

Neonatal outcome following buprenorphine maintenance for opiate dependency

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Abstract

Methadone substitution improves maternal and neonatal outcomes. However methadone induced neonatal abstinence syndrome (NAS) is common. Buprenorphine-exposed neonates may be at a lower risk of NAS. Currently in the Republic of Ireland, buprenorphine does not have a special licence for use in pregnancy. We describe here the history and neonatal outcomes of the first Irish woman maintained on buprenorphine during two pregnancies.

Supervised urinalysis on this mother between and throughout both pregnancies did not reveal any illicit drug use. She delivered two post-term babies of normal birth weight and length. The second infant required treatment for NAS for 21 days with morphine sulphate. Although the use of buprenorphine in pregnancy does not remove the possibility of NAS, neonatal outcomes of buprenorphine-maintained women compares favourably to methadone. As the use of buprenorphine becomes more established in Ireland, the management of buprenorphine-exposed neonates will become more common.

Key words: Neonatal abstinence syndrome; Opiate dependency; Buprenorphine.

Introduction

The incidence of heroin use in Ireland escalated throughout the 1990s before tailing off at the end of the decade,¹ only to increase again in recent years.² However, reflecting the chronic nature of opiate dependency, prevalence rates have steadily increased. Recent estimates of opiate prevalence in Ireland are based on a three-source capture-recapture study of opiate use in 2000-2001.³

This research showed that in the 15-64 year age group, 5.6/1000 of the population used opiates; local prevalence in the Dublin area was amongst the highest in Europe at 15.9/1000. In the 15-24 year age group, prevalence estimates were even higher at 32/1000 males and 17/1000 females.

Increasingly more women are entering methadone substitution treatment, the majority of childbearing age. Internationally and in Ireland, methadone, a pure opiate

agonist, is the main substitution medication used in the treatment of opiate dependency due to its proven ability to stabilise the opiate-dependent person's drug use and lifestyle.⁴ Methadone facilitates engaging and retaining an opiate-dependent individual in treatment so that at the very least, they can be offered medical, psychological and social support ('harm reduction'). For methadone-maintained mothers, treatment facilitates access to antenatal and obstetric care, which can be co-ordinated by a drug liaison midwife.

In 1999, a drug liaison midwife service was set up with one midwife attached to each of the three Dublin Maternity Hospitals. In the Republic of Ireland during 2005, there were 8,962 people prescribed methadone,⁵ of whom 2,746 were female (30.6%), with a mean age of 29 years (SD +/- 6.4 yrs). And during that year, there were 193 infants born in the three Dublin maternity hospitals to women maintained on methadone.⁶

Research has consistently demonstrated that maternal and neonatal outcomes are better in methadone-maintained mothers than for those mothers using opiates and not in treatment.⁷⁻¹⁰ However, a neonatal abstinence syndrome (NAS) occurs in 48-94% of infants exposed to methadone *in-utero*.¹¹

The signs of NAS include: high-pitched cry, rapid breathing, hungry but ineffective sucking, excessive wakefulness, tremor, vomiting and diarrhoea, hypertonicity, sweating, and rarely, seizures. In the interest of objectivity, Loretta Finnegan and colleagues developed the 'Finnegan chart' which allows the assessment and monitoring of NAS.¹² Numerical values are allocated on the basis of the presence and severity of 20 signs commonly found in neonatal withdrawal (CNS, metabolic, vasomotor, respiratory, and gastro intestinal disturbances). The numbers are added together to give a total score (maximum 46).

The aims of managing an infant who is at risk of NAS are to maintain a normal temperature, to ensure adequate sleep between feeds, to reduce hyperactivity and excessive crying, to reduce motor instability, and ensure adequate weight gain. The hospital where these infants were delivered uses the 'Liverpool approach'¹⁷ (an obstetric liaison service comprising of a multidisciplinary team from the addiction and midwifery services), and monitors for NAS with a modified version of the Finnegan Scale.

