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Buprenorphine-naloxone use in pregnancy for treatment of opioid dependence

Retrospective cohort study of 30 patients

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Abstract

Objective To examine the maternal course and neonatal outcomes for women using buprenorphine-naloxone for opioid dependence in pregnancy.

Design Retrospective cohort study comparing outcomes for the group of pregnant patients exposed to buprenorphine-naloxone with outcomes for those exposed to other narcotics and those not exposed to narcotics.

Setting Northwestern Ontario obstetric program.

Participants A total of 640 births in an 18-month period from July 1, 2013, to January 1, 2015.

Main outcome measures Maternal outcomes included route and time of delivery, medical and surgical complications, out-of-hospital deliveries, change in illicit drug use, and length of stay. Neonatal outcomes included stillbirths, incidence and severity of neonatal abstinence syndrome, birth weight, gestational age, Apgar scores, and incidence of congenital abnormalities.

Results Thirty pregnant women used buprenorphine-naloxone for a mean (SD) of 18.8 (11.2) weeks; an additional 134 patients were exposed to other opioids; 476 pregnant women were not exposed to opioids. Maternal and neonatal outcomes were similar among the 3 groups, other than the expected clinically insignificant lower birth weights among those exposed to opioids other than buprenorphine-naloxone.

Conclusion Buprenorphine-naloxone appears to be safe for use in pregnancy for opioid-dependence substitution therapy. Transferring a pregnant patient to another opioid agonist that has greater abuse potential might not be necessary.

EDITOR'S KEY POINTS

- Opioid dependence is common in northwestern Ontario, and buprenorphine-naloxone is widely used in community-based opioid-replacement programs. Although efforts are made to ensure patients use contraception, some women become pregnant while taking buprenorphine-naloxone. Switching to another maintenance agent can present challenges. This study aimed to examine the outcomes of pregnancies exposed to buprenorphine-naloxone.
- The authors found that, within the context of an established prenatal program that values opioid tapering to decrease neonatal abstinence syndrome, buprenorphine-naloxone could be safely used in pregnancy. Maternal and neonatal outcomes were generally similar to those of pregnancies exposed to other opioids and those not exposed to opioids.
- Pregnancies exposed to buprenorphine-naloxone had significantly larger (normal) birth weights than pregnancies exposed to other narcotics did ($P=.004$), and more patients taking buprenorphine-naloxone were able to cease illicit opioid use in pregnancy ($P<.001$).

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Utilisation de la buprénorphine-naloxone durant la grossesse pour traiter la dépendance aux opiacés

Étude de cohorte rétrospective portant sur 30 patientes

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Résumé

Objectif Vérifier les issues maternelles et néonatales chez des femmes qui utilisent la buprénorphine-naloxone pour une dépendance aux opiacés.

Type d'étude Étude de cohorte rétrospective comparant les issues d'un groupe de patientes enceintes exposées à la buprénorphine-naloxone aux issues de patientes exposées de d'autres narcotiques et de celles d'autres patientes non exposées à des narcotiques.

POINTS DE REPÈRE DU RÉDACTEUR

- La dépendance aux opiacés est un problème fréquent dans le nord-ouest de l'Ontario et la buprénorphine-naloxone est souvent utilisée dans des programmes communautaires de sevrage des opiacés. Même si on s'efforce de convaincre les patientes d'utiliser un moyen de contraception, certaines deviennent enceintes alors qu'elles prennent la buprénorphine-naloxone. Le fait de changer pour un autre agent de maintien peut présenter certains risques. Cette étude voulait vérifier les issues des grossesses exposées à la buprénorphine-naloxone.

- Les auteurs ont observé que dans le contexte d'un programme prénatal bien établi qui vise à réduire graduellement la consommation d'opiacés afin de diminuer l'incidence du syndrome de sevrage néonatal, on pouvait utiliser la buprénorphine-naloxone de façon sécuritaire durant la grossesse. Les issues maternelles et néonatales étaient généralement semblables à celles des grossesses exposées à d'autres opiacés et à celles qui n'y avaient pas été exposées.

- Dans les grossesses exposées à la buprénorphine-naloxone, les poids de naissance étaient normaux et significativement supérieurs à ceux des grossesses exposées à d'autres narcotiques ($P=,004$); de même, plus de patientes prenant de la buprénorphine-naloxone avaient pu cesser de consommer des opiacés interdits durant leur grossesse ($P=,001$).

