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Maternal opioid use disorder and neonatal abstinence syndrome in northwest Ontario: a 7-year retrospective analysis

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Introduction: Opioid use in pregnancy is increasing globally. In northwest Ontario, rates of neonatal abstinence syndrome (NAS) are alarmingly high. We sought to document the increasing rates of opioid exposure during pregnancy and associated cases of NAS over a 7-year period in northwest Ontario.
Methods: We conducted a retrospective chart review at the Sioux Lookout Meno Ya Win Health Centre catchment area (population 29 000) maternity program in northwest Ontario of mother–infant dyads of live births from Jan. 1, 2009, to Dec. 31, 2015. The Integrated Pregnancy Program provides maternal, neonatal and addiction care for obstetrical patients at the health centre. We collected data on prenatal opioid exposure due to illicit and opioid agonist therapy (OAT) from patient/prescription histories and urine toxicology reports. Rates of NAS (diagnosed as a Finnegan score > 7) were recorded retrospectively from neonatal hospital charts.
Results: There were 2743 live births during the study period. Opioid exposure occurred in 672 pregnancies (335 OAT, 337 illicit). The incidence of prenatal opioid exposure increased significantly between 2009 and 2012 (11.1% to 28.5%, $p < 0.001$) but remained relatively constant at around 30% thereafter. Despite this, absolute rates of NAS remained relatively stable, with an average of 22.2 cases per 1000 live births over the study period. In comparison, the North West Local Health Integration Network (LHIN) experienced an average of 52.8 cases of NAS per 1000 live births in 2009–2012. The incidence of NAS in our centre decreased significantly over the study period (17.6% of opioid-exposed pregnancies in 2009 v. 4.0% in 2015, $p = 0.001$). There was a gradual transition toward a preponderance of OAT- versus illicit-exposed pregnancies, increasing from 0% in 2009 to 76.9% in 2015 ($p < 0.001$).
Conclusion: Despite our continually increasing rates of opioid exposure in pregnancy, rates of NAS decreased annually and were substantially lower than those of our regional LHIN. In contrast to 2009, most opioid exposure in our region is now iatrogenic as a result of OAT. These improvements may be attributable in part to the rural community-based prenatal and addictions services developed in our catchment area.

Introduction : La consommation d'opioïdes pendant la grossesse est à la hausse dans le monde entier. Dans le nord-ouest de l'Ontario, le taux de syndrome de sevrage néonatal est alarmant. Nous avons tenté de documenter les taux croissants d'exposition aux opioïdes pendant la grossesse et les cas associés de syndrome de sevrage néonatal sur une période de sept ans dans le nord-ouest de l'Ontario.
Méthodes : Nous avons mené une étude rétrospective des dossiers des patientes du programme obstétrical de la région desservie par le Centre de santé Meno Ya Win de Sioux Lookout (population de 29 000), dans le nord-ouest de l'Ontario, et des naissances vivantes de la dyade mère–nourrisson pour la période du 1er janvier 2009 au 31 décembre 2015. Des soins maternels, néonataux et de traitement de la toxicomanie sont offerts aux patientes en obstétrique du Centre de santé dans le cadre d'un programme de soins intégrés pendant la grossesse. Nous avons obtenu des données sur

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l'exposition prénatale aux opioïdes due à la consommation d'opioïdes illégaux et aux traitements par agonistes opioïdes dans les antécédents des patientes, l'historique des médicaments prescrits et les rapports de toxicologie des dépistages urinaires. Le taux de syndrome de sevrage néonatal (diagnostiqué selon un score de Finnegan > 7) a été obtenu et consigné de manière rétrospective à partir des dossiers néonataux d'hôpitaux.

Résultats : Il y a eu 2743 naissances vivantes pendant la période de l'étude et 672 grossesses exposées aux opioïdes (335 aux traitements par agonistes opioïdes, 337 aux opioïdes illégaux). L'incidence de l'exposition prénatale aux opioïdes a augmenté de façon importante entre 2009 et 2012 (11,1 % à 28,5 %, $p < 0{,}001$), mais est ensuite demeurée relativement constante à environ 30 % par la suite. Malgré cela, le taux absolu de syndrome de sevrage néonatal est demeuré relativement stable, soit une moyenne de 22,2 cas par 1000 naissances vivantes pendant la période de l'étude. Par comparaison, le Réseau local d'intégration des services de santé (RLISS) du Nord-Ouest a enregistré une moyenne de 52,8 cas de syndrome de sevrage néonatal par 1000 naissances vivantes entre 2009 et 2012. L'incidence du syndrome de sevrage néonatal dans notre centre a diminué considérablement au cours de la période de l'étude (17,6 % de grossesses exposées aux opioïdes en 2009 contre 4 % en 2015, $p = 0{,}001$). Nous avons observé une transition graduelle vers la prépondérance des grossesses exposées aux traitements par agonistes opioïdes par rapport aux grossesses exposées aux opioïdes illégaux. Leur taux est passé de 0 % en 2009 à 76,9 % en 2015 ($p < 0{,}001$).

