1-1-2012

The use of naltrexone in pregnancy in opiate-dependent mothers

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10.12968/bjom.2012.20.7.503

This article was originally published as: Geraghty, S. , & Dixon, C. (2012). The use of naltrexone in pregnancy in opiate-dependent mothers. British Journal of Midwifery, 20(7), 503-506.

Opiate dependent Mothers and the use of naltrexone in pregnancy in Western Australia

Abstract

Objective: This paper will review and discuss the controversial use of naltrexone in pregnancy in Western Australia, and whether it is a viable alternative to the methadone maintenance therapy programme for pregnant opiate dependent mothers.

Design: There is an absence of sufficient evidence regarding naltrexone use in pregnancy due to the limited range of human studies.

Setting: naltrexone implants are being used in Western Australia as a treatment for opioid dependency, and although contraindicated for insertion during pregnancy there are a number of women who conceive whilst already undergoing treatment.

Participants: Pregnant mothers have limited choices for treatment for opioid dependency and withdrawal is contraindicated whilst pregnant.

Findings: A review of the available data reveals naltrexone is associated with improved maternal and fetal outcomes.

Key conclusions: Extensive research into this area in the form of large, multi-centre trials is required to confirm the results of the current research.

Keywords: naltrexone, pregnancy, methadone, opioid dependency.

Introduction

A basic exploration of the literature within the 'CINAHL' and 'PUBMED' databases on 20th March 2012 and again on 1st May 2012, focusing specifically on articles published in the last five to ten years; provided a limited amount of research specific to naltrexone implant use in pregnancy; and revealed a minimal amount of literature on the use of naltrexone in pregnancy. The aim of this discussion paper is to provide an insight into the latest research regarding the controversial use of naltrexone in pregnancy for opiate dependent women; and to explore whether naltrexone could be the optimal treatment programme for opioid dependent pregnant mothers.

Opiate use in pregnancy

Throughout Australia, the rate of women using prescribed and illicit opiates is escalating (Australian Institute for Health and Welfare (AIHW), 2010). A large proportion of these women are of childbearing age and/or pregnant and dependent on opiates.

Being dependent on a substance has been defined as a maladaptive pattern of substance use (American Psychiatric Association (APA), 1994). This usually leads to clinically significant impairment or distress (Mysels, Cheng, Nunes, & Sullivan, 2011). Altered physiological states, due to the repeated administration of a drug, can lead to a specific syndrome of withdrawal on cessation of that substance (Goradetzky, Sahakian, Robbins, & Ersche, 2010). Tolerance to a particular drug or substance may also develop, whereby continued use of the same amount of drug leads to a diminished effect, so that markedly increased amounts of the substance are required to achieve similar effect level (Haile, Kosten, & Kosten, 2010).

Opioid use is prevalent in Australia, both from illicit use and abuse of prescribed opiates which may have developed during medical treatment with opioid analgesics. In a recent household survey, it was reported that 14.7% of the Australian population, aged over 14 years, had used illicit drugs within the last 12 months (Australian Institute of Health and Welfare (AIHW), 2010). Recent illicit drug use amongst females was highest in the 20 – 29 year age group, at 24.3 % (AIHW, 2010). This same survey reported that 1 in 5 women were drinking at levels that put them at risk of harm, which is more than two standard drinks a day on average; and that the misuse of prescribed medication had risen to 4.2% (AIHW, 2010). The age groups of the women reported on in this survey are within the central time-frame period in a woman's child-bearing years.

Withdrawal from opiates during pregnancy is not recommended due to risks to the fetus in the form of increased risk of infant mortality and low birth weight for gestational age (Bell & National Working Group, 2006), and the high risk of maternal relapse (Haile, Kosten & Kosten, 2010).

The Methadone Maintenance Therapy (MMT) programme is the main prescribed therapy for opiate dependence and is essentially a synthetic opioid (Salehi, Zargar & Ramezani, 2011); which produces a slow, extended detoxification. Research suggests that methadone helps those dependent on opiates to reduce or cease their opiate use (Mattick, Breen & Kimber, 2009). This is accomplished by retaining participants in treatment and decreasing heroin use which appears to be better than treatments that do not utilise opioid replacement therapy (Mattick, Breen & Kimber, 2009). Outcomes of the MMT programme include cessation of intravenous drug use, improved physical health and nutrition, reduced criminal activity and improved social supports (Judson, Bird, O'Conner, Bevin, Loan, Schroder et al, 2010).