The decision to initiate treatment of opiate withdrawal with morphine sulphate is made if any one score is greater than 12, or the infant scores eight or more on three successive occasions.

The dose and schedule of morphine sulphate substitution is adjusted so as to maintain the daily Finnegan scores under eight, and then gradually reduced as the infant shows evidence of prospering.

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While research from our own service indicated that higher maternal methadone doses are associated with increased likelihood of NAS,¹³ debate on this issue exists in the literature.^{14,15} When NAS occurs, how long it lasts and how severe it becomes depends on many factors including other drugs used, the amounts used, when these were taken in relation to delivery, and the condition of the infant after birth.¹⁶ As a result of NAS, infants of methadone-maintained mothers may require prolonged hospitalisation,^{17,18} which in addition to disrupting family bonding, increases the costs to service providers.

Since the mid 1990s, buprenorphine (Subutex), a mixed agonist-antagonist has become increasingly available in Europe as an alternative to methadone. In 2002, legislative changes in Ireland allowed buprenorphine to be prescribed to non-pregnant people requiring substitution treatment. Whereas methadone is a full agonist at the mu-opiate receptor, and as formulated for use in Ireland, cannot be injected, buprenorphine is a partial agonist at the mu-receptor, an antagonist at the K-opiate receptor, and can be injected.

Research on adults suggests that buprenorphine may be easier to withdraw from than methadone.¹⁹ In addition buprenorphine may have advantages over methadone in pregnancy, as the incidence and severity of NAS appears to be less²⁰⁻²⁴ resulting in less distress to the infant and mother, and shorter hospital admissions. This may reflect the different receptor profile of buprenorphine.²⁵

More definitive evidence may come from the 'Mother Opioid Treatment: Human Experimental Research' project (MOTHER), the first large, multicentre, randomised, double-blind study to compare methadone and buprenorphine for the treatment of pregnant opiate-dependent pregnant women and the effect on the NAS.²⁶ Preliminary data suggests that buprenorphine results in improved birth outcomes and less neonatal abstinence syndrome relative to methadone.^{27,28}

In addition, whereas breast-fed infants of mothers who continue on methadone have been found to have less severe NAS and require as a result to be weaned off breast-feeds,²⁹ buprenorphine levels in breast milk have little or no effect on the NAS.³⁰ However as buprenorphine can be injected some argue that this undermines one of the main benefits of methadone, which is reducing injecting behaviour and the spread of blood-borne diseases.

To counter this abuse potential, buprenorphine has been combined with naloxone (Suboxone) in a 4:1 ratio. Naloxone, a pure opiate competitive antagonist with good parenteral but poor oral/sublingual bioavailability, will precipitate opiate withdrawal in opiate-dependent individuals when injected – this aversive effect lessens the risk of diversion and intravenous misuse. As a result, this combined buprenorphine preparation is likely to be the main alternative to methadone in Ireland.

Whilst teratology studies on animals reveal no embryogenic/teratogenic effects associated with methadone or buprenorphine, there are concerns of reproductive toxicity related to naloxone.³¹ Therefore women maintained on buprenorphine/naloxone who become pregnant should be switched over to buprenorphine when pregnancy is confirmed.^{31,32}

As the use of buprenorphine preparations to treat opiate-dependence becomes more established in Ireland,

conception and pregnancy while on buprenorphine treatment and the subsequent management of such pregnancies will also become more frequent.

Case report

Ms A grew up in a family with no known history of alcohol/substance misuse or psychiatric illness. She left school when she was 16 years old after passing the Junior Certificate and began working. Through associating with an older age group, she was introduced to illegal drugs. She first used heroin when she was 16 years old ('skin-popping') and quickly progressed to daily intravenous use of heroin (and cocaine). Soon she had moved out of the family home to become homeless. With the future father of her children, she spent three periods living homeless in a city in England.