Conclusion : Malgré la croissance continue de l'exposition aux opioïdes pendant la grossesse, notre taux de syndrome de sevrage néonatal a diminué annuellement et était nettement inférieur au taux du RLISS de la région. Par comparaison à 2009, la plupart des cas d'exposition aux opioïdes dans notre région sont maintenant d'origine iatrogène et liés aux traitements par agonistes opioïdes. Ces améliorations pourraient s'expliquer en partie par la création de services communautaires de soins prénataux et de traitement de la toxicomanie en régions rurales dans notre circonscription hospitalière.

INTRODUCTION

Opioid use disorder is an increasing Canadian health and social issue. In 2014, 1 in 6 Canadian residents aged 15 years or more reported using opioid analgesics, 5.2% of whom reported abusing them.[1] In a 2015 report by the Canadian Centre on Substance Abuse, 15.7% of females aged 15 years or more had used prescription opioids in the previous year.[2] According to the 2009 Canadian Maternity Experiences Survey, 6.7% of pregnant women had used street drugs in the 3 months before conception, with 1% continuing to use throughout their pregnancy.[3]

Although a national concern, opioid abuse is not evenly distributed across Canada. Ontario and Nunavut have remarkably high rates of perinatal opioid abuse.[3] Remote First Nations communities in northwest Ontario have been particularly affected, experiencing an "epidemic" of opioid-related problems in recent years.[4]

Opioid use in pregnancy is particularly challenging clinically and is increasing globally. The rate of prenatal opioid abuse in the United States increased from 1.19 cases per 1000 deliveries in 2000 to 5.63 cases/1000 deliveries in 2009.[5] In northwest Ontario, opioid exposure has been documented to occur in up to 28.6% of pregnancies in the Sioux Lookout Meno Ya Win Health Centre (SLMHC) catchment area.[6] As a result, neonatal abstinence syndrome (NAS) is encountered in this postpartum patient population.[7,8] Neonatal abstinence syndrome refers to the varied constellations of withdrawal from maternal substances and medications, including opioid use in pregnancy. Its severity and monitoring are evaluated with a signs and symptom scoring system, commonly the Finnegan scoring system.[9] A broad set of symptoms involving the central and autonomic nervous symptoms, gastrointestinal system and respiratory system may be present, necessitating pharmacological treatment. Maternal opioid use increases complications of pregnancy, including pregnancy loss, poor growth and premature labour. Subsequent neonatal withdrawal requires treatment to manage poor feeding and irritability and to prevent seizures. It is unclear whether long-term pediatric neurodevelopment is affected.[10]

In Ontario, the incidence of NAS increased from 0.9 cases per 1000 deliveries in 2002/03 to 5.1 cases per 1000 deliveries in 2011/12[11] and has continued to increase since then, with an incidence of 7.0 cases per 1000 births reported in 2013. In northwest Ontario, the rates are alarmingly high. The incidence of NAS in the North West Local

Health Integration Network (LHIN) averaged 52.8 cases per 1000 deliveries from 2009 to 2012,[10] over 50 times the incidence in southern Ontario urban centres and 10 times the provincial rate.[12]

The SLMHC, a major centre of obstetrical care, serves 31 remote First Nations communities with a catchment population of 29 000 (1/10th of the population of the North West LHIN) in a rural geographic area of 385 000 km^2. This study examines the 7-year incidence of opioid use in pregnancy and subsequent NAS rates in the context of development of rural hospital and community programs that make opioid agonist treatment (OAT) and opioid tapering available to pregnant patients.

METHODS

Background

Since 2012, prenatal care at SLMHC has been delivered via a comprehensive, generalist model of care, known as the Integrated Pregnancy Program. In the program, rural physicians, nurses and counsellors provide prenatal, addiction, postnatal and whole-family care in a single setting. The same caregivers attend the deliveries and provide postnatal maternal and neonatal care. In addition, male partners are often involved in the program and are offered concurrent treatment for addiction-related concerns at prenatal visits. This integration of prenatal and addiction care was unique in Canada when introduced and has become the mainstay of our consistent approach to addiction care in pregnancy. It has required the local development of a standardized protocol for the delivery of prenatal care for opioid-exposed pregnancies, which includes increased ultrasonography monitoring and prenatal visits.[13] Postpartum patient care in the Integrated Pregnancy Program is coordinated with community-based programs, to which the family transitions on returning home.

