Rural, Pregnant, and Opioid Dependent: A Systematic Review

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Supplementary Issue: Substance Use in Pregnancy

ABSTRACT: The nature, impact, and treatment of substance use during pregnancy are well described for women living in urban settings. Less is known about pregnant substance-using women living in rural communities. The objective of this review is to describe the existing evidence for the management of substance use in pregnant women living in rural areas. A systematic review of the literature was conducted using PubMed, Embase, and the Cochrane Database of Systematic Reviews, and the quality of the evidence was assessed using the GRADE system. Twenty-two articles that met the inclusion criteria were identified. Descriptive studies document high rates of smoking, marijuana, and polysubstance use among rural, substance-using pregnant women compared to their urban counterparts. Management of substance use disorders is limited by access to and acceptability of treatment modalities. Several innovative, integrated addiction and prenatal care programs have been developed, which may serve as models for management of substance use during pregnancy in rural settings.

KEYWORDS: opioids, pregnancy, rural and remote, addiction

Introduction

Rates of substance use during pregnancy in the United States have remained relatively stable at 4% since the early 1990s.[1] However, the pattern of substance use has shifted over that time. The introduction of long-acting oxycodone in the mid-1990s and the dramatic increase in opiate prescription that ensued have led to a rise in prescription opiate misuse.[2] Data for pregnant women from the Substance Abuse and Mental Health Services Administration (SAMHSA) in the United States reflect this trend with an increase in the number of admissions to drug treatment services for opioids from 2% in 1992 to 38% in 2012.[2,3] Opioids are now the most common reason for seeking treatment for illicit substances during pregnancy, followed by marijuana (20%), methamphetamines (15.6%), cocaine (7.4%), tranquilizers and sedatives (1.2%), and hallucinogens and PCP (0.6%).[1] The treatment of opioid dependence during pregnancy was initially described in a population of poor, inner-city heroin users.[4,5] Since that time, many studies have been carried out in urban settings to describe the management of opioid dependence during pregnancy. However, recent data have shown that there has been a demographic shift in opioid users.[6] Increasing numbers of opioid users now live in suburban and rural areas, where

people are often more affluent than in the inner city.[6] Gender balance has also changed among opioid users from predominantly young men living in the inner city to roughly equal numbers of men and women living in suburban and rural areas.[6] Among women, the highest prevalence of opioid use occurs between the ages of 20 and 29 years.[1] This is also the age group with the highest fertility rate.[7]

In addition to the demographic changes, a shift in the route of administration has also been noted in rural areas. In a study of the patterns of use in rural America, Cicero noted that since the withdrawal of long-acting oxycodone from US market in 2010, the price of prescription opiates has increased, while the price of heroin has remained low.[6] This has contributed to rising rates of heroin use in rural areas[6] as well as a shift in the route of administration from oral and intranasal to intravenous.[8] The public health implications of rising rates of intravenous drug use are considerable, particularly during pregnancy.

The nature, impact, and treatment of opioid dependence during pregnancy are well described in the literature for women living in urban settings. Given the rising rates of opioid use in rural areas, a critical appraisal of the management of opioid dependence during pregnancy in rural settings is warranted. The objective of this review is to describe the existing

evidence regarding the nature, impact, and management of opioid dependence in pregnant women living in rural areas.

Methods

A literature search of PubMed, Embase and the Cochrane Database of Systematic Reviews between July 2015 and December 2015 was conducted using the following search terms: "pregnancy," "pregnant," "prenatal," "antenatal," "postpartum," "rural," "remote," "non-urban," "nonurban," "opiate," "opioid," "methadone," "buprenorphine," "substance use," "addiction," "marijuana," "cannabis," "cocaine," and "methamphetamine." Cannabis, cocaine, and methamphetamines were included to broaden the search as they are the three most common illicit substances used along with opioids. The search was not limited to a specific period or language. Articles identified in the search were reviewed to ensure that they included a rural or remote population and to exclude duplicates. Meta-analyses, clinical trials, observational studies, case reports, and clinical practice guidelines were included in the review. If an abstract was deemed to be relevant, the article was read in full. The references in each article were reviewed to identify additional relevant papers. Figure 1 outlines the search method. The GRADE guidelines were used to assess the quality of the studies that were included in the review.[9]