There are two other treatment options available for opiate dependency in Australia. Buprenorphine is a partial opiate agonist (Wesson & Smith, 2010), which works by binding the opiate receptor and exerting a mild opioid effect, whilst blocking other opiates from binding the receptor. This relieves cravings but also reduces the opioid effects of any co-administered opioid (Sadock et al, 2009). Naltrexone is an opiate antagonist (Wesson & Smith, 2010), which is a drug that binds a cell receptor without exerting a response, but blocks the effect of another drug and thereby nullifies the effects of any co-administered opiate (Sadock et al, 2009).

Medication safety in pregnancy is directed by national evidence-based guidelines produced by the Australian Drug Evaluation Committee (ADEC). Each drug is categorised by taking into account the known harmful effects on the fetus, including birth defects, harmful perinatal effects and the potential to cause problems later in life (ADEC, 2011).

Opioid use in pregnancy has been associated with intrauterine growth restriction (IUGR); pre-term birth, low birth weight, microcephaly, meconium staining of the amniotic fluid, fetal death in-utero (FDIU) and the development of neonatal abstinence syndrome (NAS) following birth (Jones, O'Grady, Johnson, Velez & Jansson, 2010). However, withdrawal from opiates during pregnancy is not only dangerous for the fetus due to the associated fetal distress (ref), increased infant mortality and low birth weight for gestational age, but also carries a high risk of relapse for the mother. Therefore, pregnant women dependent on opiates are usually offered MMT in the first instance (New South Wales Department of Health (NSW DoH, 2006).

Methadone in pregnancy

Methadone is only legally available for use with a written prescription and enrolment on a MMT programme; it does not cause fetal anomalies, however it may affect neurobehaviours (Jansson, Di Pietro, Elko, Williams, Milio & Velez, 2011), and cause respiratory depression in neonates or neonatal abstinence syndrome (NAS) in the newborn infant (McCarthy, Leamon, Stenson, & Biles, 2008). Methadone has been associated with increased rates of ante-partum haemorrhage, increased neonatal mortality and reduced birth weight, although this is significantly lower than that associated with heroin use (Bell & Harvey- Dodds, 2008). Despite these complications methadone is considered safer in pregnancy than heroin, and is therefore recommended for use in pregnant women if opiate replacement is necessary (Winklbaur, Kopf, Ebner, Jung, Thau, & Fischer, 2008).

Women engaged on the MMT have birthed babies with improved fetal development and reduced special care nursery admission (Cleary, Eogan, O'Connell, Fahey, Gallagher, Clarke, et al, 2012). This has been achieved by increasing infant birth weight and reducing the perinatal and infant mortality rate; however the protective effects are reduced by concomitant heroin use. Furthermore, withdrawal from methadone is associated with a high risk of relapse to heroin use, and should not be encouraged during pregnancy (Bell & Harvey-Dodds, 2008).

Whilst the MMT has long been established as first line therapy for opiate dependency, it is not without its disadvantages. Short term complications include: opportunity for concomitant heroin use, drug diversion and an increased mortality rate during induction onto MMT due to fatal overdose (Tait, Ngo, & Hulse, 2007; Ngo, Tait & Hulse, 2008). The long-term disadvantages of methadone are that the patient remains opiate-dependent and therefore retains many of the associated physical, mental, emotional and social effects of drug dependence (Hulse, O'Neill, & Arnold-Reed, 2004).

Naltrexone

An alternative approach to MMT is naltrexone, a drug that enforces opiate abstinence (Haile, Kosten & Kosten, 2010). Naltrexone is a long-acting opioid antagonist that has been registered for general use in the community since 1984 (Fram, Marmo & Holden, 1989). In Australia, naltrexone is primarily registered for use in the treatment of alcoholism note it is not licensed for this purpose in the United Kingdom) (BNF, 2011); however it may also be used in opiate dependents, to help maintain abstinence from opioids by decreasing cravings and blocking the effects of opiates via competitive inhibition (Sadock, Sadock & Kaplan, 2005).

