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New Approaches in the Treatment of Opioid Dependency During Pregnancy

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Summary

Although the treatment of opioid dependence during pregnancy has received considerable attention over the past 40 years, most approaches have been based on retrospective, observational and/or clinical studies rather than well controlled clinical trials. An exciting new period appears to be emerging in which rigorous empirical data will provide recommendations for optimal treatment approaches for both the opioid dependent pregnant woman and her child.

Key Words: Pregnancy - Opioid Dependence

The management of opioid dependence during pregnancy has been a focus of attention since the early 1970's as the use of methadone for the treatment of opioid dependence became widely accepted ⁽¹⁾. In the 1970's methadone maintenance was recommended for the management of opioid dependence during pregnancy ⁽²⁾, comprehensive models of treatment, including prenatal care were identified ⁽³⁾, diagnosis of NAS was delineated ⁽⁴⁾ and scoring systems for the assessment and treatment of NAS were developed ^(5,6,7).

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Over the past 40 years, methadone maintenance has been established as the standard of care of the opioid dependent pregnant women ⁽⁸⁾ with research identifying the reduction of mortality and morbidity when provided within a comprehensive program ⁽⁹⁾, the bio-psychosocial characteristics of this special population ⁽⁹⁾, the outcome of infants born to opioid dependent women ⁽¹⁰⁾ and the lack of relationship between severity of NAS and maternal methadone dose ⁽¹¹⁾. However, this body of literature is based on retrospective and clinical studies rather than rigorous clinical trials and there is much information that is lacking.

Although there is a rich clinical literature establishing the benefits of methadone to treat opioid dependent patients during pregnancy, there are many clinical questions surrounding this effective treatment in this population that remain unanswered. This paper is organized into 4 sections which identify new questions that must be addressed if we are to be able to successfully meet the needs of the opioid dependent woman and her newborn. These questions include transitioning from opioids onto buprenorphine, addressing issues of pain management, and the assessment and treatment of neonatal abstinence from the American and European perspectives.

Transitioning from Opioids onto Buprenorphine during Pregnancy

As with all illnesses, having a greater choice of medications to treat opioid dependence helps promote patient-treatment matching and facilitate improved outcomes. Some methadone treated patients who are pregnant may desire or require a change in medication due to differing life circumstances. This desire to change medication may be due to wanting a medication that can be administered in a physician's office, minimize the possibility of interaction with other medications being taken, or one that is associated with a less intense neonatal abstinence syndrome (NAS) in the neonate ⁽¹²⁾. Thus, it is probable that some methadone treated women who become pregnant may desire to transition to buprenorphine.

Since transfers from methadone to buprenorphine occur in routine clinical practice of treating pregnant opioid dependent women, a pilot study was developed to yield information to guide possible future transfers from methadone to buprenorphine. The methodology for the transition was based on the results a randomized controlled study that compared the subjective and physiological effects of transition from short-acting opioids onto either methadone or buprenorphine. In this study 18 pregnant opioid dependent patients entering a comprehensive care centre in Baltimore, Maryland, USA, were randomized to methadone (n=10) or buprenorphine (n=8) following treatment with five days of immediate release morphine (IRM) in total daily amounts that were based on alleviating withdrawal symptoms. Total subjective opioid withdrawal scores that reflect participant discomfort on a scale from 0-64 were very low during the transition from IRM to methadone or buprenorphine (mean of 3.3 and 1.6, respectively). These low scores indicated a comfortable transition/induction from immediate release morphine to either medication. The pattern of physiological effects, ingestion of concomitant

medication and withdrawal symptomatology were similar between groups with one exception. The methadone group reported body aches being substantially reduced after stabilization on IRM to transition/induction onto methadone. Thus, based on these data, similar to non-pregnant patients, transition from short-acting opiates to buprenorphine during second or early third trimester is accomplished with minimal difficulty⁽¹³⁾.

Transitioning from methadone to buprenorphine can be unpleasant and associated with more withdrawal symptoms than transitioning from short-acting opioids to buprenorphine⁽¹⁴⁾. The intensity of the opioid withdrawal may be related to methadone and buprenorphine doses and the duration between medication doses⁽¹⁵⁾. Current United States guidelines suggest that patients transitioning from methadone to buprenorphine limit their dose of methadone to 30 mg or less for at least a week and then wait at least 24 hrs between the last methadone dose and initial buprenorphine dose to help avoid a buprenorphine precipitated withdrawal⁽¹⁴⁾. Lowering the dose of methadone and/or increasing the time between last dose of methadone and initial dose of buprenorphine may not be acceptable to some patients. This may be especially true where any withdrawal may make the patient vulnerable to relapse. Thus, the goal was to attempt to develop a protocol that would avoid both lowering the methadone dose and needing a long duration between methadone cessation and buprenorphine initiation.