Cet article a fait l'objet d'une révision par des pairs.
Can Fam Physician 2016;62:e194-200

Contexte Le programme d'obstétrique du nord-ouest de l'Ontario.

Participantes Un total de 640 naissances au cours d'une période de 18 mois, du 1^{er} juillet 2013 au 1^{er} janvier 2015.

Principaux paramètres à l'étude Les issues maternelles comprenaient le type et la date de l'accouchement, les complications médicales et chirurgicales, les accouchements extrahospitaliers, les changements dans la consommation des drogues illégales et la durée de l'hospitalisation. Celles des nouveau-nés incluaient les mortalités, l'incidence et la gravité du syndrome de sevrage néonatal, le poids de naissance, l'âge de la mère, l'indice d'Apgar et l'incidence des malformations congénitales.

Résultats Trente femmes ont utilisé la buprénorphine-naloxone durant leur grossesse, pour une durée moyenne (DS) de 18,8 (11,2) semaines; un groupe additionnel de 134 patientes a été exposé à d'autres opiacés; enfin, 476 femmes enceintes n'ont pas consommé d'opiacés. Les issues maternelles et néonatales ont été semblables dans ces 3 groupes, à l'exception de la baisse cliniquement non significative des poids de naissance généralement observée chez celles qui ont été exposées à des opiacés autres que la buprénorphine-naloxone.

Conclusion La buprénorphine-naloxone utilisée comme traitement d'une dépendance aux opiacés semblerait sécuritaire. Il ne serait donc pas nécessaire d'en changer pour un autre agoniste opiacé comportant un plus grand risque d'abus.

Buprenorphine-naloxone is a commonly used maintenance medication for nonpregnant patients with opioid dependence.¹⁻⁵ It has been demonstrated to be a safe and effective opioid agonist in outpatient and primary care settings.¹⁻⁵ Recent evidence shows buprenorphine to be equivalent or superior to methadone in managing opioid dependence in pregnancy.^{6,7} Use of the combination of buprenorphine and naloxone in pregnancy is limited by concern about fetal exposure and possible withdrawal from the naloxone component of this medication.^{6,7}

In northwestern Ontario, where opioid dependence is an epidemic, buprenorphine-naloxone is widely used in community-based programs as opioid-replacement medication.⁸ In one community in our region, 41% of adults aged 20 to 50 years had taken this maintenance therapy in the preceding 2 years.⁹ This sublingual preparation is favoured in community-based addiction programs owing to its safety profile and efficacy.¹⁻⁵ The naloxone component is intended to deter diversion to an intravenous route and the buprenorphine component is effective for managing narcotic cravings.¹⁻⁵

Although efforts are made to ensure patients use contraception while taking buprenorphine-naloxone, some women with opioid dependence in our region become pregnant while participating in this maintenance program.^{9,10} The combination medication buprenorphine-naloxone is rated category C by the US Food and Drug Administration (potential benefits should outweigh the potential risk).¹¹ Once the pregnancy is known and brought to the attention of health care providers, a decision is made to continue with the buprenorphine-naloxone or switch the patient to another long-acting narcotic. Long-acting morphine and single-agent buprenorphine are common choices.¹²

As the MOTHER study in 2010 and a 2014 meta-analysis informed us of the efficacy and safety of buprenorphine in pregnancy, our study is in large part an observational study of naloxone exposure in early pregnancy in the context of community-based treatment of opioid dependence.^{7,13,14} Systemic absorption of low-dose sublingual naloxone is considered minimal owing to first-pass effect.^{15,16} Outside of research centres, there is no easily applied measure of fetal well-being beyond late pregnancy ultrasound, nonstress testing, and actual birth outcomes.^{17,18}

Our hypothesis is that buprenorphine-naloxone constitutes a safe harm-reduction strategy in pregnant women using opioids.

