Original Article

Differences in hospital length of stay between neonates exposed to buprenorphine versus methadone in utero: A retrospective chart review

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Abstract

Introduction: Neonatal abstinence syndrome is a growing concern in neonatal intensive care units in rural and remote settings.

Methods: A retrospective chart review was conducted of 180 mother–infant dyads born with in utero exposure to buprenorphine (n=60), methadone (n=60) or to other opioids (n=60) to determine neonatal length of stay in hospital, number of days on morphine, day of life of initiation of morphine and the need for phenobarbital.

Results: The length of stay in hospital for neonates was 5.8 days shorter (95% confidence interval [CI] 6.1 to 8.5 days) for buprenorphine exposure in utero compared to methadone (P=0.001). For neonates requiring treatment for Neonatal abstinence syndrome, those with in utero exposure to buprenorphine required 6.1 fewer days (95% CI 2.5 to 9.7) of treatment with morphine than those exposed to methadone (P<0.0005). There were no statistically significant differences in day of life of initiation of morphine therapy for each of the study groups. The proportion of neonates requiring adjuvant therapy with phenobarbital was statistically significantly higher in neonates exposed to methadone in utero than either buprenorphine or illicit opioids (P<0.0005).

Conclusions: Retrospective data suggest that neonates with in utero exposure to buprenorphine experience a shorter length of stay in hospital, fewer days of treatment with morphine for neonatal abstinence syndrome, and less use of phenobarbital than neonates exposed in utero to methadone. This suggests that Ontario provincial guidelines should be updated to recommend buprenorphine as first line for replacement therapy in pregnancy.

Keywords: *Buprenorphine; Methadone; Neonatal abstinence syndrome; Opioid dependence; Pregnancy.*

Canada is in the midst of an epidemic of prescription opioid abuse, the effects of which are seen in neonatal intensive care units where there are rising admission rates for neonatal abstinence syndrome (NAS). In Ontario, rates of NAS rose from

approximately 1 per 1,000 live births in 2002/2003 to 6 per 1,000 live births in 2015/2016 (1). NAS refers to the cluster of withdrawal symptoms that occurs due to fetal exposure to opioids during pregnancy. The duration and severity of NAS

symptoms vary with the half-life of the opioid with longer acting opioids tending toward a longer duration of symptoms. There is no conclusive evidence that NAS has been associated with long-term neurodevelopmental harms in children, whereas ongoing maternal substance use is associated with poor child development outcomes (2).

Although NAS is time-limited, it can result in prolonged and costly stays in hospital and in the neonatal intensive care unit. In 2015 to 2016, approximately 32 hospital beds per day were occupied by infants suffering from NAS (1). Additionally, NAS disproportionately affects infants born in northern Ontario, particularly those born in First Nation communities, further increasing the health care burden in communities that are already underserved (3).

Methadone treatment (MT) is currently the gold standard for managing opioid dependence during pregnancy. In opioid-dependent pregnant women, MT is associated with increased antenatal care, improved fetal growth, decreased mortality and fewer complications compared to ongoing opioid abuse (4–6). This has contributed to the development of several Ontario and Canadian guidelines recommending the use of MT as a cost effective and safer alternative for use in opioid-dependent mothers (4–8). The majority of NAS is caused by maternal MT in pregnancy, however, the severity of NAS symptoms is independent of the maternal dose (9–11).

Buprenorphine treatment (BT) is an alternative to MT that has been shown to be effective in the management of opioid dependence in pregnancy with a lower overdose risk compared to methadone (4,12–14). There is no significant difference between BT and MT in terms of potential maternal side effects. Several studies of NAS following BT, including a double-blinded randomized controlled trial, showed that buprenorphine use in pregnancy is associated with significantly less neonatal morphine treatment, an approximately 7-day shorter stay in hospital, and an approximately 5-day shorter duration of treatment for NAS compared to MT (15–20). Buprenorphine has also been shown to have less fetal cardiac and movement suppression than methadone (4,21,22), improved neonatal growth parameters (23) and less severe NAS symptoms (22,24,25). Unlike methadone, Health Canada does not require an exemption for prescribing buprenorphine, making it more accessible in remote communities (4). Methadone requires a special physician prescribing license and licensed pharmacy; therefore, it is not available in remote Northern communities. Buprenorphine is primarily offered through community suboxone programs run by individual First Nations in these communities (3,26).