Community programs for opioid use disorder were in place in over 20 of the 31 remote First Nations communities in the SLMHC catchment area throughout the study period. These programs combine traditional Indigenous healing practices and counselling with OAT treatment in an attempt to foster community involvement. The programs have been well received by the communities and have resulted in positive community-wide changes, including decreases in criminal charges and drug-related medical evacuations and increased school attendance.[14] The programs have a strong cultural presence, and aftercare includes traditional land-based activities and elder teachings where available.[15] A recent study of 6 of these programs showed high OAT retention rates (83.5% at 6 months) and high rates of negative results of urine drug screening (85%).[15]

Design and data sources

We conducted a retrospective chart review of all live births at the SLMHC from Jan. 1, 2009, to Dec. 31, 2015. Opioid exposure was recorded throughout pregnancy and was classified as exposure due to illicit drug use versus exposure due to OAT. Illicit exposure included nonprescribed opioids and street drugs, and OAT exposure included buprenorphine, buprenorphine–naloxone and methadone treatment. Data on prenatal opioid use were gathered from a combination of patient histories, electronic prescription records and urine toxicology results. The point at which women were started on an OAT program ranged from preconception to second trimester. Women on an OAT program who had positive urine test results for illicit opioids were included in the illicit-exposed group.

Neonatal abstinence syndrome was diagnosed with the Finnegan scoring system, in which neonatal pharmacological treatment is considered following 3 consecutive scores greater than 7.[9] We calculated rates of prenatal opioid exposure (illicit, OAT and total) for each of the 7 years from 2009 to 2015. Rates of NAS were also calculated and expressed relative to opioid-exposed deliveries as well as all live births regardless of exposure. We derived comparative Ontario rates from hospital discharge "most responsible diagnosis" data sources. We used the Pearson χ^2 test to compare rates of prenatal opioid exposure and NAS across time using IBM SPSS V.23 for Windows.

Ethics approval

Ethics approval for this study was obtained from the Sioux Lookout Research Review and Ethics Committee.

RESULTS

There were 2743 live births at the SLMHC during the study period. Rates of OAT and illicit drug use throughout pregnancy and associated cases of NAS across the study period are summarized in Table 1. Opioid exposure occurred in 672 cases, 337 of

Table 1: Incidence of prenatal opioid exposure and neonatal abstinence syndrome among live births at the Sioux Lookout Meno Ya Win Health Centre from 2009 to 2015

Variable	Year; no. (%) of live births							*p* value
	2009 *n* = 307	2010 *n* = 356	2011 *n* = 424	2012 *n* = 425	2013 *n* = 411	2014 *n* = 406	2015 *n* = 414	
Opioid exposure*	34 (11.1)	63 (17.7)	103 (24.3)	121 (28.5)	108 (26.3)	117 (28.8)	126 (30.4)	< 0.001
Type of exposure								
Illicit	34 (11.1)	58 (16.3)	93 (21.9)	61 (14.4)	35 (8.5)	27 (6.6)	29 (7.0)	< 0.001
OAT	0 (0.0)	5 (1.4)	10 (2.4)	60 (14.1)	73 (17.8)	90 (22.2)	97 (23.4)	< 0.001
OAT exposure in exposed neonates	0 (0.0)	5 (7.9)	10 (9.7)	60 (49.6)	73 (67.6)	90 (76.9)	97 (77.0)	< 0.001
Neonatal abstinence syndrome								
All neonates	6 (2.0)	7 (2.0)	12 (2.8)	14 (3.3)	12 (2.9)	5 (1.2)	5 (1.2)	0.3
Exposed neonates	6 (17.6)	7 (11.1)	12 (11.6)	14 (11.6)	12 (11.1)	5 (4.3)	5 (4.0)	0.001

OAT = opioid agonist therapy.
*$p < 0.001$ for comparison between 2009 and 2012; $p = 0.6$ for comparison between 2012 and 2015.

which were due to illicit drug use and 335 of which involved patients receiving OAT. In our region, buprenorphine is the main OAT medication used, and it accounted for 94% of cases of OAT exposure, with methadone accounting for the remaining 6%. Oxycodone and morphine accounted for 62% and 26%, respectively, of illicit exposures. After a rapid increase in rates of total opioid exposure between 2009 and 2012 (11.1% to 28.5%, $p < 0.001$), the incidence remained unchanged thereafter, remaining stable around 30% ($p = 0.6$) (Fig. 1).