During the first visit in 2000, she developed a femoral vein thrombosis, and commenced methadone maintenance treatment for the first time. On returning to Ireland, she completed a three-month outpatient detoxification, but relapsed and went back to England with her boyfriend. After several months of chaotic drug use, she self-detoxed and returned to Ireland, where she remained abstinent for about 18 months.

In 2004, she and her boyfriend returned to England for the last time. Again they lived a homeless drug-dependent lifestyle until Ms A was identified and engaged into treatment. During the assessment process, she discovered she was pregnant (and positive for hepatitis C).

Instead of methadone, she chose buprenorphine substitution treatment, and stabilised on 12mg. Emergency accommodation was arranged for her but not her partner, as he did not enter treatment, and subsequently they lost contact. Late in her pregnancy, Ms A decided to return to live with her parents in Dublin. In January 2005 as arranged, she presented for treatment to the Drug Treatment Centre Board. She was 21 years old and 36 weeks pregnant.

A decision was made to continue buprenorphine rather than switch to methadone due to her imminent delivery. Ms A was assigned a drug liaison midwife and linked in with the obstetric services.

Her urines were closely monitored and remained negative for all drugs of abuse. One month later she gave birth to a healthy baby. A few weeks later, on release from prison, her partner returned to live with her in Ireland.

Ms A continued buprenorphine maintenance treatment following the birth of her baby and became pregnant again after a few months. Early in her second pregnancy, Ms A complained of symptoms that she associated with opiate withdrawal. These settled on increasing the dose of buprenorphine incrementally to 16mg.

Late in this second pregnancy, her partner returned to England and unfortunately died from a brain haemorrhage. Ms A moved back to live with her parents, did not relapse and continued to give clean urines. She gave birth to her second child in early 2006. During both pregnancies, she abstained from alcohol, and tried to smoke less than 10 cigarettes per day.

Neonatal outcomes

Table 1 compares the birth parameters of these two infants. Both of this woman's pregnancies were without complication. Both infants were delivered post-term, and

Table 1: Birth parameter comparison for baby one and baby two

Characteristic	Baby one Primigravida	Baby two Para 1+0
Mother's weight at booking	Not known	52kg
Exposed to buprenorphine	After conception	At conception (12mg)
Buprenorphine dose at delivery	12mg once daily	16mg once daily
Antenatal ultrasound	Normal	Normal
Gestational age	41 + 1	42
Delivered by	Spontaneous vaginal delivery	Induced vaginal delivery
Sex of infant	Female	Male
Weight of infant	3.24kg	3.6kg
Lowest weight	2.89kg	3.24kg
Length of infant (crown-heel)	49cm	51cm
Head circumference (32-37 cm)	35cm	35cm
Apgar score 1, 5 minutes	9, 10	9, 10
Maximum NAS score	9 (x 2)	16
Length of stay in Neonatal ICU	Not admitted	29 days
Length of substitution treatment	Not initiated	21 days – day 2 to day 23
Total length of hospital stay	5 days	30 days – ready for d/c D26
Six week check-up	Normal – weight 4.57 kg Head circum 37cm	Normal – weight 4.71 kg Head circum 38 cm

were healthy at delivery, with normal birth weights for gestational age relative to the mother's height (157cm) and weight. Neurodevelopmental examinations at six months were also normal. Neither infant was breastfed.

Baby one

This infant girl was a spontaneous non-instrumental vertex-vaginal delivery, during which the mother did not require analgesia. She developed mild symptoms of neonatal abstinence in the first day, with a maximum Finnegan score of nine on two occasions. These scores reflected mild irritability overnight due to mild tremors, sneezing, loose stools and secondary excoriation of the buttock area. Treatment for NAS was not required. By day five she was gaining weight, and was ready for discharge with her mother. The baby's weight on discharge was 2.84kg, and two weeks later was 3.25kg. At this check-up, the mother reported very occasional sweating episodes but no jitteriness.

