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Short communication

Buprenorphine medication-assisted treatment during pregnancy: An exploratory factor analysis associated with adherence

Jessica L. Coker[a,*], David Catlin[b], Shona Ray-Griffith[a], Bettina Knight[a], Zachary N. Stowe[c]

[a] Departments of Psychiatry and Obstetrics and Gynecology, University of Arkansas for Medical Sciences, 4301 W. Markham Street, #843, Little Rock, AR, 72205 USA
[b] College of Medicine, University of Arkansas for Medical Sciences, 4301 W. Markham Street, Little Rock, AR, 72205 USA
[c] Department of Psychiatry, University of Wisconsin, 6001 Research Park Blvd, Madison, WI, 53719 USA

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ABSTRACT

Background: : The treatment of pregnant women with opioid use disorder is challenging due to the myriad of physical, mental, and social complications. Factors influencing adherence to buprenorphine during pregnancy have not been identified.

Materials and methods: : Pregnant women with opioid use disorder followed in a tertiary clinic were included in a retrospective chart review from buprenorphine induction through delivery. All women who had been evaluated and treated with buprenorphine from January 1, 2014, to September 31, 2016, were included. Adherence was defined as follows: 1) adherent: attended follow up visits, negative urine toxicology screens, and phase advancement; 2) moderately adherent: attended follow up visits until delivery, had not completed six negative urine toxicology screens, or had positive urine toxicology screens (i.e., no phase advancement); 3) non-adherent: missed follow up visits and did not stay in treatment until delivery. Sociodemographic characteristics, family psychiatric history, current and lifetime psychiatric and childhood trauma along with treatment factors were compared by category of adherence.

Results: : 64 women met criteria for inclusion in this study with 41 (64%) adherent; eight (13%) moderately adherent; and 15 (23%) non-adherent. In the non-adherent group compared to the adherent group, the clinician-rated opioid withdrawal scale score was significantly higher, and the daily buprenorphine dose at last visit was significantly lower.

Conclusions: : Women who were non-adherent to buprenorphine during pregnancy had higher severity of opioid withdrawal symptoms and lower doses of buprenorphine. These findings should be further explored with the goal of optimizing care without increasing risk for neonates.

1. Introduction

The national opioid crisis has increased attention on the treatment of pregnant women with opioid use disorder (OUD). Recent literature reports an increase in opioid prescriptions during pregnancy and parallels between an increase in the prevalence of OUD during pregnancy and the number of women seeking OUD treatment (Bateman et al., 2014; Desai et al., 2014; Martin et al., 2015). American College of Obstetrics and Gynecologists (ACOG), 2012 and World Health Organization (WHO), 2014 Treatment Guidelines recommend medication-assisted treatment (MAT) with methadone or buprenorphine (BUP) during pregnancy in women with identified OUD.

Treatment of OUD during pregnancy is largely based on the goals of increasing prenatal care, decreasing illicit substance use, and improving outcomes for infants compared to non-treated OUD. The landmark MOTHER study comparing maintenance medications for OUD in pregnancy demonstrated a significant difference in attrition between pregnant women randomized to methadone (n = 73 completers) versus buprenorphine (n = 58 completers) (Jones et al., 2010). Notably, 71% of the women in the buprenorphine group who dropped out reported being “dissatisfied” with buprenorphine. In order for treatment to be effective and attain the goals noted above, treatment adherence is essential. To our knowledge, factors influencing adherence to buprenorphine treatment during pregnancy have not been identified. The current study was a retrospective exploratory analysis of factors that may influence adherence to buprenorphine treatment during pregnancy.

* Corresponding author.
E-mail addresses: jlcoker@uams.edu (J.L. Coker), dmcatlin@uams.edu (D. Catlin), SLRaygriffith@uams.edu (S. Ray-Griffith), btknight@uams.edu (B. Knight), zstowe@wisc.edu (Z.N. Stowe).