There was a significant transition toward OAT over the study period ($p < 0.001$). In the initial year of the study, 2009, all cases of opioid exposure during pregnancy were as a result of illicit drug use (Fig. 1). From 2009 to 2011, the proportion of OAT-exposed pregnancies gradually increased, and OAT accounted for over 50% of exposed pregnancies from 2013 onward. In 2015, the final year of the study, 76.9% of prenatal opioid exposure was due to OAT.

Despite increasing rates of prenatal opioid exposure, our incidence of NAS relative to all live births remained relatively constant over the study period. The 7-year average rate of NAS was 22.2/1000 live births. Neonatal abstinence syndrome occurred in 2.2% (standard deviation 0.83%) of all live births over the study period (range 1.2% in 2014 and 2015 to 3.3% in 2012). When considering only the 672 opioid-exposed pregnancies, our rates of NAS decreased significantly over the study period (Fig. 2). In 2009, 17.6% of opioid-exposed infants received pharmacological treatment for NAS, compared to 4.0% by 2015 ($p < 0.001$) (Table 1). Over the study period, NAS occurred in 9.1% (standard deviation 4.7%) of all narcotic-exposed pregnancies.

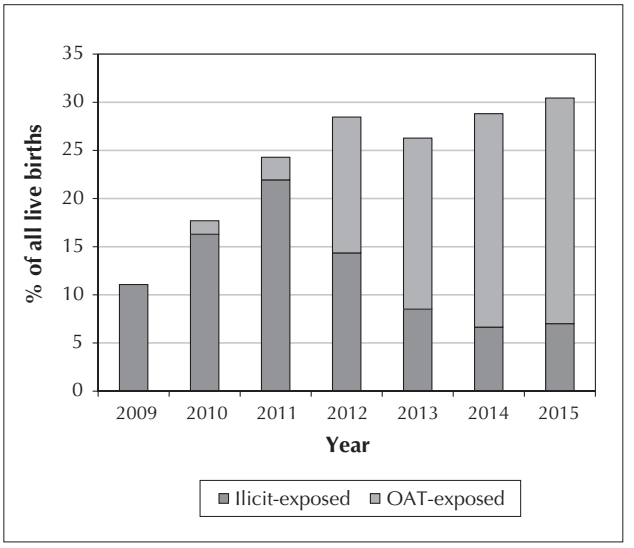


Fig. 1. Annual incidence of prenatal opioid exposure (illicit and opioid agonist therapy) as a proportion of all live births from 2009 to 2015. OAT = opioid agonist therapy.

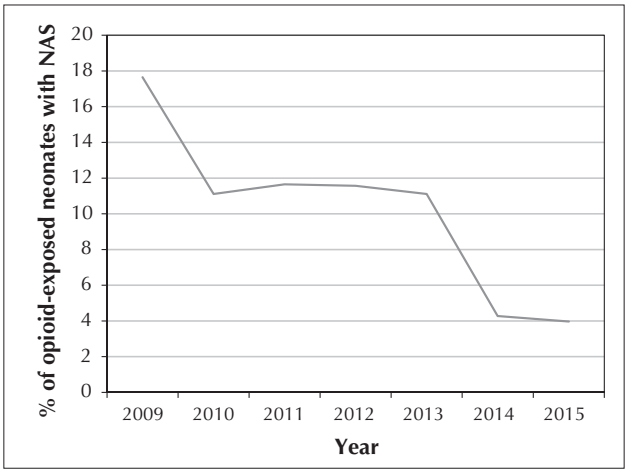


Fig. 2. Annual incidence of neonatal abstinence syndrome (NAS) as a proportion of opioid-exposed neonates from 2009 to 2015.

DISCUSSION

The incidence of opioid exposure during pregnancy in northwest Ontario is staggeringly high, remaining relatively stable at around 30% of all deliveries in 2012–2015. Despite the consistently high rates of prenatal opioid exposure, the incidence of NAS relative to opioid exposure decreased significantly over the study period, from 17.6% in 2009 to 4.0% in 2015.