Our catchment area of 30 000 patients in northwestern Ontario includes 25 000 mostly First Nations patients in remote communities who receive their initial pregnancy care at the nursing stations in their communities.¹⁹ Methadone is not available in such remote areas, as there is no local prescribing or dispensing capacity.¹⁰

Changing a pregnant woman's opioid to single-agent buprenorphine requires sending written requests to Health Canada and the manufacturer, and it is usually weeks or months before the request is approved and the medication arrives. Because buprenorphine is not approved by Health Canada, the physician must receive and store the medication, rather than use commercial pharmacies. The alternative is a long-acting morphine preparation, which has been commonly used in our Integrated Pregnancy Program (IPP).¹² If the patient and physician decide to change from the prepregnancy maintenance use of buprenorphine-naloxone to another agent, there might be a prolonged delay for administrative reasons, or the patient might decide to continue taking buprenorphine-naloxone. The IPP is a multidisciplinary program supporting pregnant women, their partners, and their family members, with or without addictions.¹² It is a hospital outpatient clinic with nurses, counselors, physicians, and lactation consultants. The program has women from remote communities come to Sioux Lookout, Ont, for consultations during pregnancy and confinement for delivery. The program strives to provide comprehensive care to the family as a unit, including opioid-dependence treatment if needed. Opioid exposure during pregnancy occurs in up to 28% of pregnancies in our region.¹² Harm-reduction strategies include narcotic weaning in pregnancy to reduce the incidence of neonatal abstinence syndrome (NAS), as well as opioid-substitution therapy. The IPP program coordinates opioid-substitution therapy and aftercare with remote community-based addiction programs, which often involves use of buprenorphine-naloxone.⁹ This study documents a cohort of women using buprenorphine-naloxone during pregnancy and describes the course and outcomes of their pregnancies.

METHODS

In this retrospective cohort study, maternal and neonatal data were collected from the Sioux Lookout Meno Ya Win Health Centre IPP program and from obstetric program and hospital records between July 1, 2013, and January 1, 2015, on all births beyond 20 weeks. Primary neonatal outcomes were incidence of congenital anomalies, stillbirths, birth weight, gestational age, Apgar scores, and incidence of NAS. Primary maternal outcomes included out-of-hospital deliveries, medical and surgical complications, route and time of delivery, change in illicit drug use, and length of stay.

Data were analyzed using Excel and SPSS, and analyses included independent-samples *t* tests for continuous data and Pearson χ^2 or Fisher exact tests, as appropriate, for categorical data. The study group was women exposed to buprenorphine-naloxone during

pregnancy. Two comparison groups included pregnant women exposed to other narcotics during the same period and pregnant women not exposed to opioids. We used the nonexposed group as a normal control group and the group exposed to other narcotics to observe any outcomes in narcotic-exposed pregnancies that might vary as a result of exposure to buprenorphine-naloxone in particular. Ethics approval was granted by the Sioux Lookout Meno Ya Win Health Centre Research Review and Ethics Committee.

RESULTS

We collected data from all 640 deliveries from July 1, 2013, to January 1, 2015. There was a total of 164 narcotic-exposed pregnancies (25.6%), including 30 patients taking buprenorphine-naloxone at the commencement of their pregnancy (Table 1). The 164 patients in the narcotic-exposed group includes 34 patients who were taking opioid-replacement therapy at the time of conception (30 taking buprenorphine-naloxone and 4 taking other opioid agents) and 130 patients who were solely using illicit narcotics. Of the total group of narcotic-exposed (prescribed and illicit) pregnancies, all were offered opioid maintenance therapy and tapering during their pregnancy. Of the

combined 164 narcotic-exposed pregnancies, 56 (34.1%) decreased their dose of illicit narcotics and 73 (44.5%) had quit by the time of delivery. For those women who reported quitting, results were confirmed by point-of-care testing and confirmatory chromatography urine drug screening. The group-specific rates of illicit narcotic use at delivery are listed in Table 2.

Five women took buprenorphine-naloxone throughout their pregnancies and they had results similar to the nonexposed pregnancies, but also included 1 mild case of NAS and 1 postpartum hemorrhage. Three of these 5 had quit using any additional illicit drugs at the time of delivery, and opioid maintenance for all 5 was managed with an average of 4 mg (range 1 to 6 mg) of buprenorphine-naloxone at delivery. There were no cases of congenital anomalies or stillbirths among these 5 patients.