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2. Material and methods

The Women's Mental Health Program (WMHP) at the University of Arkansas for Medical Sciences (UAMS) is located in a tertiary academic setting and receives referrals across the state for treatment of mental illness, including substance use disorders, during pregnancy and up to one year postpartum. A retrospective chart review of pregnant women with OUD treated with buprenorphine was performed including women who were treated as an outpatient from January 1, 2014, to September 31, 2016. Women were included if they had at least one outpatient appointment and were prescribed buprenorphine, but there were no other exclusion criteria. After referral to the WMHP, pregnant women with opioid use disorder on buprenorphine were clinically enrolled in a phase-advancement clinic that started as weekly visits during Phase 1, with advancement to subsequent phases (Phase 2 – bimonthly visits, Phase 3 – monthly visits) based on negative, observed urine toxicology for illicit substances as well as compliance with group therapy and follow-up visits for medication management. Every clinic visit included an observed urine drug screen, medication management with a psychiatrist, one-hour group therapy, and both patient (i.e., Subjective Opiate Withdrawal Scale) and clinician (i.e., Clinical Opiate Withdrawal Scale) rated scales of opioid withdrawal symptoms. This study was approved by the University of Arkansas for Medical Sciences Institutional Review Board.

Subjects were categorized into three groups: 1) adherent: attended follow up visits, negative urine toxicology screens, and phase advancement; 2) moderately adherent: attended follow up visits until delivery, had not completed six negative urine toxicology screens, or had positive urine toxicology screens (i.e., no phase advancement); 3) non-adherent: missed follow up visits and did not stay in treatment until delivery. This was an exploratory analysis of factors associated with buprenorphine success including lifetime psychiatric diagnoses [i.e., structured clinical interview (SCID-IV)], childhood trauma (i.e., Childhood Trauma Questionnaire), and sociodemographic characteristics. Continuous variables were compared using one-way ANOVA, and all other variables were compared separately by 1) adherent vs. moderately adherent and 2) adherent vs. non-adherent using the z-test to compare proportions (SigmaPlot).

3. Results

A total of 64 pregnant women with OUD and prescribed buprenorphine were included and were categorized as follows: 1) 41 (64%) adherent; 2) Eight (13%) moderately adherent, and 3) 15 (23%) non-adherent. There were no sociodemographic differences between the three groups. The findings were inconclusive as to whether or not an association was present for both comorbid psychiatric illness or childhood trauma (Table 1).

In the non-adherent group, examination of treatment-related variables demonstrated a significantly higher clinician-rated opioid withdrawal scale score at last visit ($p = 0.035$) and a lower daily dose of buprenorphine (mg/day) at last visit ($p = 0.006$) compared to the two adherent groups (Table 2). As expected, the non-adherent group also had a less total number of days in treatment and scheduled visits than the adherent groups.

4. Discussion

This study provided novel data on factors associated with adherence to buprenorphine treatment during pregnancy with a retention rate similar to those previously published in non-pregnant women (Kakko et al., 2003). We found significantly higher clinician-rated withdrawal scores and lower buprenorphine daily dose at the last visit suggesting that adherence during pregnancy in the current sample was influenced by the severity of withdrawal symptoms and clinical response (i.e., dosing strategy). It is feasible that non-adherent pregnant women may have left treatment prior to dose optimization. Adherent women had more days in treatment and more scheduled appointments compared to the other two groups that did not seem to be impacted by gestational time of enrollment. Our previous study in a non-pregnant population suggested that early childhood trauma was associated with adherence (Kumar et al., 2016); however, it was inconclusive that a history of childhood trauma or co-morbid psychiatric illnesses impacted adherence to treatment during pregnancy. Of importance, the majority of the women in this study did have a co-morbid psychiatric illness (range 71–100%) and childhood trauma (averaging low to moderate levels across all trauma types) that is congruent with biopsychosocial development models of substance use disorders.

Limitations include a small sample size that may not have allowed the detection of significant differences, specifically for co-morbid psychiatric illness and impact of childhood trauma. We were also limited by the inability to re-contact women to determine reasons for discontinuation in the treatment. There is no indication that participants informed clinicians they were dissatisfied with treatment prior to non-adherence.

In order to optimize adherence to treatment during pregnancy, these data suggested that more aggressive buprenorphine dosing strategies early in treatment targeting rapid control of withdrawal symptoms may enhance adherence through delivery. In this current study, dosing was not based on a standard protocol, and medication was increased based on clinical assessment and patient reports. Notably, Jones et al. (2010) utilized a less aggressive buprenorphine dosing strategy of 2 mg increments. The optimal dosing strategy must be weighed against potential risks to neonates during the postpartum period warranting further exploration regarding the impact of dosing on outcomes as current evidence is inconclusive. Induction of MAT in an inpatient setting may provide prompt symptom control; however, adherence did not seem impacted based on inpatient versus outpatient induction of BUP.

To our knowledge, this is the first study that examined factors associated with buprenorphine adherence during pregnancy. In a comparable study completed at 12 months postpartum (O'Connor et al., 2018), women who entered treatment prior to 13 weeks' gestation were more likely to remain in treatment. Our current study did not find that gestational timing of enrollment significantly differed between adherence groups.

