PCSS Guidance

Topic: Pregnancy and Buprenorphine Treatment

Original Author: Judith Martin, M.D.

Updated: 11/29/2021 (A. Benjamin Srivastava, M.D.)

Guideline Coverage:
This topic is also addressed in:
1. TIP 43: Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs, SAMHSA 2008.
2. TIP 40: Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction, pp.68-70. http://www.kap.samhsa.gov/products/manuals/tips/numerical.htm

Clinical Questions:
1. If a female patient of child-bearing age is requesting buprenorphine treatment, what should I do? (i.e. informed consent, birth control, etc)
2. If a patient is already on buprenorphine. Should I keep her on it during **a** pregnancy?
3. Does it matter whether she is given the mono (buprenorphine) or combo (buprenorphine/naloxone) product?
4. If a new opioid-dependent patient is pregnant and requests buprenorphine treatment, what should I do?
5. Is buprenorphine treatment during pregnancy safe?
6. How can detoxification (medically supervised withdrawal) be carried out if a pregnant patient wants to stop all opioids, including buprenorphine?
7. How does buprenorphine treatment compare with methadone treatment for pregnant women?
8. Does treatment of pregnant women change, depending on whether the patient abuses heroin or prescription opioids?
9. Is breastfeeding safe while taking buprenorphine?
10. What neonatal withdrawal is expected when mothers take buprenorphine?

Background:
Approximately 7% of women report prescription opioid use during pregnancy (Ko et al 2020). Heroin or prescription opioid abuse during pregnancy is often closely associated with a multitude of environmental factors that can contribute to adverse consequences including fetal growth restriction, premature labor, miscarriage and low birth weight, an important risk factor for later developmental delay. Methadone maintenance has been the treatment of choice for opioid-dependent women since the 1970s, and given in the context of comprehensive care improves outcomes compared to heroin. Treatment of pregnant opioid-dependent womenwith methadone, in combination with prenatal care, has been found to reduce the incidence of

neonatal mortality due to low birth weight (Finnegan et al. 1977). However, prenatal methadone exposure may result in a neonatal withdrawal syndrome (sometimes called neonatal abstinence syndrome; NAS).

Although neonatal opioid withdrawal can be treated successfully with pharmacotherapy, the effects of intra-uterine narcotic exposure on the developing nervous system are not fully characterized. Methadone-exposed neonates have consistently been found to smaller lateral ventricles and smaller head circumferences during the first few months of life, but there do not appear to be any developmental sequelae related to prenatal opioid exposure (Kaltenbach and Finnegan 1989). However, in carefully selected patients, detoxification may be accomplished during the second or early third trimester (Stanhope et al. 2013).

The neonatal abstinence syndrome is characterized by signs and symptoms indicating opioid withdrawal,including dysfunction of the autonomic nervous system, gastrointestinal tract and respiratory system. With appropriate intervention, withdrawal signs can be alleviated without damaging consequences. If a withdrawal syndrome occurs, it typically peaks at three days after birth, andeven in carefully managed patients on split dosing requires treatment in over 40 percent of cases.(Finnegan 1992). Yet certain differences in the profile of neonatal abstinence syndrome between methadone- and buprenorphine-exposed neonates have been identified. Total NAS score and several specific signs (tremors, hyperactive Moro reflex, excessive irritability, failure to thrive) have been observed to be significantly more frequent in methadone-exposed neonates, while sneezing was more frequent among buprenorphine-exposed neonates. Also, methadone-exposed infants require treatment significantly earlier in the postnatal period than do buprenorphine-exposed infants (Gaalema et al.2012).

Pharmacologic treatment of NAS is variable in practice, with high quality randomized controlled trials (RCT) lacking. A recent meta-analysis including studies buprenorphine, clonidine, diluted opium/clonidine, morphine, methadone, and phenobarbital found that sublingual buprenorphine was considered the optimal treatment in terms of reduction in length of treatment and length of stay (Disher et al, 2019). In a blinded trial comparing buprenorphine to morphine in 63 infants diagnosed with NAS, buprenorphine was associated with a shorter length of stay and duration of treatment. In a multi-center blinded RCT involving 117 infants diagnosed with NAS, infants receiving methadone had a shorter length of treatment compared with infants treated with morphine. However, methadone and buprenorphine have not yet been compared head to head in an RCT. Thus either methadone or buprenorphine is appropriate pharmacologic treatment for NAS (Wachman 2019).

Overall, findings from comparative studies of methadone and buprenorphine, including randomized clinical trials, indicate that both medications are effective in preventing relapse to illicit opioids in opioid-dependent pregnant patients. Advantages of buprenorphine include fewer barriers to treatment (patients do not need to come to a clinic daily) and fewer dosage adjustments during pregnancy, and less severe NAS (Minozzi et al. 2020).

