patients who initiated medically assisted withdrawal in Luty et al. (2003), only 24 were available for follow-up. Fetal demise is an extreme consequence of fetal stress; nonlethal fetal stress could have been missed in the largest study, which had no fetal monitoring component (Bell et al., 2016). In summary, all studies are case series, lack comparison groups, and have poor follow-up of patients who leave treatment. It is difficult to establish fetal safety with such limited data, given the strong bias toward the null by inclusion of only the most compliant patients. Finally, maternal and/or fetal stress could be linked to epigenetic modifications that impact the development of chronic disease.

Evidence of fetal safety to support the equivalence of medically assisted withdrawal to opioid agonist pharmacotherapy is insufficient. Research examining the safety of medically assisted withdrawal itself and the specific fetal risks related to maternal relapse is needed.

MATERNAL-FETAL DYAD TREATMENT EFFICACY: RELAPSE

Treatment efficacy is generally described as (1) ability to complete short-term withdrawal, (2) retention in comprehensive services such as counseling, and (3) avoidance of relapse. Of these, relapse is the most dangerous, with increased risk of repeated cycles of withdrawal, maternal infectious disease acquisition (and subsequent vertical transmission), and maternal overdose and/or death. Recent case series on medically assisted withdrawal report relapse rates ranging from 17% to 96% (average 48%). Given the high loss to follow-up in these studies, it is likely that the actual relapse rate is higher than reported. One of the few studies to compare opioid agonist pharmacotherapy with medically assisted withdrawal found increased relapse for medically assisted withdrawal than for opioid agonist pharmacotherapy (Jones et al., 2008). Furthermore, no study of medically assisted withdrawal has examined maternal outcomes after delivery and into the postpartum period, a particularly vulnerable time for relapse.

The treatment of OUD during pregnancy involves more than medication (with or without medically assisted withdrawal), as behavioral interventions are needed to help mother and child live to their full potentials. Opioid agonist pharmacotherapy has been demonstrated to improve retention in counseling—no such data exist for medically assisted withdrawal.

Finally, patient autonomy and choice is imperative at all stages of treatment and recovery. It is unethical to force women to involuntarily withdraw from opioids. There are women who strongly desire medically assisted withdrawal as the first line of treatment, others request medication, and still others choose withdrawal but reconsider medication during the treatment process. Some trials of medically assisted withdrawal did not offer alternatives to women seeking treatment. A role of the provider is to offer all treatment options and provide factually correct information about treatment modalities and support the patient in whatever she chooses. Women who consider withdrawal but later decide to proceed with medication have improved outcomes: similar to opioid-agonist-maintained women and better than women who declined maintenance (Jones et al., 2008).

NEONATAL OUTCOME: NEONATAL ABSTINENCE SYNDROME

Neonatal abstinence syndrome (NAS) is an expected and treatable outcome of prenatal opioid exposure. In parallel with the current opioid epidemic, rates of NAS have increased as has the cost of care (Patrick et al., 2015). Approximately 50% of NAS cases result from maternal opioid-agonist pharmacotherapy. Thus, there is increased interest in medically assisted withdrawal to ''prevent NAS.'' Minimizing or eliminating the risk of NAS may be a motivator for pregnant women seeking medically assisted treatment, as the idea of the newborn experiencing withdrawal can compound feelings of guilt and shame (Lund et al., 2012; Cleveland and Bonugli, 2014).

Unfortunately, collective data indicate that NAS occurs as frequently in women with successful medically assisted withdrawal as women treated with opioid agonist medication. Only one study demonstrated a decrease in NAS (Stewart et al., 2013). Therefore, the potential to reduce neonatal intensive care unit utilization by maternal medically assisted withdrawal currently lacks supporting data. The lack of a predictable relationship between NAS and medically assisted withdrawal is likely due to the myriad of factors that drive NAS severity beyond prenatal opioid exposure (Kaltenbach and Jones, 2016). Medically assisted withdrawal should not be considered the only intervention to reduce NAS in women with OUD.

TREATMENT EFFECTIVENESS: THE MOTHER-INFANT DYAD

Parenting is stressful. Data suggest parental stress impacts the mother-infant relationship more strongly than fetal exposure to opioid agonist pharmacotherapy (Sarfi, Smith, Waal, Sundet, 2011). Data on the parental stress experienced by women with OUD who are not on opioid agonist pharmacotherapy are lacking. The most important variable in the ability to retain custodial care of the newborn is relapse. As such, the ability to remain free of substance use and engaged in comprehensive care postpartum is critical to the effectiveness of treatment during pregnancy. All women with substance use disorders could benefit from comprehensive care that plans, monitors, and assesses the short- and long-term impact of treatment (Jones et al., 2013). It is unknown to what extent opioid agonist pharmacotherapy

versus medically assisted withdrawal during pregnancy impacts parenting.

SUMMARY

The general rejection of medically assisted withdrawal for pregnant women with OUD originated from a weak research base. The landscape of treatment and our understanding of the addiction process have evolved since the 1970s. Although recent case series do not support the association between medically assisted withdrawal and fetal demise, the data do demonstrate a high rate of relapse. The current opioid epidemic and the increase in NAS have led to a re-examination of medically assisted withdrawal, especially among women already on opioid agonist pharmacotherapy. The data do not support a clear benefit of medically assisted withdrawal for the maternal-newborn dyad or the equivalence of medically assisted withdrawal to opioid agonist pharmacotherapy, as medically assisted withdrawal increases the risk of maternal relapse and poor treatment engagement, and does not improve newborn health. The balance of findings supports maintaining the standard of care recommending opioid agonist pharmacotherapy for pregnant women with OUD. Research is needed to determine which select women may be good candidates for successful medically assisted withdrawal. Such research should include newborn, maternal, and mother-child dyad outcomes. The impact of NAS for mother, baby, and society should not be ignored. There are modalities such as breastfeeding, rooming-in, smoking cessation, and choice of opioid agonist medication that provide opportunities to decrease the impact of NAS. Each modality requires engagement of the mother for successful implementation. As with most chronic diseases, optimal control of maternal disease offers the best neonatal outcome.

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