



The American College of
Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

Office of the Executive Vice President

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William K. Hallman, PhD
Chair, Risk Communication Advisory Committee
US Food and Drug Administration
White Oak Campus
10903 New Hampshire Ave
Silver Spring, MD 20993

RE: Risk Communication Advisory Committee Meeting on Methadone and Buprenorphine Use during Pregnancy

Dear Dr. Hallman:

On behalf of the American College of Obstetricians and Gynecologists (the College), a national medical organization representing nearly 60,000 members who provide health care for women, and the American Society of Addiction Medicine (ASAM), thank you for the opportunity to provide comments on the use of methadone and buprenorphine during pregnancy in regards to your June 8-9, 2015, Risk Communication Advisory Committee meeting on the topic.

The College and ASAM strongly encourage the Food and Drug Administration to remove their *Boxed Warning* on methadone and buprenorphine. Moreover, the College and ASAM have and will continue to strongly support the use of methadone and buprenorphine as a standard of care treatment for women who are addicted to opioids before, during, and after pregnancy.

Opioid addiction is a chronic, relapsing brain disease that can occur at any stage in a person's lifetime. Most non-addicted women who use substances before pregnancy are able to change their behavior (i.e., quit or minimize their use) during pregnancy in efforts to maximize health outcomes for their baby. Those who are unable to make these behavior changes have a substance use disorder. In other words, continued substance use in pregnancy is indicative of addiction.¹ This holds true for opioid use during pregnancy, and – as such – treatment should reflect the same, best-practice, evidence-based standards as other chronic medical conditions (Cornelius 2000).

In this case, the standard of care for opioid addiction is opioid assisted treatment (OAT), which includes methadone and buprenorphine. Unlike illicit opioid use, OAT provides a known quantity of a known medication and has been demonstrated to be safe and effective treatment for opioid addiction, even during pregnancy. Since the 1970's, maintenance therapy with methadone has been the standard

treatment of heroin addiction during pregnancy, and more recently has been used for non-heroin opioid addiction (Center for Substance Abuse Treatment 2005, ACOG 2012). Emerging evidence supports the use of buprenorphine for OAT during pregnancy (ACOG 2012). Although buprenorphine treatment seems to be associated with a shorter and less severe period of neonatal abstinence syndrome compared to methadone, more women seem to adhere to methadone therapy than buprenorphine therapy (Jones 2010). This suggests that both medications should remain readily available for care of these women. **OAT has been associated with improved maternal and fetal outcomes for pregnant women with opioid addiction**, as it can prevent complications of illicit opioid use and narcotic withdrawal, encourage prenatal care, reduce criminal activity, reduce the risk of contracting infections (including human immunodeficiency virus), and avoid the risks to the patient of associating with a drug culture (Jones 2010, ACOG 2012).

While the data regarding the benefits of OAT in pregnancy are well described in terms of maternal health, prenatal care, infant birth weight, and preterm birth, all medications – including medications administered during pregnancy -- have both benefits and risk. The risks associated with OAT, however, are less well-characterized. There are few data linking maternal opioid use to fetal growth restriction or congenital anomalies (ACOG 2015). Any concern for congenital malformations in the infant has only been associated with short acting opioids, although studies demonstrating this association (Broussard 2011) had design flaws that did not control for the indication of use or residual confounding. Additionally, the relative risks listed in these studies were so small that it is not clear whether or not they are clinically relevant.

Most women using OAT have uncomplicated pregnancies and infants with average birth weights and high APGAR scores. While 55-94% of neonates with significant exposure to opioids will experience neonatal abstinence syndrome (NAS) (ACOG 2015), only around 53% of infants born to mothers using OAT will require some treatment NAS ranging from swaddling to detoxification (Kaltenbach 2012). **However, it should be emphasized that NAS is an expected and treatable condition from which no long-term effects for the infant have been described in the 40 years since OAT has been employed** (Jones 2010, Otero 2011).