Of the approximately 1,500 deliveries per year at the Thunder Bay Regional Health Sciences Centre (TBRHSC), up to 30% of the mothers are opioid exposed (Perschino N., 2014, Personal Communication). The catchment area of the hospital includes women who reside in urban, rural and remote communities including a large Indigenous population. The pattern of opioid

use and routes of administration also differ from that reported in previous studies in this area—prescription opioid misuse is common compared to heroin use which is rare (3). Current data indicate that, among neonates exposed to opioids in utero, approximately 7% require admission to neonatal intensive care units for medical management of NAS followed by an inpatient stay on the paediatrics unit (15).

This retrospective chart review aims to determine the hospital length of stay and medical treatment for neonates exposed to opioids in utero at a tertiary referral centre that serves a large rural and remote population as well as a large Indigenous population.

METHODS

Participants

A retrospective chart review to identify neonates exposed to opioids in utero admitted to the TBRHSC from January 1, 2012 to December 31, 2014 determined via a search of the electronic medical records. Three groups of 60 randomly selected mother–infant dyads were included in the study. Grouping was determined by the type of in utero opioid exposure: methadone, buprenorphine or non-methadone/non-buprenorphine opioids. Neonates with major congenital anomalies, significant metabolic or genetic conditions, who were less than 37-week gestational age (preterm), or who were born to mothers with severe pre-eclampsia were excluded from the study.

Data collection

A data abstraction form was used to collect retrospective data from the electronic and paper medical records available at the TBRHSC.

The following maternal data was collected: maternal age, ethnicity, antenatal care, social and community services accessed during pregnancy, highest level of education achieved, other illicit drug use, other prescription medication use, maternal weight, antenatal serologies, maternal hepatitis C status, past medical history, mental health history, child protective services involvement, length of stay in Thunder Bay, maternal length of stay in hospital and maternal residence (postal code). The following neonatal data was collected: birth weight gestational age, head circumference, Apgar score at 1 minute, Apgar score at 5 minutes, cord gas pH, cord gas base excess and apprehension of the child by child protective services. The primary outcome for the study was length of stay in hospital for the newborn. Secondary outcomes included day of life of initiation of treatment with morphine, need for adjuvant medication during treatment of NAS (phenobarbital) and number of days on morphine.

Statistical analysis

A Monte Carlo simulation was used to estimate the sample size necessary to achieve a power close to 95%, which suggested a minimum sample size of 47 neonates in each group (27). A Shapiro-Wilk test, Levene's test of homogeneity of variability

and boxplots were conducted to determine if the data could be considered equivalent to normal distribution. Categorical variables are presented as percentages while continuous variables are presented as a mean with 95% confidence intervals (CI). Group comparisons were performed using a one-way analysis of variance for continuous variables with Games-Howell post hoc analysis. Group comparisons were performed using a Pearson chi-square test with pairwise comparisons for post hoc analysis for categorical variables. Data analysis was performed with SPSS statistical software Version 20 (SPSS Inc., Chicago, IL). A P value less than 0.05 indicated statistical significance.

Ethics

Ethics approval was granted by the TBRHSC and the Lakehead University Research Ethics Boards.

RESULTS

A total of 1,367 infant—mother dyads were identified that met search criteria (see Figure 1) with other dyads excluded for multiple reasons. Random selection and chart review stopped after 60 charts were included in each group. Thus, only 931 of the 1,367 charts randomly selected were screened. Primary and secondary outcome data was available for all the participants. Demographic data were incomplete for some of the variables.