The few reports of transferring pregnant women from methadone to buprenorphine indicate that it is possible to transition pregnant women in the second or third trimester from oral methadone (8 to 70 mg) doses to sublingual buprenorphine (up to 10 mg). The major withdrawal complaint was dysphoric mood^(16, 17).

This was an open-label exploratory study with a flexible dosing protocol⁽¹⁸⁾. Participants (n=4) were outpatients between 22-30 weeks pregnant who desired transfer to buprenorphine and were currently stabilized on methadone for at least 4 weeks were selected from the Centre for Addiction and Pregnancy, Baltimore, Maryland. The patients screened for this study were considered stabilized on methadone based on the clinical observations of the treatment staff (i.e. no objective evidence of illicit opioid use or patient requests for dose increases). Participants were inpatients for the duration of their study participation. The study was approved by the Johns Hopkins Bay View Medical Centre Institutional Review Board for human studies.

Patient responses and clinical observations determined subsequent IRM and buprenorphine dosing. Patients were first observed for two days while receiving their clinically determined methadone dose. Methadone was then discontinued and IRM was administered for five days at doses tailored to minimize withdrawal from methadone. IRM was then discontinued and transition to buprenorphine was then attempted over the next three days. Although the subjective and objective withdrawal scores were moderate to low over the course of the methadone to IRM to buprenorphine transition, none of the participants remained on buprenorphine more than 5 days. Two of the participants were withdrawn from the study and returned to methadone and the other two participants elected to withdraw from the study due to the "clear headed" way buprenorphine made them feel. One participant had anhydroamniosis and fetal

tachycardia attributed to cocaine use. Other fetal assessments during the transitions were within normal limits.

Given the experience from these four participants, several aspects of the transition should be examined in the future to improve the tolerability of the transition. It may be necessary to increase the duration of stabilization on IRM before the transfer to buprenorphine. Other aspects to examine are administering the smaller amount of the split dose first (e.g., between 2-4 mg).and/or administer subsequent 2 mg buprenorphine doses at intervals throughout the day based on patient symptomatology. Providing immediate release morphine in between buprenorphine dosing times may also help relieve the discomfort associated with breakthrough withdrawal.

Since transfer from methadone to buprenorphine is occurring in routine care, it is important to gather information regarding the maternal and fetal safety and efficacy of these transfers. Evidence from well-controlled evaluations of patients undergoing transfers should be reported and patients should be informed of the risks of making medication changes and supported in selecting the medication that is best for them.

Intrapartum and Postpartum Management of Pain

One of the continuing challenges in the treatment of opioid dependent pregnant patients that has not received adequate attention is the management of intrapartum and postpartum pain. In general, there has been a reluctance to provide adequate pain treatment to opioid dependent patients receiving medication assisted treatment based on the mistaken belief that a maintenance dose of opioid addiction treatment medication also relieves acute pain ⁽¹⁹⁾. The reality is that long-term opioid pharmacotherapy produces tolerance for the analgesic effects of opioid treatment medications with the result that the maintenance dose provides little or no pain relief ⁽²⁰⁾. This is especially salient for opioid dependent pregnant women presenting for delivery. To further complicate the situation, it is also often thought that providing any additional opioid medication would have an additive effect causing respiratory depression and possible overdose making pain management in labour and the immediate post-partum period a challenge for both opioid maintained women and their clinicians. Two studies, one preliminary study from Toronto, and one from the United States have looked at intra and post partum pain management in methadone and buprenorphine maintained women.

The preliminary study is a retrospective chart review of 90 women who received prenatal care and delivered at St Joseph's Health Centre in Toronto. Three groups were compared, women receiving methadone maintenance (n=30), non-maintained substance using women (n=30) and a non-using comparison group (n=30). Only women with singleton births were included, exclusion criteria included detoxification during pregnancy, non-compliance with methadone maintenance, and less than 4 prenatal visits. The mean methadone dose at delivery for methadone maintained women was 102 mg with a range of 30mg -210mg. As one would expect, the comparison group had the highest rate of adequate prenatal care at 97% (adequate defined as fists visit

at <3 months gestation and total number of visits >9), with the methadone maintained group at 50%, and the non-maintained substance users at 33%. No significant difference was found in the use of intra partum analgesia with approximately 70% of each group receiving epidural analgesia. There was also no difference between groups in the use of pain medication during the first three days postpartum, however, morphine was more often used in the methadone maintained group and this group also seemed to have a greater need for pain management overall, (see Table 1).

