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Review Article

Risks of Methadone use as Substitute Therapy for Opioid Addiction during Pregnancy and use of Clonidine as a Plausible Alternative

Abstract

Detoxification of opioid addiction during the pregnancy has been avoided since 1970 after some reports showed untoward outcome including stillbirth and acute narcotic withdrawal syndrome in neonates. It was recommended at that time to avoid detoxification until more data was collected and improved monitoring of fetal homeostasis became available. Since then methadone has been used for both maintenance and detoxification for opiate addiction while scant work was done to find alternative therapies even though improved technology for monitor fetal homeostasis has made more alternatives to therapy available. Methadone use during pregnancy carries real risks in terms of psychological and behavior development of the neonate and may have neuro-adaptation leading to changes in neurotransmitter function that may lead to abnormal adolescent behavior as the child grows. We suggest that detoxification should again be considered in place of opioid due to improved monitoring of fetal and maternal homeostasis, especially for women using less than 75 mg/day of methadone. For others, clonidine should be considered as an alternative to methadone.

Introduction

The prevalence of illicit opiate use during pregnancy along with other substances has been increasing [1,2]. The prevalence of opioid abuse or dependence during pregnancy increased from 0.17% in 1998 to 0.39% in 2011 for an increase of 127% [3]. There is firm evidence that pregnancy outcome is worse in women using opiates than in the general population [1,4,5]. Deliveries associated with maternal opioid abuse or dependence compared with those without opioid abuse or dependence were associated with an increased odds (adjusted odds ratio) of maternal death during hospitalization, cardiac arrest, intrauterine growth restriction, placental abruption, length of stay more than 7 days, preterm labor, oligohydramnios, transfusion, stillbirth, premature rupture of membranes, and cesarean delivery [3]. Another problem for about 50% of neonates of opioid-addicted mothers is development of neonatal abstinence syndrome (NAS) requiring opiate treatment for opioid withdrawal after birth [6,7].

It is important to note that detoxification treatment has been avoided since 1970 based on reports showing untoward outcomes including stillbirth and acute narcotic withdrawal (NAS) during pregnancy and after birth. It was recommended at the time to avoid detoxification until more data became available to monitor fetal homeostasis [8]. Since that time, methadone has been being used for maintenance and detoxification from illicit opiate use [9]. However, little has been done to find alternatives, despite improvements in technology to monitor fetal homeostasis and the availability of alternative drugs to treat narcotic addiction during pregnancy.

While methadone is considered very effective, many questions have been raised concerning its use during pregnancy:

a) Is methadone itself not a narcotic?

b) Are we not just substituting one narcotic for another?

c) What are the advantages and disadvantages of using methadone in place of other opiates including heroin itself?

Plausible answers to these questions are: Methadone is a non-euphoric opiate substitute. It is a long acting opiate and complete agonist that assures a smooth detoxification with minimal swings in blood levels that guard against repeated withdrawals. It is manufactured by a licensed pharmaceutical company and prescribed and dispensed by health care professionals. Doses are individualized and quantity is controlled and monitored by both federal and the state governments. Improved pregnancy outcomes were also reported in methadone-maintained gravida patients [10,11], without increased prenatal mortality compared with illicit opiates. However, a bad pre- or postnatal outcome is still more likely than in the general (non-opioid abuse) population and the improvement in normal birth rate is most likely due to better prenatal care than the methadone treatment itself [12].

Methadone treatment has several other advantages. It can reduce illicit drug-seeking behavior, reduce the trading of sex for drugs and mothers, and increase the likelihood of receiving prenatal care with higher infant birth weights [13-15]. Methadone treatment assures stable methadone bioavailability and stable blood levels [16]. Because it is a long acting medicine, methadone assures reduced fetal distress from repeated withdrawals as opposed to inconsistent availability and the short-acting nature of illicit drugs with wide fluctuations of blood drug levels.

However there are several disadvantages in the use of methadone

during pregnancy:

a) Its use encourages continued drug use as many pregnant women continue to use methadone as a preferable opiate after the pregnancy because it is more readily available from legal medical dispensaries.

b) Chronic methadone use has been found to interfere with proper hormonal balance in mothers that can lead to adverse reproductive effects [17]. It is well known that the important primary hormones of pregnancy, estrogen and progesterone, are produced first by the ovaries and later by the placenta. These hormones help to maintain the uterine lining for uterine growth and increased blood flow; they also help to develop breast tissue for milk production. They also regulate bone density and trigger the development of vital fetal organs, such as heart, kidneys, liver, and brain. Progesterone, in particular, relaxes smooth muscle and softens cartilage, thus and limbering up joints and ligaments.

It is not surprising that a deficiency of progesterone during development can cause fetal non-viability. The effect of methadone on plasma estradiol levels and its effect on target tissues via uterine cAMP and cGMP was investigated by Bui et al. [17], in rats; they used an analgesic dose of methadone (5 mg/kg) and observed that methadone decreased the plasma level of estrogen, FSH, LH, ACTH and cortisol. They concluded that methadone exerts pronounced effects on lowering hormonal secretion and transport by the fetus during pregnancy and that this interferes with proper neonatal development and growth [17].