5. Conclusions

Severity of withdrawal symptoms and lower doses of buprenorphine were associated with non-adherence to buprenorphine treatment during pregnancy until delivery. Further studies on optimizing buprenorphine management (i.e., dosing protocols) during pregnancy are warranted to improve adherence.

Contributors

Dr. Coker contributed to the overall project aims, gathering and collection of data, obtaining IRB approval, drafting and editing of manuscript and submission process. Mr. Catlin contributed to the overall project aims, collection and organization of data, and editing of manuscript. Dr. Ray-Griffith contributed to the overall project aims, gathering and collection of data, and editing of manuscript. Ms. Knight contributed to the collection of data and editing of manuscript. Dr. Stowe contributed to the overall project aims, collection of data, and editing of manuscript. All authors read and approved final manuscript.

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Table 1
Characteristics of pregnant women on buprenorphine.

Variable	Adherent[a] (n = 41)	Moderately Adherent (n = 8)	P-Value[b]	Non-Adherent[a] (n = 15)	P-Value[b]
Demographics/Obstetrical					
Age, mean (SD), years	28 (4)	29 (5)	–	29 (6)	0.52
Employment, No. (%)	11 (27)	1 (12)	0.65	7 (47)	0.28
White, No. (%)	31 (76)	7 (88)	0.78	13 (87)	0.60
High School Graduate, No. (%)	34 (83)	5 (63)	0.42	13 (87)	0.96
Married, No. (%)	15 (37)	3 (38)	0.73	5 (33)	0.97
Medicaid Insurance, No. (%)	21 (51)	7 (87)	0.14	10 (67)	0.45
Positive Tobacco Use, No. (%)	27 (67)	4 (50)	0.61	7 (47)	0.29
Gravida, mean (SD)	3 (2)	3 (2)	–	3 (2)	0.839
Parity, mean (SD)	2 (2)	2 (1)	–	1 (1)	0.952
Family History of Addiction, No. (%)	(n = 39)	(n = 7)		(n = 14)	
+ Mother	15 (39)	1 (14)	0.40	3 (21)	0.37
+ Father	14 (36)	4 (57)	0.53	8 (57)	0.29
+ Sibling	9 (23)	2 (29)	0.89	3 (21)	0.83
Structured Clinical Interview for DSM-IV Diagnosis, No.(%)					
	(n = 39)	(n = 8)		(n = 14)	
Any Non-Substance Use Axis I Disorder	34 (82)	8 (100)	0.45	11 (71)	0.63
Major Depressive Disorder	23 (59)	5 (63)	0.85	6 (43)	0.47
Bipolar Disorder	2 (5)	0 (0)	0.74	1 (7)	0.69
Posttraumatic Stress Disorder	21 (51)	4 (50)	0.74	5 (36)	0.51
Childhood Trauma Questionnaire, mean (SD)					
	(n = 40)	(n = 8)		(n = 10)	
Emotional Abuse	12 (6)	12 (6)	–	14 (5)	0.504
Physical Abuse	10 (6)	9 (7)	–	12 (9)	0.254
Sexual Abuse	10 (7)	9 (7)	–	12 (9)	0.773
Emotional Neglect	13 (5)	12 (5)	–	12 (4)	0.994
Physical Neglect	9 (5)	9 (4)	–	9 (3)	0.927
Denial	8 (4)	7 (4)	–	7 (3)	0.726

[a] Adherent is defined as retention in treatment until delivery with non-adherent defined as attrition prior to delivery.
[b] P-values for dichotomous variables are presented as adherent vs moderately adherent, adherent vs non-adherent. Significance $p < 0.05$.

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Conflict of interest

Dr. Coker has received research support from Arkansas Children's Research Institute and National Institute on Drug Abuse. She has served as a physician (non-compensated) on clinical trials sponsored by SAGE, Janssen, and Boerhringer Ingelheim Pharmaceuticals. She has never served as a consultant to any biomedical or pharmaceutical corporation. Neither she nor family members have ever held equity positions in biomedical or pharmaceutical corporations.

Mr. Catlin has no potential conflicts of interest.

Dr. Ray-Griffith currently receives clinical trial support from Neuronetics and has received clinical trial support from Sage Therapeutics. She has never served as a consultant to any biomedical or pharmaceutical corporation. Neither her nor family members have ever held equity positions in biomedical or pharmaceutical corporations.