Demographic data collected for participants are detailed in Tables 1 and 2. There were no statistically significant differences between the groups in terms of maternal medical conditions including diabetes, hypertension, mental health concerns, gestational diabetes and nonsevere pre-eclampsia. A smaller proportion of the buprenorphine group had positive antenatal

serologies for hepatitis B or C, 1.7% (1), versus the methadone group, 25.4% (15), $P=0.001$. The mode of delivery was similar between each group with no statistically significant differences in Caesarean section rates and operative delivery rates. The percentage of families involved with the hospital social worker was around 90% for all groups. A smaller proportion of the buprenorphine group were involved with child protective services, 31.7% (19), versus the methadone group, 75% (45), $P<0.001$. However, rates of infant apprehension after delivery were 1.7% in the buprenorphine group, 11.7% in the methadone group and 5% in the other opioid group, which was not statistically significant.

The outcome data for the study are detailed in Table 3. The average length of stay in hospital for neonates with in utero exposure to methadone was 14.5 days (95% CI 11.9 to 17.1), to buprenorphine was 8.7 days (95% CI 7.3 to 10.1) and to non-buprenorphine, non-methadone opioid was 7.3 days (95% CI 6.1 to 8.5). There was a 5.8 day (95% CI 5.1 to 8.5) shorter length of hospital stay for neonates exposed to buprenorphine compared to methadone ($P=0.001$). There were no statistically significant differences between the buprenorphine and the non-buprenorphine, non-methadone opioid exposure groups.

There were no statistically significant differences in day of life of initiation of morphine therapy for different in utero exposure to opioids. On average, morphine therapy was started on day of life 2 ($P=0.122$). Regardless of the type of opioid exposure, maternal length of stay in hospital was 4 to 5 days, thus, infants and mothers can be separated for up to 5 to 12 days. Of the 180 neonates in this study, 79 received morphine treatment for NAS: 35 (44%) were exposed to methadone, 25 (32%) were exposed to buprenorphine and 19 (24%) were exposed to a non-buprenorphine, non-methadone opioid.

Figure 1. Data flow chart for participant inclusion.

Table 1. Maternal demographic data

Variable		Buprenorphine	Methadone	Other opioids	P value Buprenorphine vs. methadone	P value Buprenorphine vs. other opioids
Maternal Age (years)		25.2 (23.9–26.4)	27.0 (25.8–28.1)	24.0 (22.5–25.5)	0.142 ^c	0.461 ^c
Maternal Weight (kg)		70.3 (66.3–74.4)	72.6 (68.4–76.9)	72.0 (66.9–77.2)	0.766 ^c	
Education ⁺	Elementary School	27 (79.4%)	11 (44%)	25 (69.4%)	0.003 ^{*,a}	>0.05 ^a
	High School	6 (17.6%)	14 (56.0%)	7 (19.4%)	0.003 ^{*,a}	>0.05 ^a
	College	1 (2.9%)	0 (0.0%)	4 (11.1%)	>0.05 ^b	>0.05 ^b
	Data Missing	26 (43.3%)	35 (58.3%)	24 (40%)	N/A	
Ethnicity by self-report	Caucasian	1 (1.7%)	10 (16.7%)	5 (8.3%)	0.015 ^{*,a}	>0.05 ^a
	Indigenous	59 (98.3%)	50 (83.3%)	55 (91.7%)	0.015 ^{*,a}	>0.05 ^a
Community	Urban	5 (8.3%)	43 (71.7%)	21 (35%)	<0.001 ^{*,a}	<0.001 ^{*,a}
	Rural/remote	55 (91.7%)	17 (28.3%)	39 (65%)	<0.001 ^{*,a}	<0.001 ^{*,a}
Prescription Medications ⁺	Present	13 (92.9%)	28 (90.3%)	18 (81.8%)	1.000 ^b	0.628 ^b
	Data Missing	46 (76.7%)	35 (58.3%)	38 (63.3%)	N/A	
Cigarettes		49 (87.5%)	53 (93.0%)	55 (94.8%)	0.334 ^a	0.334 ^a
Alcohol		3 (5.4%)	6 (10.5%)	8 (13.8%)	0.490 ^b	0.204 ^b
Marijuana		5 (8.9%)	14 (24.6%)	17 (29.3%)	>0.05 ^a	0.021 ^a
Illicit Prescription Opioids		23 (41.1%)	26 (45.6%)	53 (91.4%)	>0.05 ^a	<0.005 ^a
Cocaine		2 (3.6%)	8 (14.0%)	5 (8.6%)	0.145 ^a	0.145 ^a
Other Illicit Drugs		3 (5.4%)	3 (5.3%)	3 (5.2%)	1.000 ^b	1.000 ^b