Animal models also show that prenatal methadone administration can restrict body and brain growth in utero and postnatal that is greater than that due to malnutrition alone [18]. Brain catecholamine levels measured in opiate-dependent offspring were decreased; it was suggested that the long-term consequence of such a delay in neuronal maturation may contribute to CNS dysfunction as they grow into adulthood [11,18-21].

Non-stress tests in utero have shown that methadone treatment of the mother significantly decreased fetal activity, e.g. body movements and respiratory activity, and that this was most notable just after methadone treatment [22].

In human babies the incidences of NAS requiring treatment and recommended follow-ups were shown to be significant with about 37% of newborns requiring hospital admission for observation [23,24]. Symptoms of NAS occurred for up to 2 weeks after birth [11]. NAS can be observed in infants of mothers taking as low as 20 mg/day of methadone. Other complications and the opiate withdrawal symptoms of infants born to mothers using methadone, when compared with other illicit opiate-dependent mothers, were found to occur at similar frequencies but the symptoms were worse among methadone users. Convulsive seizures and hyperbilirubinemia [13], were more frequent among babies of methadone users, and hyaline membrane disease was found to occur in babies of methadone users but not in babies of heroin users. Nerve reflexes in infants were found to be more depressed in mothers taking methadone [10]. Long-term consequences of methadone during gestation were prolonged withdrawal from NAS and slower than normal physiological and psychological development including enhanced irritability, cognitive disturbances, tremors and abnormal EEG patterns [19,25-27].

Kaltenbach et al. [28], compared the use of prenatal methadone with that of other illicit opiates by following 45 children whose mothers were given methadone therapy during pregnancy. They evaluated cognitive function of 27 and 18 preschool children exposed to methadone or an illicit opioid, babies respectively. The researchers used the McCarty inability test scale for children and followed them up to the age of 3-1/2 to 4-1/2-year of age. The mean dose of methadone administered to the mothers was38.4 mg/day; approximately 92% of those children required pharmacotherapy for NAS. The general cognitive inability of the children exposed to methadone was not different from that children exposed to illicit opioids; also there were no differences in the impairment to perceptual quantitative memory and motor function [28], unfortunately this study did not have a non-opioid control group. Also, children were not followed beyond the age of 5 years; this means they could not address normal adolescent behaviors such as risk-taking, novelty seeking, heightened sensitivity to peer pressure, or depression. Moreover, this means they could not examine the increased likelihood of illegal or legal drug use and abnormal behaviors, which may reflect incomplete development of brain regions, especially myelination of frontal lobe regions that that are involved in processing of executive control, motivation, and neuro-adaptation to the neurotransmitters that control behavioral responses.

In view of those side effects and the disadvantages of methadone substitution for illicit narcotics, a more comprehensive strategy is required improve or supplant the current use of methadone substitution for illicit opioids in pregnant women. Factors to consider for successful opiate-independent treatment are to consider genetic factors, effects of a candidate drug on neurotransmitters and neurochemistry, and also the long-term effect on dorsal brain function with the consideration of increased disability later in life. Another factor to consider is whether the drug selected will allow the willpower to initiate a voluntary behavior to convert the chronic addiction use/abuse of the drug to a recovery oriented system which means shifting the focus of care from episodic chronic symptoms to stabilization, and then to patient-controlled/client directed long-term care where the disease is not managed, but rather the recovery.

A novel pharmacological treatment strategy might include substitution of methadone with an antagonist like naloxone [29,30] or naltrexone combined with receptor blockers that could prevent or blunt some unwanted actions of the drugs. Also one might consider altering the mechanism mediating reinforcement and reducing drug concentration at the site of action either by increasing drug catabolic pathways, preventing its crossing of the blood-brain barrier, or producing an aversion to a drug, as does, for example, disulfiram. Another medication that may be useful is tizanidine, a topical nasal and ophthalmic decongestants. Its primary action is on the locus coeruleus [31,32], which is the brain site considered most affected with opiate dependence. Tizanidine is believed to work by decreasing norepinephrine levels in the locus coeruleus thus reducing sympathetic outflow.

Unique characteristic of the person is also very important for evaluating a successful opiate substitution. For example, research has shown that opiate treatment will be more successful in patients who have a relatively low incidences of depression and anxiety, who are older and better educated, who do not live with substance abuse-dependent people, and who are employed and less socially marginalized [33]. One opioid in buprenorphine [34,35]. It is can be used in the place of methadone and has some benefits over methadone [36-38].

Considering all these factors, a multiple faceted approach is needed to treat and prevent NAS and reduce infant morbidity. Indeed, detoxification may be one strategy followed by relapse prevention. Presently, as better methods become available, as for example the improved technology to monitor fetal homeostasis, detoxification can be considered again during pregnancy, while avoiding detoxification during the first 2 weeks of pregnancy when a miscarriage is more likely to occur, and in the last trimester when premature birth is more likely to occur.