The larger group of women exposed to buprenorphine-naloxone ($n=30$, including the 5 described above) used the medication for a mean (SD) of 18.8 (11.2) weeks (Table 1). The mean (SD) exposure time was lower (15.9 [8.58] weeks) if the 5 women who remained on the medication throughout their pregnancies were excluded.

The comparison group exposed to other opioids ($n=134$) was composed primarily of 130 patients not taking pre-pregnancy substitution therapy, including 40 patients who managed their dependence through

Table 1. Maternal characteristics and outcomes

CHARACTERISTICS	A: EXPOSED TO BUPRENORPHINE-NALOXONE (N = 30)	B: EXPOSED TO OTHER OPIOIDS (N = 134)	P VALUE (A-B)	C: NOT EXPOSED TO OPIOIDS (N = 476)	P VALUE (A-C)
Mean (SD) age, y	26.1 (4.03)	25.4 (4.56)	.442	24.9 (6.17)	.296
Mean (SD) gravidity	4.4 (2.50)	3.9 (2.03)	.240	3.2 (2.22)	.004
Mean (SD) time taking buprenorphine-naloxone, wk	18.8 (11.20)	NA	NA	NA	NA
Initial mean (SD) dose of buprenorphine-naloxone, mg	9.2 (6.20)	NA	NA	NA	NA
Smoker, n (%)	25 (83.3)	113 (84.3)	.893	229 (48.1)	<.001
Alcohol use, n (%)	6 (20.0)	32 (23.9)	.649	98 (20.6)	.938
Type 2 diabetes, n (%)	2 (6.7)	3 (2.2)	.227	14 (2.9)	.244
Hypertension, n (%)	3 (10.0)	8 (6.0)	.424	29 (6.1)	.426
Hepatitis C, n (%)	1 (3.3)	7 (5.2)		1 (0.2)	.115
History of marijuana use, n (%)	4 (13.3)	49 (36.6)	.014	46 (9.7)	.514
Urine positive for THC, n (%)	4 (13.3)	35 (26.1)	.137	28 (5.9)	.104
Gestational diabetes, n (%)	3 (10.0)	13 (9.7)	.960	42 (8.8)	.742
Mean (SD) gestational age, wk	38.9 (1.48)	38.6 (1.60)	.348	38.9 (1.52)	>.999
Cesarean section, n (%)	5 (16.7)	35 (26.1)	.276	120 (25.2)	.293
Postpartum hemorrhage, n (%)	3 (10.0)	10 (7.5)	.708	44 (9.2)	.752
Mean (SD) LOS, d	3.0 (1.63)	2.7 (1.71)	.382	1.9 (1.13)	<.001
Out-of-hospital delivery, n (%)	1 (3.3)	3 (2.2)	.558	10 (2.1)	.493

LOS—length of stay, NA—not applicable, THC—tetrahydrocannabinol.

Table 2. Illicit opioid drug use at delivery

OPPIOID USE	WOMEN EXPOSED TO BUPRENORPHINE-NALOXONE (N=30), N (%)	WOMEN EXPOSED TO OTHER OPIOIDS (N=134), N (%)
Quit*	24 (80.0)	49 (36.6)
Decreased	3 (10.0)	53 (39.6)
Increased	0 (0.0)	1 (0.7)
No change	1 (3.3)	23 (17.2)
Unknown	2 (6.7)	8 (6.0)

*Significantly more women in the group exposed to buprenorphine-naloxone had quit using illicit opioids at delivery ($P < .001$).

illicit sources and declined ongoing offers of prescribed maintenance medication.

Neonatal outcomes were similar between the 3 groups with the exception of the expected clinically insignificant lower birth weights among the pregnancies exposed to other opioids (Table 3).

DISCUSSION

Our study found that, within the context of an established prenatal program that values opioid tapering to decrease NAS, buprenorphine-naloxone can be safely used in pregnancy. We also found that pregnancies exposed to buprenorphine-naloxone had significantly larger (normal) birth weights than pregnancies exposed to other narcotics did ($P = .004$), and more patients taking buprenorphine-naloxone were able to cease illicit opioid use in pregnancy ($P < .001$). Maternal outcomes were similar in all 3 groups in terms of route and time of delivery and medical and surgical complications (Table 1). Neonatal outcomes were also similar between the 3 groups, except for the expected clinically insignificant lower birth weights among the pregnancies exposed to other opioids (Table 3).