A single 50mg naltrexone tablet provides protection against heroin overdose and blocks the euphoric effects of heroin for 24 hours, and has been shown to be safe and effective (Farid, McCallum, Tait, Dunlop & Hulse, 2009). The main issue limiting the utility of naltrexone has proved to be compliance, as the dependent must remain motivated to administer the drug daily (Ngo, Tait & Hulse, 2008; Hulse, Morris, Arnold-Reed & Tait, 2009). A related issue is the loss of tolerance to opioids that develops whilst on naltrexone, such that if the dependant ceases the medications and relapses back to heroin, they are at high risk of opiate overdose Jones et al, 2012). Naltrexone implants remove the onus on the dependent to self-administer the drug each day and leads to improved dependent outcomes and reduces the risk of accidental overdose (Lobmaier, Kunoe, Gossop, & Waal, 2010). Naltrexone implants are a

sustained-release preparation that maintains therapeutic blood levels for extended periods (Tait, Ngo & Hulse, 2007). Although a Western Australian-based obstetrician has pioneered a naltrexone implant that appears to satisfy the above criteria, objections to its widespread use remain strong and the use of this product has become highly controversial (Lobmaier, Gossop, Waal & Bramness, 2010). At present it may be administered only under the restrictions of a clinical trial, and research into its safety and efficacy continue (Wodak, Ali, Henry & Sansom, 2008).

The use of Naltrexone in pregnancy

Naltrexone implants have not been approved for use in pregnancy in Australia (The National Health and Medical Research Council (NHMRC). No increase in malformations or harmful effects has been observed in the use of naltrexone implants, conducted amongst a limited number of pregnant women (Hulse & O'Neill, 2002). However animal studies have shown changes offspring behaviour, neuroanatomy and biochemistry (Farid, Dunlop, Tait & Hulse, 2008). The paucity of conducted research suggests that in-utero exposure to naltrexone in rats caused increased birth weight, which is possibly caused by the blocking of the growth-suppressing effects of endogenous opioids (Farid et al, 2009).

The NHMRC and the National Clinical Guidelines both advocate that the safety and efficacy of naltrexone in pregnancy has not yet been established; therefore naltrexone should not be offered in pregnancy except in the context of clinical trials. Currently, in Western Australia, women who conceive whilst undergoing treatment with a naltrexone implant continue with their pregnancies on the understanding that the safety of naltrexone in pregnancy is not established and women are provided with informed consent (Hulse et al, 2003; Wodak et al, 2008). Babies born to mothers with naltrexone implants are usually referred for paediatric review following birth as a precautionary measure.

As pregnancy remains a contraindication with the use of naltrexone implants, women are not encouraged to conceive, however a number of women after receiving the implant have inadvertently conceived a child. From the limited research available, the neonate and obstetric outcomes have been unremarkable (Hulse, O'Neill &Arnold-Reed, 2004; Jones et al, 2012), and women have remained opiate free during the pregnancy. Prior to the implants, the women had been unstable on oral naltrexone, with multiple relapses back into intravenous

heroin use. Notably, there is no neonatal abstinence syndrome associated with the use of naltrexone, in contrast to that of MMT (Jansson et al, 2011).

A recent review of naltrexone in pregnancy (Jones, Chisolm, Jansson & Terplan, 2012), highlighted a number of pregnancy-specific issues. These included: variable adverse effect profiles related to timing of first use; potential drug interactions during labour leading to difficulty in providing effective analgesia, limited data of the effects on the breastfeeding infant, and the ethical difficulties in including pregnant women in clinical trials. Yet given that the date currently available suggests no increased risk for poor outcomes related to antenatal naltrexone exposure, the study supported our own conclusion that further research into this area would greatly benefit clinicians in the field.

Conclusion

In contrast to the methadone maintenance therapy, the approved treatment programme for pregnant opiate dependent women, naltrexone offers an opportunity to remain opiate-free throughout pregnancy. A review of the available data reveals naltrexone is associated with improved maternal and fetal outcomes - seemingly without any ill effects. However, extensive research into this area in the form of large, multi-centre trials is required to confirm the results of the current research, specifically comparing maternal and fetal outcomes with the use of either MMT or naltrexone.

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