On the contrary, the impact of not treating pregnant women has been clearly characterized. Long-term implications for the infant and mother include low birth weight, prematurity, lack of prenatal care, inability of the mother to parent, and cost to society if mothers cannot get treatment (Jones 2010). Detoxification is discouraged during pregnancy (ACOG 2012). It is not an effective, appropriate, or evidence-based treatment and is equivalent to treating a chronic illness (opioid addiction) with an acute intervention. **More notably, detoxification during pregnancy has been associated with high relapse rates of illicit opioid use (Jones 2010, Luty 2003), placing both the mother and the infant at increased risk for overdose and death; abrupt discontinuation of opioids in an opioid-dependent woman can also result in preterm labor, fetal stress manifested as elevated levels of fetal catecholamines, or fetal demise** (ACOG 2012).

Thus, the risk of not treating a pregnant woman suffering from opioid addiction far exceeds the expected and manageable risk of treating the woman with OAT (ACOG 2012). This paradigm is not

uncommon in medicine. An analogous example would be withholding anti-seizure medications in women with seizure disorders. Although there is an increased risk of congenital anomalies linked to the use of anti-seizure medications, the risks of withholding these medications are far greater. Ultimately, the interests of the pregnant woman and her fetus converge and treating a pregnant woman appropriately is in the best interest of both the woman and the fetus (ACOG 2005). Moreover, efforts to protect solely the fetus by limiting the mother's treatment or punishing her for her behavior are neither legally nor morally justified (ACOG 2005).

Despite this, there is a treatment gap in the United States wherein a large number of pregnant women who need OAT treatment are not receiving it. Already under-treated, a *Boxed Warning* discourages pregnant women in need of OAT from receiving treatment, further endangering mothers and infants. The United States is combating an epidemic of opioid use, but we cannot treat an epidemic by withholding the treatment that is the well-proven standard of care for the disease.

Instead, policy makers, legislators, and health care providers should work together to find constructive and evidence-based ways to address the needs of women with substance abuse problems (ACOG 2005). In terms of cost value, we know the improved maternal and fetal outcomes associated with OAT reduce the increased cost for treating NAS and other poor outcomes related to untreated opioid addiction during pregnancy (Roussos-Ross 2015). However, further research is still warranted to identify evidence-based practices which could minimize the risk of neonatal abstinence syndrome as well as more research on the treatment of prescription drug abuse vis a vis the risks and benefits of opioid agonist maintenance versus medication assisted withdrawal.

Obstetrician-gynecologists have an ethical obligation to serve as the patient's advocate and exercise all reasonable means to ensure that the most appropriate care is provided to the patient ([ACOG Code of Professional Ethics](#)). This includes the treatment of maternal disease with the best, evidence-based treatment plan available that appropriately balances maternal and fetal risks and benefits and includes maternal informed consent (ACOG 2009). Failure to treat substance use disorder with the same evidence-based approach applied to other chronic illnesses reduces a patient's access to health care services and resources (ACOG 2015). ACOG encourages the continued creation of substance use disorder treatment and rehabilitation centers that prioritize options for pregnant women, and it is hoped that policy makers, legislators, and health care providers will work collaboratively to continue to identify evidence-based strategies to improve treatment options and access for pregnant women with opioid addiction and other substance use disorders.

In summary, the clear maternal and fetal benefits of OAT outweigh the risks; OAT has been and will continue to be the recommended standard of care for opioid addiction during pregnancy; and a *Boxed Warning* may inappropriately dissuade providers and patients from best care, resulting in avoidable injury to pregnant woman and her baby.

Thank you for the opportunity to provide comments on important clinical matters such as opioid addiction therapy. The College and ASAM have issued numerous resources on opioid management in pregnant women for providers, patients, and policy makers as listed below. If you have any questions,

please do not hesitate to contact us or Debra Hawks, MPH, Senior Director, Practice Activities, Obstetrics and Immunization at the College, at (202) 863-2445 or dhawks@acog.org.