The incidence of prenatal opioid exposure in our catchment area is notably higher than that in other regions of Canada and the US. In 2009 in the US, 5.63 per 1000 live births were complicated by opioid exposure.[5] According to the Canadian Maternal Experiences Survey, 1% of women nationwide use street drugs during pregnancy.[3] Nunavut had the highest reported incidence of prenatal street drug use, at 8.7%.[3] The incidence of opioid exposure, excluding other street drugs such as cannabis and cocaine, in our catchment area is 30 times that of the nation and 3.5 times that of the province with the highest rate (Ontario). What is of interest is the gradual change in our catchment population from opioid exposure due to illicit opioid use to prescribed, managed OAT exposure and a subsequent decline in NAS rates among opioid-exposed pregnancies. These findings parallel the development of local hospital and community programs that make OAT and opioid tapering available to pregnant patients.

Rates of NAS are increasing in most constituencies. In the US, the incidence increased from 1.2 cases per 1000 deliveries in 2000 to 5.8 cases per 1000 deliveries in 2012.[5,12] The highest incidence of NAS documented in the US was 16.2 cases per 1000 live births in Kentucky, Tennessee, Mississippi and Alabama.[16] In a 2012 report, the incidence of NAS in Canada was documented as 3.8 cases per 1000 live births.[17] Increasing rates of NAS have been reported in Ontario, from 0.28 cases per 1000 deliveries in 1992 to 5.1 cases per 1000 deliveries in 2011/12.[11,18] Rates of NAS in Ontario in 2012 were estimated at 5.1 cases per 1000 live births,[18] versus our incidence that year of 33 per 1000. The 7-year average incidence in our study was 22.2 per 1000 live births, high, but significantly lower than the regional average of 52.8 in the North West LHIN.[10]

Despite the decreasing rates of NAS in our opioid-exposed population over the study period, prenatal opioid use (and opioid use in general) remains a major public health concern. We believe that local community and hospital initiatives in our region have contributed to the significant reduction in the incidence of NAS and the transition to managed opioid exposure through OAT.

Buprenorphine–naloxone is a common first-line agent in community-based OAT programs in our region. This is due to both the unavailability of methadone in northern Indigenous communities and the increasing body of evidence supporting buprenorphine–naloxone as a better alternative to methadone.[19–21] Given the frequency of use of buprenorphine–naloxone in addiction treatment, women commonly conceive while they are receiving it. We found that women exposed to buprenorphine–naloxone had obstetrical outcomes (preterm delivery, congenital abnormality, cesarian delivery, postpartum hemorrhage, Apgar scores, NAS and birth weight) superior to those of women with ongoing illicit opioid use and equivalent to those for non–opioid-exposed pregnancies.[19–21]

Opioid agonist tapering in the third trimester became common practice in the Integrated Pregnancy Program in 2012. An 18-month study examining this practice conducted at our centre showed a significant reduction in the incidence of NAS, from 29.5% to 18.1% of opioid-exposed pregnancies ($p = 0.003$), as a result of the tapering protocol.[19] About half of the patients on the OAT program agreed to opioid dosage tapering in the third trimester and successfully stopped or decreased their total opioid dosage. OAT tapering in pregnancy is standard practice at SLMHC and is done with patient consent and close outpatient monitoring for withdrawal symptoms.

Limitations

Urine drug screening in patients receiving OAT has limitations. If a patient is already receiving methadone or buprenorphine–naloxone OAT, additional use of street methadone or buprenorphine–naloxone cannot be detected, as the test result will already be positive. In addition, we did not include the few pregnant patients who were prescribed narcotic medications for medical reasons in our analysis.

Many different NAS scoring systems exist, including the Finnegan, modified Finnegan and Lipsitz scores, which makes comparison of NAS rates between studies difficult. In the literature, the incidence of NAS is reported in several different ways, such as cases with a Finnegan score greater than 7, cases with NAS as the most responsible diagnosis and the presence of any NAS symptoms. Many studies did not identify their criteria for diagnosing NAS, which limited our ability to reliably compare our rates with provincial, national and global rates.

We limited our estimates of NAS to cases with a Finnegan score greater than *7*, in which pharmacological treatment is indicated, which is a common definition and likely best aligns with "most responsible diagnosis," used in many hospital discharge analyses. We avoided including the many neonates with lower scores, as such scores are more prone to interobserver variability and over- and underreporting. Our method allowed our estimates to be compared with those of studies that included only neonates who received pharmacological treatment.

A major limitation of this study is that it was not designed to determine the cause of the reduction in NAS rates. It was an observational study of the parallel development of rural hospital and community programs and decreasing rates of NAS in opioid-exposed pregnancies, documenting a temporal association.