Results

One randomized clinical trial (RCT) was identified along with two secondary analyses of this RCT. The remaining studies identified were observational or made use of administrative databases. As a result, a collapsed GRADE system was applied to the review, making use of the quality categories of high, medium, and low, which includes both low- and very low-quality studies. Under this system, the one RCT was classified as high-quality evidence, two secondary analyses of the RCT were classified as medium quality, and all other studies included in the review were classified as low quality.
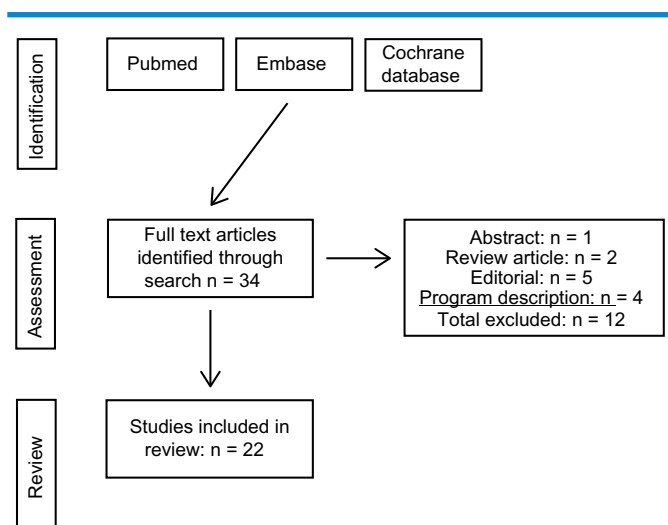

Figure 1. Flowchart of Literature Search.

The studies identified in this review can be broadly grouped into three thematic areas: studies that characterize the nature of substance use during pregnancy in rural settings; studies that juxtapose urban and rural opioid-using pregnant women; and studies that describe outcomes of programs or services that have been tailored to rural, opioid-using pregnant women.

Characterization of substance use in rural pregnant women. Early reports of substance use during pregnancy in rural communities were largely descriptive and have documented the prevalence of drugs of abuse.[10–13] The most common drugs of abuse between 1989 and 1999 were marijuana, opiates, and cocaine, followed by benzodiazepienes, barbituriates, and amphetamines.[10–13] Reports that appeared much later moved beyond prevalence data and instead described particular issues that affect rural pregnant women including smoking and its interaction with substance use during pregnancy,[14,15] intimate partner violence,[16] hepatitis C testing,[17] and access to treatment (Table 1).[18]

Urban rural differences. Several studies compared opioid-dependent, rural pregnant women to their urban counterparts. The MOTHER study is the only randomized controlled trial that included pregnant, rural, opioid-dependent women.[19] The remainder of the studies were either secondary analyses of the MOTHER trial or small observational studies.

The MOTHER trial was a multisite, double-blind, double-dummy, flexible-dosing, randomized controlled trial that investigated buprenorphine in the management of opioid dependence during pregnancy compared to methadone.[19] The trial included a site in Austria (Vienna), three urban US cities (Baltimore, Maryland; Philadelphia, Pennsylvania; and Detroit, Michigan), and three rural US communities (Providence, Rhode Island; Burlington, Vermont; and Nashville, Tennessee). A site in Canada (Toronto, Ontario) screened women but did not have any participants enrolled in the study. The MOTHER trial concluded that compared to methadone, buprenorphine was acceptable for managing opioid dependence during pregnancy. In addition, buprenorphine resulted in less severe neonatal abstinence syndrome (NAS). These results applied to both the urban and rural sites.

Secondary analyses of the MOTHER trial sought to understand differences between rural and urban participants (Table 2).[21–24] Overall, rural women participating in the MOTHER trial were more likely to be younger, employed, White, and have a planned pregnancy compared to urban women.[21–24] Rural women were also more likely to volunteer for the study, and, if enrolled in the study, they were more likely to be retained in the study.[21,23] Furthermore, rural women often required lower doses of methadone or buprenorphine to manage their symptoms.[24] Finally, infants had lower rates of treatment for NAS and also had shorter hospital stays for NAS.[23,24] The study authors note that, although a standard protocol was used at all sites in the MOTHER trial, local variation did exist in terms of both screening methods and treatment protocols, which may lead to biased results.

Table 1. Characterization of substance use in rural pregnant women.