Baby two

In contrast, baby two was induced at two weeks post-term. This delivery was more distressing for the mother, as on this occasion she required pethidine analgesia. The third stage of delivery took 35 minutes. The placental cord was around this infant's neck, but the baby was not distressed, cried at delivery, and Apgar scores were normal. Mild but significant symptoms of NAS developed within the first 24 hours (Finnegan Scores 6, 5).

On day two, this baby boy was admitted to the neonatal intensive care unit in order to facilitate the mother attending

her partner's cremation. The mother was subsequently discharged on day five.

Symptoms of NAS continued to increase during the second day (8, 4, 11) peaking at 15 by 42 hours, at which time substitution treatment with morphine sulphate was initiated (0.2mg every three hours). The dose was gradually reduced, and the interval between doses slowly extended, so that by day nine the infant was stable on 0.1mg every six hours and had reached a lowest weight of 3.24kg. With a gain of 10g by day 10, the interval was extended to eight-hourly, however the infant became distressed, but settled again on six-hourly doses.

During the next few days this regime was continued whilst the baby continued to put on weight. Detoxification was recommenced at day 16 and successfully completed on day 23. The total duration of treatment with morphine sulphate was 21 days. This period of detoxification was also complicated by a pseudomonas eye infection treated with topical gentamycin from day six, and augmented with fucidic acid from day 25. The infant was ready for discharge on day 26 (weight 3.84kg), but this was deferred until day 30 for non-medical reasons (weight 4.10 kg).

Discussion

This unique case history describes the neonatal outcomes of two infants delivered to a mother who successfully stabilised on buprenorphine substitution therapy. Unlike baby one, baby two had a prolonged hospital stay as a result of significant NAS. The duration of treatment was similar to the mean treatment period shown in a previous Irish study by

Coghlan and colleagues in the same maternity hospital.¹⁸ This study showed that the mean duration of treatment for an infant with NAS was 21.8 days (range 1-62 days); however, only six of the 43 infants reviewed were exposed to methadone alone, with a mean duration of treatment of 17 days.

The widely diverse degree of NAS between these two infants and the documented history of illicit drug abstinence by their mother, make it easier to appreciate that even in such ideal circumstances, it is not possible to predict the likelihood and degree of NAS a newborn might experience. Other factors must contribute to opiate related NAS, an area warranting further research.

Possible other factors contributing to the severity of NAS in baby two's case might include:

- Exposure to buprenorphine from conception
- As with methadone, the possibility of a dose effect. Early pregnancy symptoms can mimic withdrawal,¹⁷ and this may explain the mother's need for an increased dose in the first trimester
- Six days older at delivery – pre-term babies appear to be less effected by NAS, and reasons postulated include a shorter duration of exposure to drugs, and a less mature nervous system³³
- Labour was induced
- Pethidine was administered which may have contributed to opiate withdrawal
- Psychosocial stress factors related to the sudden death of the mothers partner. Perhaps she smoked more as a result of this unexpected event. Research has shown that nicotine can contribute to NAS in methadone-exposed neonates³⁴
- Did urine drug toxicology accurately reflect abstinence from illicit drugs? New clients to the addiction services initially provide twice weekly, and later weekly, random urine samples, which are tested for the presence of opiates, methadone, benzodiazepines, cocaine, amphetamine, cannabis and alcohol. Short acting non-benzodiazepine sedatives are not routinely screened for. However the duration of negative toxicology suggests that she was truly abstinent.

Conclusion

Buprenorphine treatment for pregnant opiate-dependent women compares favourably to methadone. As this case shows, widely diverse neonatal outcomes can still be expected with buprenorphine substitution in pregnancy even when only exposed to buprenorphine *in-utero*. As the use of buprenorphine preparations for substitution and maintenance becomes more established in Ireland, the need to manage buprenorphine-exposed neonates will become more common.

Declaration of Interest: None.

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