The second study analysed data from a double blind, double dummy clinical trial

Table 1. Post Partum Pain Management				
	Study Cohort			
	MMT	Non-MMT	CNT	p
Post PCA pump	13.3%	6.7%	3.3%	0.33
Any post partum pain meds	86.7%	90.0%	80.0%	0.53
Likelihood of Morphine day 1	13.3%	6.7%	0.0%	0.05
Likelihood of Morphine use day 2	16.7%	6.7%	0.0%	0.02
Likelihood of Morphine use day 3	13.3%	0.0%	0.0%	0.01
Likelihood of Morphine use day 4	3.3%	0.0%	0.0%	0.33
Tylenol day 1	46.7%	53.3%	50.0%	0.87
Tylenol day 2	53.3%	63.3%	46.7%	0.42
Tylenol day 3	43.3%	33.3%	40.0%	0.71
Tylenol day 4	23.3%	13.3%	23.3%	0.51
Tylenol with Codeine day 1	23.3%	10.0%	16.7%	0.37
Tylenol with Codeine day 2	23.3%	13.3%	26.7%	0.40
Tylenol with Codeine day 3	23.3%	23.3%	13.3%	0.51
Tylenol with Codeine day 4	23.3%	23.3%	6.7%	0.11
Tylenol with Codeine day 5	6.7%	6.7%	6.7%	1.00
Ibuprofen day 1	23.3%	26.7%	26.7%	0.94
Ibuprofen day 2	30.0%	33.3%	40.0%	0.71
Ibuprofen day 3	33.3%	30.0%	31.0%	0.96
Ibuprofen day 4	16.7%	10.0%	10.0%	0.67
Ibuprofen day 5	6.7%	3.3%	3.3%	0.78

investigating the efficacy of buprenorphine compared to methadone in the treatment of opioid dependent pregnant women ⁽¹²⁾. This study compared the post partum pain scores of women maintained on buprenorphine (n=8, mean dose 10mg/day) and women maintained on methadone (n=10, mean dose 80mg/day). No difference was found in post partum pain scores using treatment as usual protocols. There was also no differ-

ence in the use of pain medications between groups, however methadone maintained patients appeared to use more analgesics.

Although these data are limited, they suggest that the use of epidural analgesia and the use of non-opioid analgesics in the post partum period relieve pain in both methadone maintained and buprenorphine maintained women. These preliminary results also indicate the need for systematic studies to determine optimal pain control strategies for pregnant opioid dependent women.

Neonatal Abstinence Syndrome: An Update on Assessment and Treatment

Although the assessment and treatment of Neonatal Abstinence Syndrome (NAS) has been at the forefront of treatment for opioid dependent pregnant women for the past 35 years, the literature that supports this standard of care has been conducted primarily in the mid 1970's and early 1980's. Several scoring systems have been developed to aid in the assessment of NAS and the determination to initiate pharmacotherapy^(5, 6, 7) with the Finnegan scale the most widely used in the United States⁽²¹⁾.

The Finnegan scale assigns a weighted score to 31 individual signs of NAS. Infants are scored every 4 hours. The need for pharmacological intervention is indicated when the total score is 8 or greater for three consecutive scores or when the average of 3 consecutive scores is 8 or greater. If the score is 12 or higher for two consecutive intervals or the average of two consecutive intervals is 12 or greater, pharmacotherapy is initiated immediately. Pharmacological intervention is not indicated if consecutive total scores or the average of any 3 consecutive scores continues to be 7 or less during the first 4 days of life⁽²²⁾. Although the majority of intensive care nurseries in the United States report the use of the Finnegan scale, only 33% report that they adhere to the protocol as written, whereas 67% use a "modification" of the scale⁽²¹⁾.

The choice of medication use for the management of NAS is usually physician or institution driven. In 1998, the American Academy of Pediatrics reviewed common medications used in the treatment of NAS and recommended tincture of opium as the recommended agent for treatment of opioid abstinence⁽²³⁾. Until then, paregoric had been the drug of choice. However, the review of the literature indicated that there are very few studies that compare the efficacy of different treatment for NAS. The Academy's recommendation was based on the precept that drug selection should match the type of agent causing the withdrawal and that a 25-fold dilution of tincture of opium contains the same concentration of morphine equivalent as paregoric without the additives or high alcohol content of paregoric. A recent survey of practices in neonatal intensive care nurseries across the USA reported that 36% used morphine sulphate solution, 27% used tincture of opium, and 20% used methadone⁽²¹⁾.