Data are n (%) or mean (95% CI) unless otherwise specified, ^a Pearson chi-square test used, ^b when assumptions for the Chi-squared test were not met multiple Fisher's Exact test were used, ^c one-way analysis of variance with Tukey post hoc analyses used, * Bold values are statistically significant difference $p < 0.05$, + more than 50% of the data is missing.

Table 2. Neonatal characteristics

Variable		Buprenorphine	Methadone	Other Opioids	P value Buprenorphine vs. methadone	P value Buprenorphine vs. other opioids
Gestational Age (weeks)		39.5 (39.3–39.7)	39.2 (38.9–39.5)	39.3 (39.0–39.6)	0.425 ^c	
Birth Weight (g)		3,711 (3,587–3,836)	3,346 (3,214–3,477)	3,493 (3,372–3,613)	+366 (157–575), P<0.0005 ^{*,c}	+219 (8.7–429), P=0.039 ^{*,c}
Head Circumference (cm)		35.2 (34.9–35.6)	34.2 (33.7–34.6)	34.8 (34.4–35.2)	+1.1 (0.4–1.8), P=0.001 ^{*,c}	0.221 ^c
Apgars at 1 min of life		9 (4–9) ^d	9 (2–9) ^d	9 (1–9) ^d		N/A ^e
Apgars at 5 min of life		9 (7–10) ^d	9 (7–9) ^d	9 (2–9) ^d	0.132 ^e	

Data are n (%) or mean (95% CI) unless otherwise specified, ^a Pearson chi-square test used, ^b when assumptions for the chi-squared test were not met multiple Fisher's Exact test were used, ^c one-way analysis of variance with Tukey post hoc analyses used, ^d median (range), ^e Mann–Whitney test were used * Bold values are statistically significant difference $P < 0.05$.

The required days of treatment with morphine for neonates with in utero exposure to methadone were 10.4 days (95% CI 7.7 to 13), to buprenorphine was 4.3 days (95% CI 2.9 to 5.6) and

to non-buprenorphine, non-methadone opioids was 3 days (95% CI 1.7 to 4.3). There were 6.1 (95% CI 2.5 to 9.7 days) fewer days of treatment with morphine for those exposed to buprenorphine

Table 3. Outcome measures

Variable	Buprenorphine	Methadone	Other opioids	Difference (P value) Buprenorphine vs. methadone	Difference (P value) Buprenorphine vs. other opioids
Length of Stay (days)	8.7 (7.3–10.1)	14.5 (11.9–17.1)	7.3 (6.1–8.5)	–5.8 (P=0.001^{a,b})	+1.4 (P=0.315 ^b)
Number of Days on Morphine (days)	4.3 (2.9–5.6)	10.4 (7.7–13.0)	3.0 (1.7–4.3)	–6.1 (P<0.001^{a,b})	+1.3 (P=0.376 ^b)
Day of Life of Initiation of Morphine	2.6 (2.2–3.0)	1.9 (1.4–2.5)	2.0 (1.5–2.4)	+0.7 (P=0.122 ^b)	+0.6 (P=0.122 ^b)
Adjuvant Medication (Phenobarb)	4 (6.7%)	21 (35%)	3 (5.0%)	–17 (P<0.001^a)	+1 (NS ^a)

Data are n (%) or mean (95% CI) unless otherwise specified, ^a Pearson chi-square test used, ^b one-way analysis of variance with Tukey post hoc analyses used, * statistically significant difference P<0.05. NS Bold values are statistically not significant difference or P>0.05.

compared to methadone (P<0.001). There were no statistically significant differences between the buprenorphine and the non-buprenorphine, non-methadone opioid exposure groups.