Buprenorphine is pregnancy category C; there are limited data in humans, but potential benefits may warrant use of the drug in women despite potential risks. Physicians should use buprenorphine in pregnancy using a risk/benefit analysis, informing the patient about comparative lack of long-term studies with buprenorphine treatment. A recent secondary analysis failed to support failed to find a relationship between maternal dose at delivery and any of 10 neonatal clinical outcomes, including NAS severity (Jones et al. 2014) Methadone is also a pregnancy categoryC medication, although with longer clinical use, and methadone maintenance is the current standard of care in the US. Repeated episodes of fetal withdrawal are considered harmful, hence tapering or detoxification is relatively contraindicated. Breastfeeding while in treatment with buprenorphine is likely safe, due to its known poor oral bioavailability, in spite of the package insert statement that it is not recommended.

Recommendations:

Level of evidence: Low/moderate, three trials of pregnant women comparing outcomes for buprenorphine and methadone (Minozzi 2020). There is still a need for randomized controlled trials of adequate sample size comparing different opioid agonist maintenance treatments.

There is no difference bin treatment dropout rate between methadone and buprenorphine (Minozzi 2020). Rates of neonatal abstinence syndrome are similar among infants born to methadone- vs. buprenorphine-maintained mothers, but symptoms were less severe for infants whose mothers were treated with buprenorphine maintenance (Thomas et al. 2014). Pregnant patients should be offered either buprenorphine or methadone maintenance when available, to prevent relapse in the mother and to avoid withdrawal in the fetus. Pregnant opioid-dependent women should be co-managed with an obstetrician familiar with high-risk pregnancy and neonatal withdrawaltreatment.

If a patient is taking buprenorphine during pregnancy, every effort should be made to prevent fetal withdrawal. The way to do this is to prevent maternal withdrawal by encouraging regular and adequate dosing, and by discouraging tapers. Surrogate markers for fetal withdrawal are maternal withdrawal, including craving, and increase in fetal motion. If a patient absolutely refuses maintenance and desires medically supervised withdrawal, this should be carried out in collaboration with obstetric care, if possible with fetal monitoring. It is thought that the second trimester is the safest time to carry out medically supervised withdrawal in order to avoid miscarriage or premature labor.

If the patient is being maintained on buprenorphine during pregnancy, most experts recommend that she be given the mono product, as few studies have investigated the efficacy of buprenorphine with naloxone, though a recent recent meta-analysis showed that offspring of women who received buprenorphine-naloxone during pregnancy were less likely to require treatment for NAS than those who received other opioid agonist medications without associated adverse events (Link 2020).

A retrospective study of the relationship between breastfeeding and neonatal abstinence syndrome in women maintained on buprenorphine during pregnancy found that more than three quarters of women chose to breastfeed their infants after birth (O'Connor et al. 2013). Although the findings did not reach statistical significance, infants who were breastfed has less severe NAS and were less likely to require pharmacologic treatment (23.1% vs. 30.0%) than infants who were not breastfed. In a prospective study involving 10 buprenorphine-maintained women and 9 breastfed infants, infant plasma buprenorphine/buprenorphine metabolite concentrations were undetectable were low at day 14; maternal buprenorphine dose was correlated with maternal plasma and milk buprenorphine concentrations. (Jansson 2016)

In summary, it is essential that clinicians take a collaborative, multidisciplinary care approach for pregnancies complicated by chronic narcotic use (Stanhope et al. 2013). A growing body of evidence suggests that management of opioid dependence with either methadone or buprenorphine is appropriate during pregnancy and breastfeeding. Prescription monitoring programs such as the Risk Evaluation and Management Strategy (REMS) may help to prevent inappropriate prescribing or diversion.

References:

1. Kaltenbach, K. and L. Finnegan (1987). "Perinatal and developmental outcome of infants exposed to methadone in-utero." NeurotoxicolTeratol 9(4): 311-313.
2. Finnegan L, D. Reeser D., et al. (1977). "The effects of maternal drug dependence on neonatal mortality." Drug and Alcohol Dependence 2(2): 131-140.
3. Finnegan, LP.,Kaltenbach, K., 1992. Neonatal abstinence syndrome. In: Hoekelman, R.A.. Nelson, N.M. (eds), Primary Pediatric Care. 2nd ed. Mosby Yearbook, Inc., St Louis, pp1367-1378.
4. McCarthy, J., M. Leamon, et al. (2005). "High-dose methadone maintenance in pregnancy: maternal and neonatal outcomes." American Journal of Obstetrics and Gynecology 193(3 Pt 1): 606-610.
5. Johnson R, Jones H, et al. (2003). "Use of buprenorphine in pregnancy: patient management and effects on the neonate." Drug and Alcohol Dependence 70 (2 Suppl): S87-S101.
6. Lacroix, LC, Berrebi, et al. (2004). "Buprenorphine in pregnant opioid-dependent women: first results of a prospective study." Addiction 99:209-214.
7. Lejeune C, Simmat-Durand L, Gourarier L, Aubisson S; the Grouped'EtudesGrossesse et Addictions (GEGA). Prospective multicenter observational study of 260 infantsbom to 259 opiate-dependent mothers on methadone or high-dose buprenophine substitution. Drug Alcohol Depend. 2005 Oct 26;
8. Jones H., Johnson R., et al. (2005). "Buprenorphine versus methadone in the treatment of pregnant opioid-dependent patients: effects on the neonatal abstinence syndrome." Drug and Alcohol Dependence 79(1): 1-10.
9. Fischer G, Ortner R, Rohrmeister K, Jagsch R, Baewert A. Langer M, Aschauer H. Methadone versus buprenorphine in pregnant addicts: a double-blind, double-dummy comparison study. Addiction. 2006 Feb; 101 (2):275-81.
10. Kraft WK, Gibson E, Dysart K, Damie VS, Larusso JL, Greenspan JS, Moody DE, Kaltenbach K, Ehrlich ME (2008) Sublingual buprenorphine for treatment of neonatal abstinence syndrome: a randomized trial. Pediatrics 122(3): 601-7.
11. Gaalema DE, Scott TL, Heil SH, Coyle MG, Kaltenbach K, Badger GJ, Arria AM, Stine SM, Martin PR, Jones HE (2012) Differences in the profile of neonatal abstinence syndrome signs in methadone- versus buprenorphine-exposed neonates. Addiction 107 Suppl : 53-62.
12. Jones HE, Finnegan LP, Kaltenbach K (2012) Methadone and buprenorphine for the management of opioid dependence in pregnancy. Drugs 72(6): 747-57.