Ms. Knight currently receives research support from the National

Table 2
Treatment related outcomes affecting adherence to outpatient care to delivery among pregnant women.

	Adherent[a] (n = 41)	Moderately Adherent (n = 8)	P-Value[b]	Non-Adherent[a] (n = 15)	P-value[b]
Inpatient Induction, No. (%)	18 (44)	5 (63)	0.55	7 (47)	0.92
Total Days in Treatment, mean (SD)	201 (58)	159 (44)	–	53 (46)	< 0.001
No. of Schedule Appointments, mean (SD)	21 (7)	20 (4)	–	9 (5)	< 0.001
No. of Missed Appointments, mean (SD)	2 (2)	2 (2)	–	2 (2)	0.811
Estimated gestational age at enrollment, mean (SD)	20 (9)	27 (6)	–	20 (9)	0.130
Positive UDS at enrollment, No. (%)	20 (49)	4 (50)	0.74	10 (67)	0.37
Positive UDS for opioids at enrollment, No. (%)	9 (22)	2 (25)	0.78	6 (40)	0.31
Positive UDS for non-opioids at enrollment, No. (%)	15 (37)	3 (38)	0.73	8 (53)	0.44
COWS enrollment, mean (SD)	5 (5)	5 (2)	–	6 (4)	0.568
COWS last visit, mean (SD)	3 (3)	4 (5)	–	7 (4)	0.035
SOWS enrollment, mean (SD)	22 (17)	12 (5)	–	23 (19)	0.335
SOWS last visit, mean (SD)	10 (15)	10 (15)	–	16 (20)	0.099
Previous MAT treatment, No. (%)	6 (15)	0 (0)	0.56	2 (13)	0.81
BUP daily dose at last visit, mg, mean (SD)	17 (7)	14 (8)	–	10 (9)	0.006

[a] Adherent is defined as retention in treatment until delivery with non-adherent defined as attrition prior to delivery. UDS: urine drug screen; COWS: clinical opioid withdrawal scale; SOWS: subjective opioid withdrawal scales; MAT: medication assisted treatment; BUP: buprenorphine.
[b] P-values for dichotomous variables are presented as adherent vs moderately adherent, adherent vs non-adherent. Significance $p < 0.05$.

Institutes of Health (NIH). Her adult son is employed by GlaxoSmithKline and has stock options as part of his employment.

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References

American College of Obstetrics and Gynecologists (ACOG), 2012. Opioid abuse, dependence, and addiction in pregnancy. Committee opinion No. 524. Obstet. Gynecol. 119, 1070–1076.

Bateman, B.T., Hernandez-Diaz, S., Rathmell, J.P., Seeger, J.D., Doherty, M., Fischer, M.A., Huybrechts, K.F., 2014. Patterns of opioid utilization in pregnancy in a large cohort of commercial insurance beneficiaries in the United States. Anesthesiology 120, 1216–1224.

Desai, R.J., Hernandez-Diaz, S., Bateman, B.T., Huybrechts, K.F., 2014. Increase in prescription opioid use during pregnancy among medicaid-enrolled women. Obstet. Gynecol. 123, 997.

Jones, H.E., Kaltenbach, K., Heil, S.H., Stine, M., Coyle, M.G., Arria, A.M., O'Grady, K.E., Selby, P., Martin, P.R., Fischer, G., 2010. Neonatal abstinence syndrome after methadone or buprenorphine exposure. N. Engl. J. Med. 363, 2320–2331.

Kakko, J., Svanborg, K.D., Kreek, M.J., Heilig, M., 2003. 1-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: a randomised, placebo-controlled trial. Lancet 361, 662–668.

Kumar, N., Stowe, Z.N., Han, X., Mancino, M.J., 2016. Impact of early childhood trauma on retention and phase advancement in an outpatient buprenorphine treatment program. Am. J. Addict. 25, 542–548.

Martin, C.E., Longinaker, N., Terplan, M., 2015. Recent trends in treatment admissions for prescription opioid abuse during pregnancy. J. Subst. Abuse Treat. 48, 37–42.

O'Connor, A.B., Uhler, B., O'Brien, L., Knuppel, K., 2018. Predictors of treatment retention in postpartum women prescribed buprenorphine during pregnancy. J. Subst. Abuse Treat. 86, 26–29.

World Health Organization (WHO), 2014. Guidelines for the Identification and Management of Substance Use and Substance Use Disorders in Pregnancy. Available at. http://www.who.int/substance_abuse/publications/pregnancy_guidelines/en/.