Neonates requiring adjuvant therapy with phenobarbital included 21 (75%) with in utero exposure to methadone, 4 (14%) with in utero exposure to buprenorphine and 3 (11%) with in utero exposure to non-buprenorphine, non-methadone opioid. The proportion of neonates requiring adjuvant therapy with phenobarbital was statistically significantly higher in neonates exposed to methadone in utero than in either the infants exposed to buprenorphine or non-buprenorphine, non-methadone opioids, P<0.001. There were no other statistically significant differences between groups.

DISCUSSION

The primary purpose of this study was to assess the differences between in utero exposure to buprenorphine and methadone, which is the current opioid replacement therapy recommended by the Provincial Council for Maternal and Child Health and the College of Physician and Surgeons of Ontario clinical practice guidelines as well as the Canadian Paediatric Society (5–7). The inclusion of a third group, those exposed to non-buprenorphine, non-methadone opioids in utero, was intended to provide a real-world comparator as not all women who misuse opioids are engaged in a treatment program. This group is heterogeneous in terms of the type, frequency and timing of exposure (26). As a result, outcomes for this group were similar to the buprenorphine group when looking at primary and secondary outcomes but differ when looking at measures such as birth weight, head circumference and APGAR scores.

This study was powered to detect differences between lengths of stay in hospital for neonates. It also looked at three secondary outcomes. Our results show that buprenorphine use in pregnancy is associated with an approximately 6-day shorter stay in

hospital, an approximately 6-day shorter duration of treatment for NAS and statistically significantly less adjuvant therapy with phenobarbital compared to methadone. There were no statistically significant differences noted for different in utero exposures to opioids for day of life of initiation of morphine.

While there were no statistically significant differences between groups in terms of concurrent substance use, it is important to note that our study population has a high rate of concurrent alcohol (5 to 11%), marijuana (9 to 25%), cocaine (4 to 14%) and illicit prescription opioid use (41 to 46%) which is specific to the population included in this study.

There were some statistically significant differences between the groups which were unlikely to have biased the results presented above. The mothers with exposure to buprenorphine during pregnancy were more likely to be Indigenous, more likely to live in a remote or rural community, less likely to be involved with child protective services and less likely to have attained high school education than those exposed to methadone as determined from self-reports documented on the provincial antenatal record. These differences are likely due to the use of buprenorphine primarily through community suboxone programs run by individual First Nations, whereas mothers living in Thunder Bay are typically on methadone therapy. These results are unlikely to affect the primary outcome as neonates are routinely admitted until they are completely weaned off morphine therapy, regardless of maternal social concerns.

There were some statistically significant differences between the groups which may have biased the results presented above. First, the higher rates of maternal hepatitis C in the methadone group compared to the buprenorphine group (25% versus 2%) may confound the study results as individuals with hepatitis C are more likely to have used intravenous drugs, and thus, have more severe opioid dependence (28). Second, neonates exposed to buprenorphine in utero versus methadone, were on average larger for

gestational age and were more likely to be Indigenous. Regional health data suggests that these two variables may be related. The North West LHIN has the highest proportion of Indigenous people (19.8%) (29), the lowest rate of small for gestational age infants (6.8% compared to a provincial average of 9.4%) and the highest rate of large for gestational age infants (16.3% compared to a provincial average of 10.0%) in Ontario (30).

The results of this study are consistent with a larger double-blinded randomized controlled study of 175 pregnant women by Jones et al in 2010 (16) which showed that buprenorphine use in pregnancy is associated with a 7-day shorter length of hospital stay and a 6-day shorter duration of treatment with morphine compared to methadone. This study, and others done previously, primarily included women addicted to heroin from inner city populations who had significant improvements in their socioeconomic status and health when they were started on any medical management for opioid addiction (15–25,31). The population serviced by the TBRHSC is mainly women dependent on prescription opioids from remote Northern communities that do not have significant changes in their socioeconomic status with initiation of medical management for their opioid addiction (3). Thus, it was difficult to extrapolate the results of prior studies to the population serviced in Northern Ontario.