13. Jones HE, Dengler E, Garrison A, O'Grady KE, Seashore C, Horton E, Andringa K, Jansson LM, Thorp J (2014). Neonatal outcomes and their relationship to maternal buprenorphine dose during pregnancy. Drug and Alcohol Dependence (ahead of print).
14. Debelak K, Korrone WR, O'Grady KE, Jones HE. Buprenorphine + naloxone in the treatment of opioid dependence during pregnancy- initial patient care and outcome data (2013). American Journal of Addiction 22(3): 252-4.
15. Lund IO, Fischer G, Welle-Strand GK, O'Grady KE, Debelak K, Morrone WR, Jones HE (2013). A comparison of Buprenorphine + Naloxone to Buprenorphine and Methadone in the Treatment of Opioid Dependence during Pregnancy: Maternal and Neonatal Outcomes. Substance Abuse Research and Treatments 7: 61-74.
16. Stanhope TJ, Gill LA, Rose C (2013). Chronic opioid use during pregnancy: maternal and fetal implications. Clinics in Perinatology 40(3): 337-50.
17. O'Connor AB, Collett A, Alto WA, O'Brien LM (2013). Breastfeeding rates and the relationship between breastfeeding and neonatal abstinence syndrome in women maintained on buprenorphine during pregnancy. Journal of Midwifery Women's Health 58(4): 383-8.
18. Minozzi S, Amato L, Bellisario C, Ferri M, Davoli M (2013). Maintenance agonist treatments for opiate-dependent pregnant women. Cochrane Database Syst Rev 12: xx-xx.
19. Thomas CP, Fullerton CA, Kim M, Montejano L, Lyman DR, Dougherty RH, Daniels AS, Ghose SS, Delphin-Rittmon ME (2014) Medication-assisted treatment with buprenorphine: assessing the evidence. Psychiatr Serv 65(2): 158-70.
20. Sokya M. Buprenorphine use in pregnant opioid users: a critical review (2013) CNS Drugs 27(8): 653-62.
21. Ko, et al. Vital signs: Prescription opioid pain reliever use during pregnancy- 34 U.S. Jurisdictions, 2019. MMRW 69(28);897-903.
22. Disher T, Gullickson C, Singh B, et al. Pharmacological treatments for neonatal abstinence syndrome: a systematic review and network meta-analysis. *JAMA Pediatr.* 2019;173(3):234–243.
23. Wachman EM, Werler MM. Pharmacologic Treatment for Neonatal Abstinence Syndrome: Which Medication Is Best? *JAMA Pediatr.* 2019;173(3):221–223.
24. Minozzi S, Amato L, Jahanfar S, Bellisario C, Ferri M, Davoli M. Maintenance agonist treatments for opiate-dependent pregnant women. 2020;11(11): CD006318
25. Link HM, Jones H, Miller L, Kaltenbach K, Seligman N. Buprenorphine-naloxone use in pregnancy: a systematic review and metaanalysis. Am J Obstet Gynecol MFM. 2020 Aug;2(3):100179. doi: 10.1016/j.ajogmf.2020.100179. Epub 2020 Jul 3. PMID: 33345863.
26. Jansson LM, Spencer N, McConnell K, Velez M, Tuten M, Harrow CA, Jones HE, Swortwood MJ, Barnes AJ, Scheidweiler KB, Huestis MA. Maternal Buprenorphine Maintenance and Lactation. J Hum Lact. 2016 Nov;32(4):675-681. doi: 10.1177/0890334416663198. Epub 2016 Sep 26. PMID: 27563013.

PCSS Guidances use the following levels of evidence*:
High = Further research is very unlikely to change our confidence in the estimate of effect
Moderate= Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low = Any estimate of effect is very uncertain.

Type of evidence:
Randomised trial = **high**
Observational study = **low**

Any other evidence = **very low**

* Grading quality of evidence and strength of recommendations
British MedicalJournal.**2004:328:1490-**