Sincerely



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¹ Addiction is a primary, chronic disease of brain reward, motivation, memory, and related circuitry. Dysfunction in these circuits leads to characteristic biological, psychological, social, and spiritual manifestations. This is reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviors.

Addiction is characterized by inability to consistently abstain, impairment in behavioral control, and craving, diminished recognition of significant problems with one's behaviors and interpersonal relationships, and a dysfunctional emotional response. Like other chronic diseases, addiction often involves cycles of relapse and remission. Without treatment or engagement in recovery activities, addiction is progressive and can result in disability or premature death (ASAM 2011).

References

[Alcohol abuse and other substance use disorders: ethical issues in obstetric and gynecologic practice](#). Committee Opinion No. 633. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2015;125:1529-37.

American College of Obstetricians and Gynecologists. Code of professional ethics of the American College of Obstetricians and Gynecologists. Washington, DC: American College of Obstetricians and Gynecologists; 2011. Available at: <http://www.acog.org/-/media/Departments/National-Officer-Nominations-Process/ACOGcode.pdf?dmc=1&ts=20150520T1546118670>. Retrieved May 22, 2015.

American Society of Addiction Medicine. Public policy statement: definition of addiction. Chevy Chase (MD): ASAM; 2011. Available at: <http://www.asam.org/for-the-public/definition-of-addiction>. Retrieved May 21, 2015.

Broussard CS, Rasmussen SA, Reefhuis J, Friedman JM, Jann MW, Riehle-Colarusso T, et al. Maternal treatment with opioid analgesics and risk for birth defects. National Birth Defects Prevention Study. *Am J Obstet Gynecol* 2011;204:314.e1,314.11.

Center for Substance Abuse Treatment. Medication-assisted treatment for opioid addiction during pregnancy. In: Medication-assisted treatment for opioid addiction in opioid treatment programs. Treatment Improvement Protocol (TIP) Series 43. HHS Publication No. (SMA) 12-4214. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2005. Available at: <http://www.ncbi.nlm.nih.gov/books/NBK64164/pdf/TOC.pdf>. Retrieved May 26, 2015.

Cornelius MD, Day NL. The effects of tobacco use during and after pregnancy on exposed children. *Alcohol Res Health* 2000;24:242-9.

[Informed Consent](#). ACOG Committee Opinion No. 439. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2009; 114:401-8.

Luty J, Nikolaou V, Bearn J. Is opioid detoxification unsafe in pregnancy? *J Subst Abuse Treat* 2004;24:363-7.

Jones HE, Kaltenbach K, Heil SH, Stine SM, Coyle MG, Arria AM, et al. Neonatal abstinence syndrome after methadone or buprenorphine exposure. *N Engl J Med* 2010;363:2320-31.

Kaltenbach K, Holbrook AM, Coyle MG, Heil SH, Salisbury AL, Stine SM, et al. Predicting treatment for neonatal abstinence syndrome in infants born to women maintained on opioid agonist medication. *Addiction* 2012;107 Suppl 1:45-52.

[Maternal decision making, ethics, and the law](#). ACOG Committee Opinion No. 321. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2005;106:1127–37.

[Opioid abuse, dependence, and addiction in pregnancy](#). Committee Opinion No. 524. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2012;119:1070–6.

Otero C, Kaltenbach K. Medication assisted treatment during pregnancy, postnatal and beyond. Lake Forest (CA): Children and Family Futures; 2011. Available at: <http://www.cffutures.org/presentations/webinars/medication-assisted-treatment-during-pregnancy-postnatal-and-beyond>. Retrieved May 21, 2015.

Roussos-Ross K, Reisfield G, Elliot I, Dalton S, Gold M. Opioid use in pregnant women and the increase in neonatal abstinence syndrome: what is the cost? *J Addict Med* 2015;9:222-5.