Several pharmacological agents are considered here that are based on one of strategies discussed above. One of these is clonidine. Clonidine has been used to treat detoxification in the general population with very reasonable success [33]. It is a centrally acting alpha 2 adrenergic agonist and it belongs to the family of imidazolines. Clonidine has been used to treat hypertension, premenopausal symptoms and attention deficit disorders; it is also used as an anesthetic premedication and to assist smoking cessation. Clonidine is used in treating Tourette's syndrome and for agitation associated with conduction disorders. It has been used successfully to treat alcohol and opiate withdrawals. When used in pregnancy clonidine did not alter fetal heart rate and variability, had no apparent short-term effect on the sympathetic nervous system, and no untoward effect on inducing preeclampsia [39]. It was found to be safe as a therapeutic option for sedation and control of opiate withdrawal symptoms and pain in neonates [40]. Clonidine is rapidly cleared in the early post-natal period [41].

Below is a short synopsis of studies on clonidine as an alternative to methadone in treating opioid addiction in pregnant women:

Thornton et al. [42], found that clonidine administered orally to hypertensive pregnant woman does not affect fetal heart rate or short-term variability by the antenatal assessment CTG and concluded that there is no short-term effect of clonidine on the fetal sympathetic nervous system.

Horvath et al. [40], in a blinded study, compared alpha-methyldopa with clonidine in 100 pregnant women and found that neither drug caused significant hypotension nor rebound hypertension in the neonates.

Tuimala et al. [39], reported that clonidine was an effective treatment for pre-eclampsia.

Rothenberger et al. [43], reported that clonidine reduced vascular resistance or cardiac output in hypertensive pregnant patients but that lower cardiac output was associated with reduced neonatal birth weight.

Chavez-Valdez et al. [44], reported that fentanyl and clonidine might be safer therapeutic options for sedation and the control of opiate withdrawal and pain in neonates.

Esmaelli et al. [45], suggested treatment of neonatal abstinence syndrome with clonidine in place of opiates based on its lack of short-term adverse cardiovascular effects.

A case reported by Omera et al. [46], reported that clonidine was as effective an option for the symptoms of neonatal tramadol abstinence.

Agathe et al. [47], concluded that adding clonidine to standard opiate therapy for detoxification in utero due to exposure to methadone or heroin reduced the duration of pharmacotherapy for neonatal abstinence syndrome without having adverse short-term cardiovascular effects.

Ala-Kokko et al. [48], observed no vasoconstrictor effect of clonidine and found no alpha 2 adrenergic receptors in the umbilico-placental circulation, although they found a significant vasoconstrictive effect of hydralazine. They also found that clonidine crosses the placenta extensively, but had no teratogenic effect on animals or in clinical practice, and that it does not appear to have any deleterious effect on fetal growth, mortality and morbidity,

Conclusion

The common practice of using methadone as substitution therapy for illicit opioids during pregnancy carries real risks in terms of unknown and uninvestigated risks of impaired psychological and behavioral development as the child develops. The possibility of maligned neuro-adaptation leading to changes in neuro-transmitter function in utero could lead to abnormal child and adolescent behavior in terms of risk-taking, novelty seeking, and altered executive functions, that could include reduced IQ, drug-seeking behavior, and psychiatric disturbances.

A review of the available literature suggests that detoxification may be considered in place of substitution as a better technology than methadone, especially in those pregnant women who are mildly dependent on illicit opioids and who require less than 75 mg/day of methadone. There are now better methods available to monitor fetal and maternal health during drug detoxification. Clonidine may be considered as a good therapeutic option to decrease withdrawal symptoms as it acts on A2 receptors in the locus coeruleus to decreasing norepinephrine release and thus decrease sympathetic outflow. Dexmedetomidine, which has similar effects as clonidine is not useful because it is an IV drug only. Clonidine may be a suitable option in a subclass of patients who are highly motivated, older, better educated and employed. Other attributes would be patients with low levels of depression and anxiety, who are less socially marginalized and who do not live with substance abuse-dependent people. However, because clonidine was not found to be very effective in preventing the craving for narcotics, behavioral therapy especially motivational interviewing and cognitive betterment therapy, may be combined with other behavioral therapies for better results and to avoid relapses into opioid abuse. Moreover, more research is needed to follow the long-term effect of opiate use on impairing brain development in terms of behavioral and psychological development.

Key Points

- Methadone is an effective, safe, and proven treatment of opioid addiction during pregnancy
- Potential limitations of methadone use during pregnancy and brain development are emotional and psychological disturbances like impulsiveness and drug-seeking behavior that persists into adulthood
- Animal studies suggest hormonal changes and changes in receptor density and adaptation underlie these changes in behavior
- Advances in maternal and pre- and post natal monitoring during pregnancy can help to reduce opioid-related morbidity
- Clonidine is a well proven choice for symptomatic relief in a subset of the individuals who have a low level of addiction, are very motivated, to protect their infant or who refuse to take opioid substitution therapy
- Adjuvant medications can be used to reduce the craving for opioids and to provide comfort

Further research in animal and human models is required to determine the long term effect of opioid addiction, including methadone, on psychological and emotional brain development

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