Few other studies report outcomes from buprenorphine-naloxone exposure in pregnancy.

A 2013 American retrospective study reported on 10 exposed women.²⁰ Eight of these women were already taking maintenance therapy at the time of conception, as was the case with the 30 participants in our study. A 2013 publication used data from the same 10 participants and compared them with data from other opioid-maintenance medication programs; the authors found outcomes similar to those for patients taking methadone or single-agent buprenorphine.²¹

Another 2015 study compared 31 mother-neonate dyads treated with buprenorphine-naloxone with a similar number of pregnancies treated with methadone maintenance. They demonstrated a 50% reduction in the incidence of NAS and an equal reduction in the length of stay for the buprenorphine-naloxone treated group.²² The average dose of buprenorphine-naloxone in this study was 14.4 mg, higher than our 9.2 mg average dose, but our dose was a maintenance dose for women already stable on the medication, not an induction dose. This study did not undertake narcotic weaning during the pregnancies and excluded any births with congenital anomalies. It also did not record the length of time or initiation point for maintenance in the pregnancy. The positive comparison to a similar methadone-maintained group gives a clear signal that buprenorphine-naloxone therapy is about to find its place in opioid-dependence treatment in pregnancy.

Our comparison groups were not chosen to systematically show the effect on outcomes of buprenorphine-naloxone exposure in pregnancy, but to demonstrate its place in an obstetric program dealing with a heavy load of opioid-dependent women. The buprenorphine-naloxone cohort in our study was heterogeneous, as its members underwent medication switching and tapering as clinically indicated or

Table 3. Neonatal characteristics and outcomes

NEONATAL CHARACTERISTICS	A: EXPOSED TO BUPRENORPHINE-NALOXONE (N=30)	B: EXPOSED TO OTHER OPIOIDS (N=134)	P VALUE (A-B)	C: NOT EXPOSED TO OPIOIDS (N=476)	P VALUE (A-C)
Preterm (<37 wk), n (%)	1 (3.3)	6 (4.5)	.799	19 (4.0)	.857
Mean (SD) birth weight, g	3569.0 (491.91)	3243.7 (557.2)	.004	3531.0 (590.2)	.730
Mean (SD) 1-min Apgar score	8.8 (0.47)	8.7 (1.05)	.611	8.6 (1.1)	.323
Mean (SD) 5-min Apgar score	9.0 (0.18)	8.9 (0.83)	.513	8.9 (0.71)	.442
Any NAS score, n (%)	6 (20.0)	22 (16.4)	.637	0 (0.0)	<.001
NAS score >7, n (%)	0 (0.0)	12 (9.0)	.126	0 (0.0)	>.999
Stillbirths, n (%)	0 (0.0)	1 (0.7)	>.999	3 (0.6)	>.999
Congenital anomalies, n (%)	1 (3.3)	0 (0.0)	.180	1 (0.2)	.115
Male sex, n (%)	15 (50.0)	74 (55.2)	.657	243 (51.1)	.911
Transfer to tertiary care, n (%)	1 (3.3)	5 (3.7)	>.999	9 (1.9)	.460

NAS—neonatal abstinence syndrome.

preferred by the patient throughout pregnancy. Despite this limitation, we did believe it was useful to describe this reasonably sized prospective cohort who took buprenorphine-naloxone during the first trimester of their pregnancies, even without an ideal comparison group.

We demonstrated very few differences among our comparison groups in this study. Because the group exposed to other narcotics included patients who refused any prescribed maintenance therapy and often continued their illicit narcotic use, this group had the lowest birth weights (3243.7 g, $P = .004$), below the Canadian average of 3300 g.²³ As expected, both exposed groups had longer lengths of stay ($P < .001$) and more of their neonates experienced some NAS symptoms ($P < .001$) than the neonates in the nonexposed group did. Neonatal abstinence syndrome in narcotic-exposed pregnancies seems to generally affect approximately 20% of our deliveries, with few affected neonates historically requiring pharmacologic treatment for Finnegan scores of 8 or greater, likely owing to narcotic tapering, which has become routine in our practice.^{8,12} A recent study of 94 methadone-maintained pregnant women demonstrated a rate of higher Finnegan scores requiring pharmacologic treatment at 26.6%, while only 7.3% of our opioid-exposed participants had Finnegan scores above 7.²⁴ This might be owing to our narcotic-dose tapering during pregnancy or lower doses of total opioid use at delivery.¹²