Our current study results, in conjunction with previous larger prospective studies conducted in the USA, create a more compelling argument for changing the current provincial practice guidelines and the recent Canadian Paediatric Society practice point to recommend buprenorphine as first line therapy in opioid-dependent women during pregnancy. Any measures that decrease length of stay can improve resource utilization, enhance bonding with parents, facilitate return to the community of origin, and improve quality of life for these mothers and infants. Further research should be conducted into the day of life of initiation of morphine therapy and neonates requiring treatment for NAS to further inform guidelines.

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References

- Ordean, A. Neonatal Abstinence Syndrome Clinical Practice Guidelines 2016 [Internet]. Provincial Council for Maternal and Child Health; February 1, 2017. <<http://www.pcmch.on.ca/wp-content/uploads/2017/02/NAS-Webinar-Presentation-Slides-2016.pdf>>. Accessed May 28, 2018.
- Ornoy A, Michailovskaya V, Lukashov I, Bar-Hamburger R, Harel S. The developmental outcome of children born to heroin-dependent mothers, raised at home or adopted. *Child Abuse Negl* 1996;20(5):385–96.
- Kelly L, Dooley J, Cromarty H, et al. Narcotic-exposed neonates in a first nations population in Northwestern Ontario: Incidence and implications. *Can Fam Physician* 2011;57(11):e441–7.
- Canada, Health Canada. Best Practices: Methadone Maintenance Treatment [Internet]. Ottawa, Ont.: Health Canada, 2002 (cited October 22, 2017). <<http://www.deslibris.ca/ID/250764>>. Accessed May 28, 2018.
- College of Physicians and Surgeons. Methadone Maintenance Treatment Program Standards and Clinical Guidelines [Internet]. 2011 (cited October 22, 2017). <<https://www.cpso.on.ca/uploadedFiles/members/MMT-Guidelines.pdf>>. Accessed May 28, 2018.
- Lacaze T, O'Flaherty P. Practice Point: Management of Infants Born to Mothers Who Have Used Opioids During Pregnancy. January 11, 2018. <<https://www.cps.ca/en/documents/position/opioids-during-pregnancy>> (cited February 17, 2018). Accessed May 28, 2018.
- Provincial Council for Maternal and Child Health. Neonatal Abstinence Syndrome (NAS) Clinical Practice Guidelines [Internet]. 2016. <<http://www.pcmch.on.ca/wp-content/uploads/2016/12/NAS-Clinical-Guideline-Update-2016Nov25.pdf>> (cited October 22, 2017). Accessed May 28, 2018.
- Wong S, Ordean A, Kahan M; Maternal Fetal Medicine Committee; Family Physicians Advisory Committee; Medico-Legal Committee; Ad hoc Reviewers; Special Contributors. Substance use in pregnancy. *J Obstet Gynaecol Can* 2011;33(4):367–84.
- Berghella V, Lim PJ, Hill MK, Cherpes J, Chennat J, Kaltenbach K. Maternal methadone dose and neonatal withdrawal. *Am J Obstet Gynecol* 2003;189(2):312–7.
- Cleary BJ, Eogan M, O'Connell MP, et al. Methadone and perinatal outcomes: A prospective cohort study. *Addiction* 2012;107(8):1482–92.
- McCarthy JJ, Leamon MH, Parr MS, Anania B. High-dose methadone maintenance in pregnancy: Maternal and neonatal outcomes. *Am J Obstet Gynecol* 2005;193(3 Pt 1):606–10.
- Handford C, Kahan M, Srivastava A, Cirone S, Sanghera S, Palda V. Buprenorphine/Naloxone for opioid dependence: Clinical practice guideline [Internet]. Centre for Addiction and Mental Health. 2011. <https://www.cpso.on.ca/uploadedFiles/policies/guidelines/office/buprenorphine_naloxone_gdlns2011.pdf> (cited October 22, 2017). Accessed May 28, 2018.
- Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev* 2014;(2):CD002207.
- Unger A, Metz V, Fischer G. Opioid dependent and pregnant: What are the best options for mothers and neonates? *Obstet Gynecol Int* 2012;2012:195954.
- Jones HE, Johnson RE, Jasinski DR, et al. Buprenorphine versus methadone in the treatment of pregnant opioid-dependent patients: Effects on the neonatal abstinence syndrome. *Drug Alcohol Depend* 2005;79(1):1–10.
- Jones HE, Kaltenbach K, Heil SH, et al. Neonatal abstinence syndrome after methadone or buprenorphine exposure. *N Engl J Med* 2010;363(24):2320–31.
- Kakko J, Heilig M, Sarman I. Buprenorphine and methadone treatment of opiate dependence during pregnancy: Comparison of fetal growth and neonatal outcomes in two consecutive case series. *Drug Alcohol Depend* 2008;96(1–2):69–78.
- Lacroix I, Berrebi A, Garipuy D, et al. Buprenorphine versus methadone in pregnant opioid-dependent women: A prospective multicenter study. *Eur J Clin Pharmacol* 2011;67(10):1053–9.
- Pritham UA, Paul JA, Hayes MJ. Opioid dependency in pregnancy and length of stay for neonatal abstinence syndrome. *J Obstet Gynecol Neonatal Nurs* 2012;41(2):180–90.
- Wachman EM, Newby PK, Vreeland J, et al. The relationship between maternal opioid agonists and psychiatric medications on length of hospitalization for neonatal abstinence syndrome. *J Addict Med* 2011;5(4):293–9.
- Salisbury AL, Coyle MG, O'Grady KE, et al. Fetal assessment before and after dosing with buprenorphine or methadone. *Addiction* 2012;107(Suppl 1):36–44.
- Thomas CP, Fullerton CA, Kim M, et al. Medication-assisted treatment with buprenorphine: Assessing the evidence. *Psychiatr Serv* 2014;65(2):158–70.
- Welle-Strand GK, Skurtveit S, Jones HE, et al. Neonatal outcomes following in utero exposure to methadone or buprenorphine: A national cohort study of opioid-agonist treatment of pregnant women in Norway from 1996 to 2009. *Drug Alcohol Depend* 2013;127(1–3):200–6.
- Coyle MG, Salisbury AL, Lester BM, et al. Neonatal neurobehavior effects following buprenorphine versus methadone exposure. *Addict Abingdon Engl* 2012;107(Suppl 1):63–73.
- Gaalema DE, Scott TL, Heil SH, et al. Differences in the profile of neonatal abstinence syndrome signs in methadone- versus buprenorphine-exposed neonates. *Addiction* 2012;107(Suppl 1):53–62.

