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The Worldwide Opioid Epidemic

Implications for Treatment and Research in Pregnancy and the Newborn

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1. Scope of the Problem

The use of opioids has increased dramatically in the 21st century. Recent reports from North America,[1,2] China,[3] Australia,[4] UK,[5] Europe,[6] Russia,[7] and India[8] describe what has become a worldwide epidemic. The most recent estimate cites over 1.7 million individuals in the US aged 12 years or older who are dependent on, or abuse, prescription pain medications.[9] It has been estimated that 8% of the population of Afghanistan, the main source of the world's opium, is addicted to drugs, mainly opium or heroin.[10]

With the possible exception of alcohol, the effect of drugs of abuse, including opioids, on the developing fetus and newborn has not received as much attention as the adult population.[11] In the US in 2004 and 2005 the rate of illicit drug use during pregnancy was 3.5%.[11] It has been estimated that in 2009 the US public health and medical costs associated with neonates who were exposed to opioids *in utero* was between $US70.6 and $US112.6 million.[12]

2. Neonatal Issues Associated with Exposure to Opioids *In Utero*

Methadone has been regarded as the gold standard to treat opioid-addicted patients, including women who are pregnant. Methadone is used by hundreds of thousands of women around the world, the majority of whom are of childbearing age, in methadone maintenance programs (MMP).

The percentage of newborns who will develop manifestations of withdrawal following *in utero* methadone exposure has not been well established, but estimates generally range between 40% and 70%.[13-15] This is commonly referred to as the Neonatal Abstinence Syndrome (NAS). This syndrome is characterized by CNS (hypotonia/hypertonia, irritability), autonomic (increased/decreased respiration, mottling of the skin, sweating), and gastrointestinal (vomiting, poor feeding, diarrhea) effects. The occurrence, severity, and time of onset of NAS are unpredictable. Several attempts have been made to determine if there is an association between the occurrence and severity of NAS and the maternal dose of methadone; however, the literature remains equivocal.[16-19]

3. Treatment of Neonatal Abstinence Syndrome

Two surveys conducted within the past 5 years[20,21] have indicated that morphine is the treatment of choice for NAS; however, there has been little research into the treatment of this syndrome. Indeed, for 25 years the use of the α2 agonist clonidine was based solely on a very small study that was conducted in 1984.[22]

Prospective studies to examine the possible long-term neurodevelopment effects of *in utero* opioid exposure have been non-existent. A relatively recent review suggested that babies exposed to opioids *in utero* are at risk for adverse effects on long-term neurodevelopment.[23] The difficulty in interpretation of retrospective studies, however, is the inability to be able to isolate the drug effect from various environmental effects on neurodevelopment.

Concurrent with the explosion in the use of opioids has been research into the placental pharmacology of methadone and, more recently, buprenorphine.[24-27] In addition, phase I studies are now being conducted with buprenorphine as a treatment for NAS.[28] Recent prospective studies into the use of clonidine for the treatment of NAS have finally confirmed the original 1984 report.[29]

In addition to the use of α2 agonists to treat newborns with NAS, the use of this class of drugs to treat the mother during pregnancy may have merit. Clonidine has been used as an adjunct agent, in addition to methadone or buprenorphine, for opioid withdrawal in adults.[30] Animal studies have demonstrated that this class of drugs is also neuroprotective for the fetus.[31,32] The highly specific α2 agonist dexmedetomidine could be studied during pregnancy. Its safety during pregnancy needs to be confirmed, but it has the potential to offer

neuroprotective effects for the developing fetus, as well as to minimize maternal opioid ingestion.

4. Methadone as a Racemic Mixture

Methadone is available commercially as a racemic mixture of the R- and S-isomers. The R-isomer acts on the μ-opioid receptor and the S-isomer is an NMDA receptor antagonist. It has been suggested that the S-isomer may be responsible for some of the side effects of methadone.[33-35] A recent editorial has questioned whether 'R' methadone may be preferential compared with the racemic 'R'–'S' compound.[36]

Pharmacogenomics may play a role in the efficacy and side effect profile of methadone. Its metabolism, especially of the S-isomer, appears to involve cytochrome P450 (CYP) 2B6.[37] CYP2B6 variants have been proposed as a risk factor in methadone-related deaths.[38] Variants of the μ-opioid receptor gene (*OPRM1*) have also been associated with methadone-related deaths.[38] Allelic variations of CYP2D6 may also play a role in the efficacy of methadone to control symptoms in persons addicted to an opioid.[39] Whether either of these types of variant is involved with the maternal response to methadone and/or the occurrence and severity of NAS in the newborn are future research questions. Differences in the P-glycoprotein (P-gp, a transporter) gene frequency may be associated with dose requirements in individuals.[39] In P-gp knockout mice the brain concentrations of S and R methadone were significantly increased compared with controls.[40]

5. Buprenorphine Substitution: Mother and Baby

There are several concerns regarding methadone. It is a dangerous drug – there have been many deaths reported in the US during the last few years that have been directly related to a methadone overdose.[41] The prescribing of methadone is highly regulated; in most jurisdictions, only specially trained physicians are allowed to prescribe the drug. This becomes problematic in non-urban areas where there may not be a methadone prescriber present. The increasing opioid epidemic also places strain on the resources of existing methadone clinics and, consequently, the newly pregnant mother who may be looking for entrance into a methadone clinic. US federal guidelines have recommended preferential admittance to methadone clinics for pregnant women.[42]

A number of recent papers suggest that the effects of NAS are less severe when the mother is taking buprenorphine compared with methadone during pregnancy.[11,12] New formulations of buprenorphine, including a subdermal implant and a sublingual soluble-film formulation, are now being tested in opioid-dependent individuals.[43,44] It is conceivable that these formulations could also be studied during pregnancy.

Whether buprenorphine will turn out to be better than methadone to treat opioid addiction during pregnancy remains to be seen. Certainly, NAS in the newborn appears to be less severe with buprenorphine.[12]

The various formulations of buprenorphine may prove to be useful in terms of treatment administration and compliance, and the use of this agent may avoid the logistic complications of having only specially licensed physicians able to prescribe methadone.

6. Need for Further Research

For over 25 years there was little research to help clinicians treat NAS. The worldwide explosion of opioid use in the 21st century has begun to generate exciting new research into the use of α2 agonists and buprenorphine, both for the mother as well as the baby. It will be important to prospectively study these various therapies. Will they possibly enable women to wean off drugs during pregnancy, will they decrease the symptoms of NAS and reduce time in hospital for the newborn, and will they, certainly the most important of all, ensure that there is no adverse effect on neurodevelopment? Well designed, prospective, multicentered trials are clearly and urgently needed. Funding agencies and governments need to recognize the implications on future generations and be willing to provide financial support to ensure that these studies can be completed.

The increasing use of opioids during pregnancy is providing an opportunity for the scientific community to thoroughly examine the pharmacology and pharmacogenomics of these drugs. It is also an opportunity for scientific investigation that will simultaneously provide an understanding of the effects of these drugs on our most vulnerable patients.

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