Rates of smoking were very high in both narcotic-exposed groups (more than 80%) and remained substantial in the nonexposed group as well (more than 50%), as has been seen in other studies in our region.^{25,26}

The finding that more of the women taking buprenorphine-naloxone quit illicit narcotic use ($P < .001$) likely reflects that the comparison group included a large number of patients who declined opioid substitution and tapering rather than any inherent attributes of the medication itself. Many in the comparison group chose to maintain their own approach to opioid dependence rather than accept prescribed opioid-substitution therapy, although more than 35% of them did quit illicit narcotics (Table 2).

The mean length of stay in both groups of opioid-exposed pregnancies is quite short, at 3 days or less. This contrasts with a recent study of methadone-maintained pregnancies with a mean stay of 15 days.²³ Many of our patients live in remote communities and stay in a hostel located next to the hospital. They are able to be seen daily as outpatients and some have maternal and neonatal outpatient dispensing of opioid-withdrawal medications in that setting.

This study demonstrates in a limited way the safety of buprenorphine-naloxone in pregnancy. Because the drug is useful for its resistance to diversion to intravenous abuse and its opioid agonist component has

a superior NAS profile than methadone, this combination medication might be a very useful medication in pregnancies complicated by opioid use disorder.¹²

Limitations


The opioid-exposed control and comparison groups were not homogeneous. This intention-to-treat prospective design followed the variable clinical course and patient preferences as negotiated throughout the pregnancy. In particular, most of those exposed to opioids other than buprenorphine-naloxone were not taking maintenance therapy before pregnancy, and many declined any substitution therapy during the pregnancy. It would stand to reason that they would have the greatest opioid-related effects and the lowest birth weights, which they did.

Small sample sizes such as those in our study are inadequate to comment on rare outcomes such as congenital anomalies, which would be the outcome of interest when examining medication exposure during the organogenesis period of the first trimester.

In a vast geographically dispersed region such as northwestern Ontario (which is the size of France), access to all commodities, including drugs of abuse, is intermittent. Both opioid-exposed groups had participants with ongoing illicit opioid use (20.0% of the buprenorphine-naloxone group and 63.4% of the group exposed to other opioids). We do not know the extent or effects of this withdrawal cycle experienced by ongoing illicit users resulting from variable availability of illicit opioids in these remote communities, many of which do not have road access.

Our outcomes are within the context of an established prenatal care program that values opioid tapering to decrease incidence of NAS. This treatment goal would affect the outcomes of both opioid comparison groups, although perhaps not equally, owing to patient preference.

Conclusion

Buprenorphine-naloxone appears to be safe in pregnancy. Larger prospective studies are warranted to understand the role it can play in the complex behavioural and chemical aspects of managing opioid use disorder in pregnancy. Transferring a pregnant patient to a different opioid agonist that has greater abuse potential might not be necessary. 

Drs Dooley, Gerber-Finn, Antone, and Guilfoyle are assistant professors in the Division of Clinical Sciences at the Northern Ontario School of Medicine in Sioux Lookout, Ont, and the Sioux Lookout Meno Ya Win Health Centre (SLMHC). **Ms Blakelock** is a researcher with the SLMHC. **Ms Balfour-Boehm** is a medical student at the Northern Ontario School of Medicine. **Ms Hopman** is a statistician in the Department of Community Health and Epidemiology at Queen's University in Kingston, Ont. **Dr Jumah** is Assistant Professor in the Division of Clinical Science at the Northern Ontario School of Medicine in Thunder Bay, Ont, a clinician researcher with the Thunder Bay Regional Research Institute, and an obstetrician-gynecologist at Thunder Bay Regional Health Centre. **Dr Kelly** is a researcher with the SLMHC.

Contributors

Dr Kelly prepared all drafts of the article and the study design. Dr Jumah participated in study design. Ms Balfour-Boehm and Ms Blakelock were research assistants who gathered the data and helped design the data collection tool. Drs Guilfoyle, Dooley, Antone, and Gerber-Finn and Ms Hopman participated in the original study design and data collection. All authors contributed to revising the article and approved the final draft.

Competing interests

None declared

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