Again, the majority of studies investigating the efficacy of medication for the treatment of NAS are from the 1970's and 1980's. However, in the past few years there have been several efforts at identifying more effective treatment protocols. Coyle et al⁽²⁴⁾ conducted a study of neonates exposed to methadone and/or heroin in which

infants were randomized to Diluted Tincture of Opium (DTO) and placebo or to DTO and Phenobarbital. Infants receiving DTO and Phenobarbital spent less time in severe withdrawal, required a lower maximum daily DTO dose, and had a significantly shorter hospital stay. However, it should be noted that they were discharged on Phenobarbital, with average outpatient medication duration of 3.5 months.

Langenfeld et al.⁽²⁵⁾ conducted a randomized double blind controlled trial comparing treatment of NAS with tincture of opium or morphine drops in 33 infants and found no significant difference in length of hospitalization, days of treatment, cumulative dose and maximum dose. Interestingly, they did find that weight gain was better in the morphine group.

Although methadone is being used for treating NAS there are very few studies to inform its use. Until 2005, there was only one study published⁽²⁶⁾. Recently two studies have been published although neither is a randomized controlled trial. Lainwala et al.⁽²⁷⁾ conducted a retrospective study of length of hospital stay in 46 infants treated with for NAs with methadone versus oral morphine and found no difference in median length of stay. Wunsch⁽²⁸⁾ also conducted a chart review of 19 infants comparing paregoric to methadone in treating NAS and found no difference in length of stay, time to NAS <9, and rate of decrease for NAS.

While it is encouraging that there is some new work in this area, it is clear that much more information is needed from randomized controlled trials. There is currently an ongoing multi-site double blind, double dummy clinical trial, Maternal Opioid Treatment Experimental Research (MOTHER) examining the safety and efficacy of methadone compared to buprenorphine in pregnant opioid dependent women and their neonates. While the MOTHER trial exceeds the scope of this paper, there are two aspects that are relevant to this discussion: the scoring of NAS and the treatment of NAS.

The MOTHER Neonatal Abstinence Score Scale is a revision of the Finnegan scale. Two items have been added; failure to thrive and excessive irritability. Nine items are no longer scored thereby reducing the length of the Finnegan scale. The items eliminated are myoclonic jerks, mottling, convulsions, retractions, nasal flaring, excessive sucking, projectile vomiting, watery stools, and fever 38.4C. However, the scoring sheet is designed to capture the deleted items, i.e. present/absent so that the data can be analysed to determine if the need to treat is concordant with the original Finnegan scale.

In the MOTHER study, morphine sulphate oral solution is being used to treat NAS but the treatment protocol differs from the traditional approach of dose based on mg/kg. In this protocol, treatment/dose is based on entirely on symptoms, i.e. if an infant scores between 9-12, the infant would receive .04mg of morphine solution; scores of 13-16 would receive .08 mg; 17-20, .12mg; 21-24, .16 mg; 25 or above, .20 mg. This study will be able to provide important data on treatment by symptom.

The European Perspective

The importance of standardized approaches in the treatment of this target group seems to be the key-element in reaching the best out-come for the pregnant substance dependent women (in the majority of cases, women present themselves with multiple substance dependence at the first contact with a treatment unit) and the for neonate (around 60 % exhibit neonatal abstinence syndrome after opioid exposure during pregnancy). However a patchwork of approaches to addiction treatment has been observed in Europe, matched by a heterogeneous approach to the treatment of neonatal abstinence syndrome in the different countries. Unfortunately, Eastern European countries quite often are lacking the option of opioid maintenance therapy because of their legal restrictions, or are only able to provide it to a limited extent.

In addition to non-medication treated pregnant women in the European Union countries; an increasing number of women are becoming pregnant while receiving opioid maintenance therapy. The majority of reports have been provided from France^(29, 30) where buprenorphine also has high prescribing patterns in women of child bearing age. However, many use other drugs, such as benzodiazepines and nicotine and around 50% of women have a co-dependent partner, which can be a barrier to effective treatment.

There are limited data from controlled clinical trials in pregnant women as they are often excluded from trials. Current knowledge is based on animal data, case reports, and small clinical series. The main gaps in our knowledge today surround treatment retention, the pharmacokinetics, pharmacodynamics, and pharmacogenomics following methadone and buprenorphine treatment, the effects of additional opioid consumption, appropriate dosing and the management of NAS.