26. Kelly L, Guilfoyle J, Dooley J, et al. Incidence of narcotic abuse during pregnancy in Northwestern Ontario: Three-year prospective cohort study. *Can Fam Physician* 2014;60(10):e493–8.
27. Landau S, Stahl D. Sample size and power calculations for medical studies by simulation when closed form expressions are not available. *Stat Methods Med Res* 2013;22(3):324–45.
28. Robinson JL. Vertical transmission of the hepatitis C virus: Current knowledge and issues. *Paediatr Child Health* 2008 ;13(6):529–41.
29. North West Local Health Integration Network. Aboriginal Health Programs and Services Analysis & Strategies [Internet]. DPRA Canada. 2010. <http://www.northwestlhin.on.ca/resources/~media/sites/nw/uploadedfiles/Home_Page/Report_and_Publications/NW%20LHIN%20Aboriginal%20Health%20Programs%20and%20Services%20Analysis%20and%20Strategy.pdf>. Accessed May 28, 2018.
30. Better Outcomes Registry & Network (BORN). Provincial Overview of Perinatal Health in 2011–2012 [Internet]. 2013. <<https://www.bornontario.ca/assets/documents/regionalreports/Provincial%20Overview%20of%20Perinatal%20Health%202011%20-%202012.pdf>> (cited October 22, 2017). Accessed May 28, 2018.
31. Jones HE, O'Grady KE, Johnson RE, Velez M, Jansson LM. Infant neurobehavior following prenatal exposure to methadone or buprenorphine: Results from the neonatal intensive care unit network neurobehavioral scale. *Subst Use Misuse* 2010;45(13):2244–57.