PCSS Guidance

Topic: Pregnancy and Buprenorphine Treatment

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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:
The prevalence of opioid use among pregnant women ranges from 1-2% to as high as 21% (Minozzi et al. 2013). 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 women with 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).

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 (NAS) is a generalized disorder, occurring in over half of opioid-dependent women, characterized by signs and symptoms indicating opioid withdrawal, including dysfunction of the autonomic nervous system, gastrointestinal tract and respiratory system.1 With appropriate intervention, withdrawal signs can be alleviated without damaging consequences. If a withdrawal syndrome occurs, it typically peaks at three days after birth, and even in carefully managed patients on split dosing requires treatment in over 40 percent of cases.2 There are case studies showing that buprenorphine is safe and effective for the treatment of neonatal abstinence syndrome (Kraft et al. 2008).3,4 A large non-randomized observational prospective study comparing methadone and buprenorphine showed similar neonatal outcomes with both medications.5 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).

There are no specific studies examining maternal and neonatal outcomes following buprenorphine treatment during pregnancy using women who were dependent on prescription opioids. 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. Fetal monitoring has suggested that buprenorphine results in less fetal cardiac and movement suppression than does methadone. In addition, buprenorphine results in less severe neonatal abstinence syndrome than does methadone (Jones et al. 2012).

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 the still unproven status of 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 category C 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. A growing body of observational and controlled trials suggests that buprenorphine is emerging as a first-line treatment for pregnant opioid users.

Recommendations:
Level of evidence: Low/moderate, three trials of pregnant women comparing outcomes for buprenorphine and methadone (Minozzi et al. 2013). There is still a need for randomized controlled trials of adequate sample size comparing different opioid agonist maintenance treatments.

Although methadone maintenance is associated with better treatment retention than buprenorphine, buprenorphine maintenance during pregnancy was associated with improved maternal and fetal outcomes, compared with no medication-assisted treatment. 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 methadone maintenance when available, to prevent relapse in the mother and to avoid withdrawal in the fetus. Pregnant patients should be informed that buprenorphine is not a proven treatment during pregnancy, and the clinician should obtain the patient's signature documenting her refusal of methadone maintenance and her understanding of the unproven status of buprenorphine treatment during pregnancy. Pregnant opioid-dependent women should be co-managed with an obstetrician familiar with high-risk pregnancy and neonatal withdrawal treatment.

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 MSW 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, and the combination product has been suggested to possibly have teratogenic effects in (Sokya 2013). For women who become pregnant while using the combination product, switching to the mono product is recommended.

In the case of unstable patients, smaller prescriptions, observed dosing, or more frequent visits are recommended, to avoid injection abuse of the mono product. But there is growing evidence that the combination product may also be safe in pregnancy. A small study of 10 opioid-dependent women treated with the buprenorphine + naloxone film product concluded that maternal findings were unremarkable and comparable to those seen with the mono product (Debelak et a l. 2013). While four out of ten neonates were treated for neonatal abstinence syndrome (NAS), its severity was similar to outcomes observed with the mono product. And a recent meta-analysis comparing buprenorphine/naloxone to buprenorphine and methadone in the treatment of opioid dependence during pregnancy found no significant differences in maternal outcomes for buprenorphine + naloxone, compared to buprenorphine, methadone, or methadone-assisted withdrawal (Lund et al. 2013). Preliminary findings suggested no adverse maternal or neonatal outcomes associated with the use of the combination product during pregnancy. Neonatal head circumference was significantly higher in the group exposed in utero to buprenorphine + naloxone, compared to neonates exposed to methadone-assisted withdrawal. This finding is consistent with earlier studies suggesting that opioid maintenance is associated with better prenatal care and lower risk of relapse than is abstinence without pharmacologic support.

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 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:

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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
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