CONCLUSION

Narcotic abuse continues to be a major health care concern in northwest Ontario, especially in the Indigenous population. Despite high rates of prenatal opioid exposure in the SLMHC catchment area, the incidence of NAS remains relatively low compared to regional rates. This may be due in part to our integrated, generalist approach to treating opioid use during pregnancy, use of buprenorphine–naloxone OAT and tapering OAT dosages in the third trimester. Our findings highlight the importance of a patient- and family-centred approach to treating opioid abuse during pregnancy, both in hospital and in the community, and the value of developing innovative rural programing.

REFERENCES

1. Health Canada. *Canadian Alcohol and Drug Use Monitoring Survey: summary of results for 2012*. 2014. Available: www.hc-sc.gc.ca/hc-ps/drugs-drogues/stat/_2012/summary-sommaire-eng.php#s4 (accessed 2018 Feb. 22).
2. Canadian drug summary: prescription opioids. Ottawa: Canadian Centre on Substance Abuse; 2015.
3. *What mothers say: the Canadian Maternity Experiences Survey*. Ottawa: Public Health Agency of Canada; 2009.
4. *Prescription drug abuse state of emergency*. Resolution 09/92. Nishnawbe Aski Nation; 2009.
5. Patrick SW, Schumacher RE, Benneyworth BD, et al. Neonatal abstinence syndrome and associated health care expenditures: United States, 2000–2009. *JAMA* 2012;307:1934-40.
6. 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:e493-8.
7. 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:e441-7.
8. Kelly L, Minty B, Madden S, et al. The occasional management of narcotic exposure in neonates. *Can J Rural Med* 2011;16:98-101.
9. Finnegan LP, Connaughton JF Jr, Kron RE, et al. Neonatal abstinence syndrome: assessment and management. *Addict Dis* 1975;2:141-58.
10. Finnegan L. *Substance abuse in Canada: licit and illicit drug use during pregnancy: maternal, neonatal and early childhood consequences*. Ottawa: Canadian Centre on Substance Abuse; 2013.
11. MHASEF (Mental Health and Addictions Scorecard and Evaluation Framework) Research Team. *The mental health of children and youth in Ontario: a baseline scorecard*. Toronto: Institute for Clinical Evaluative Sciences; 2015.
12. North West LHIN. Population health profile. 2014. Available: www.northwestlhin.on.ca/aboutourlhin.aspx (accessed 2018 Feb. 21).
13. Ryan G, Dooley J, Gerber Finn L, et al. Maternal–fetal monitoring of opioid-exposed pregnancies: analysis of a pilot community-based protocol and review of the literature. *J Obstet Gynaecol Can* 2017;39:443-52.
14. Kanate D, Folk D, Cirone S, et al. Community-wide measures of wellness in a remote First Nations community experiencing opioid dependence: evaluating outpatient buprenorphine–naloxone substitution therapy in the context of a First Nations healing program. *Can Fam Physician* 2015;61:160-5.
15. Mamakwa S, Kahan M, Kanate D, et al. Evaluation of 6 remote First Nations community-based buprenorphine programs in northwestern Ontario: retrospective study. *Can Fam Physician* 2017;63:137-45.
16. Patrick SW, Davis MM, Lehmann CU, et al. Increasing incidence and geographic distribution of neonatal abstinence syndrome: United States 2009 to 2012. *J Perinatol* 2015;35:650-5.
17. Dow K, Ordean A, Murphy-Oikonen J, et al. Neonatal abstinence syndrome clinical practice guidelines for Ontario. *J Popul Ther Clin Pharmacol* 2012;19:e488-506.
18. Turner SD, Gomes T, Camacho X, et al. Neonatal opioid withdrawal and antenatal opioid prescribing. *CMAJ Open* 2015;3:E55-61.
19. Dooley R, Dooley J, Antone I, et al. Narcotic tapering in pregnancy using long-acting morphine: an 18-month prospective cohort study in northwestern Ontario. *Can Fam Physician* 2015;61:e88-95.
20. Dooley J, Gerber-Finn L, Antone I, et al. Buprenorphine/naloxone use in pregnancy for treatment of opioid dependence: retrospective cohort study of 30 patients. *Can Fam Physician* 2016;62:e194-200.
21. Jumah NA, Edwards C, Balfour-Boehm J, et al. Observational study of the safety of buprenorphine + naloxone in pregnancy in a rural and remote population. *BMJ Open* 2016;6:e011774.

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