In the case of NAS, one recent prospective study of 53 opioid-maintained pregnant mothers and their neonates found that morphine hydrochloride is the preferred therapy for neonates suffering opioid-related NAS while Phenobarbital seems to be beneficial for neonates suffering withdrawal due to maternal benzodiazepine use⁽³¹⁾.

Slow-release and standard morphine maintenance therapy have been compared in pregnant women⁽³²⁾. Both formulations were well tolerated and there were no differences in neonatal outcomes. Both medications induced NAS of a similar intensity and duration. There was, however, a significantly lower concomitant consumption of heroin and benzodiazepines in the slow-release morphine group.

As one of the pilot trials of the MOTHER study, methadone (40–100 mg/day) and buprenorphine (8–24 mg/day) maintenance therapies have been compared in 18 pregnant opioid dependent women in Austria⁽³³⁾. There was greater retention of subjects in the buprenorphine group but significantly lower use of additional opioids in the methadone group. From the data on the available 14 cases, the neonates born to the methadone-treated women (n=6) were similar in most measures to those born to buprenorphine-treated women (n=8) but had an earlier onset of NAS. Notably, a high nicotine intake was found to be associated with a smaller head circumference, regardless of opioid therapy. However the mean treatment duration of NAS for neonates of both groups (exposed in-utero to either methadone or buprenorphine) was very short with a mean

duration of 5 days, when compared to other publications who report mean durations up to 20 days. Such differences emphasize the importance of a standardized approach.

In summary, although the treatment of opioid dependence during pregnancy has received considerable attention over the past 40 years, most approaches have been based on retrospective, observational and/or clinical studies rather than well controlled clinical trials. An exciting new period appears to be emerging in which rigorous empirical data will provide recommendations for optimal treatment approaches for both the opioid dependent pregnant woman and her child.

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9th EUROPAD Forum during AATOD Conference
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HEROIN ADDICTION AND RELATED CLINICAL PROBLEMS

Chairmen:

I. Maremmani (Pisa, Italy) - M. Reisinger (Brussels, Belgium, EU)

- 1:00 pm **Icro Maremmani** (*Pisa, Italy, EU*)
Predictors of response to treatment: Methadone vs Buprenorphine.
- 1:20 pm **Matteo Pacini** (*Pisa, Italy, EU*)
The patient's resistance to methadone treatment - the clinical and therapeutic aspects.
- 1:40 pm **Barbara Lovrecic** and Mercedes Lovrecic (*Ljubljana, Slovenia, EU*)
Infectious Diseases and Mortality in Slovenian Heroin Addicts
- 2:00 pm **Pier Paolo Pani** (*Cagliari, Italy, EU*)
Psychopathology and Methadone Maintenance: the state of the art
- 2:20 pm **Lev Blagov**, (*Moscow, Russian Federation*)
Opioid Dependence and its relationship with alcoholism in young Russian men
- 2:40 pm **Alexander Kantchelov** (*Sofia, Bulgaria*)
From harm reduction to methadone-assisted therapy. 12 years of Bulgarian experience
- 3:00 pm **Aud L Krook**, Dorthe Stokka, Bernt Heger and Egil Nygaard (*Oslo, Norway*)
Successful treatment of hepatitis C genotype 3a in Norwegian opioid dependants: a pilot study
- 3:20 pm **Gilberto Gerra, A. Zaimovic, F. Brambilla, G. Friso, and C. Donnini** (*Parma and Milan, Italy, EU*)
Gene variants at risk for substance use disorders: possible interactions with environmental factors.
- 3:40 pm Nina Ebner, Bernadette Winklbaaur, Nina Kopf, Andjela Baewert, Kenneth Thau, **Gabriele Fischer** (*Vienna, Austria, EU*)
Opioid dependent pregnant women and pregnancy
- 4:00 pm **Nikolaj Kunøe**, Philipp Lobmaier & Helge Waal (*Oslo, Norway*)
Naltrexone implants to prevent relapse after inpatient treatment for opioid addiction: a randomised controlled trial.
- 4:20 pm **Andrej Kastelic** (*Ljubljana, Slovenia, EU*)
Medically Assisted Rehabilitation in Slovenian Prison
- 4:40 pm **Thomas Clausen** and Helge Waal (*Oslo, Norway*)
Patterns of mortality after opioid maintenance treatment

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