STUDY	POPULATION	FINDINGS	LIMITATIONS
Smoking			
Mehaffey et al 2010[14]	Retrospective cohort Qikiqtaaluk Region, Canada n = 918	• 81% of participants smoked • No effect on birth weight or pre-term birth for women who smoked up to 5 cigarettes per day • Women who smoked more than 10 cigarettes per day were more likely to have a low birth weight baby (OR 6.7, 95% CI 2.3–19.6), pre-term birth (OR 2.1, 95% CI 1.1–4.2) and use alcohol or illicit substances in pregnancy (OR 3.3 95% CI: 1.9 to 5.4).	• Small sample size • Lack of demographic and socio-economic data
Bailey et al 2012[15]	Prospective cohort Kentucky, USA n = 265	• 75% of participants smoked • Illicit drug use caused a similar reduction in birth weight compared to smoking • Marijuana did not cause a reduction in birth weight independent of smoking • Smoking + illicit drug use resulted in a 12% reduction in birth weight	Small sample size and polysubstance use limited ability to identify affects of specific drugs on birthweight with the exception of marijuana
Intimate Partner Violence (IPV)			
Bailey et al 2007[16]	Prospective cohort Kentucky, USA n = 104	• 80% of women experienced some form of IPV • Women who used illicit substances at the time of conception were 7 times more likely to experience physical IPV, twice as likely to experience psychological IPV compared to women with no substance use	• Self reported data • Small sample size was underpowered to detect variation between groups • Homogeneous population limits generalizability
Hepatitis C			
Liu et al 2009[17]	Retrospective cohort New South Wales, Australia One rural and two urban hospitals n = 295 methadone n = 9987 control	• 98% of the methadone group and 20% of controls were tested for HCV • Of those tested 84% of the methadone group 3% of the control group had HCV antibodies • Of those with HCV antibodies, only 18% of the methadone group and 31% of the control group were tested for HCV RNA • HCV RNA was positive for 70% of the methadone group and 59%) of the control group • Only 27% of infants born to mothers with HCV antibodies had follow up testing	• Small study population • Likely incomplete capture of HCV testing eg private clinics not included
Access to Treatment			
Jackson et al 2012[18]	Survey Kentucky, USA n = 85	• Pregnant women admitted to short-term, inpatient detoxification • Family responsibilities (37%), wait lists and paperwork for treatment (27%), stigma (15%), denial (15%), lack of social support (11%) and financial concerns (11%) • Acceptability of treatment was the primary limiting factor for treatment (51%), accessibility (49%), availability (26%) and affordability (13%)	• Small sample size • Sampling women who were able to access treatment • Homogeneous population limits generalizability

Three observational studies were identified that compared urban and rural, substance-using pregnant women in terms of birth outcomes,[25] patterns of substance use,[20,26] and utilization of treatment services.[26] Tetstall et al compared methadone-maintained pregnant women giving birth at a rural site in New South Wales, Australia, to those delivering at an urban site both in terms of the impact of rural location and indigenous identity.[25] This retrospective cohort study showed that outcomes for both groups were similar; however, rural women had significantly less involvement with child-protective services, and their infants had shorter hospital stays and were less likely to need pharmacologic treatment for NAS. The authors note that indigenous identity had less of an impact on neonatal outcomes compared to rural location. An inherent limitation of this study is underreporting due to the retrospective nature of the data collection.

Table 2. MOTHER study secondary analyses.

STUDY	POPULATION	FINDINGS	LIMITATIONS
Heil et al 2008[20]	Women screened in Vermont (n = 54) and Baltimore (n = 305)	• Per capita 3 times as many rural women presented for treatment • Rural women were more likely to be: younger, employed, White and to have a planned pregnancy	• Differences in screening methods between sites • Data was collected on a few variables – not comprehensive • Rural sample may not be representative
Unger et al 2010[21]	Women screened in rural USA (n = 160), urban USA (n = 677), Canada (n = 37) and Austria (n = 171)	• Rural women were more likely to be: younger, employed, White and to have a planned pregnancy • Benzodiazepiene use ~15% • Two thirds of women involved with the legal system	• Differences in screening methods between sites • Differences in screening sample size may result from availability of treatment at those locations
Baewert et al 2012[22]	Women enrolled in Austria (n = 37), rural USA (n = 39) and urban USA (n = 55)	Compared to urban women, rural women: • More likely to be younger and employed • Younger age at initiation of heroin • Less likely to have polysubstance use • Less likely to use cocaine and opioids • More likely to use cannabis • Shorter hospitalization for NAS • Less likely to leave the study	• Within MOTHER study there were treatment differences at different sites
Kirchner et al 2015[23]	Women enrolled in Austria (n = 37), rural USA (n = 39) and urban USA (n = 55)	Compared to urban women, rural women had: • Lower doses of methadone and buprenorphine • Lower rates of cocaine use • Higher rates of cannabis • Higher rates of breastfeeding • Lower rates of treatment for NAS	• Within MOTHER study there were treatment differences at different sites

Shannon et al surveyed 114 women in Kentucky, USA, regarding substance use in the 30 days prior to admission to a short-term inpatient treatment facility.[20] Compared to urban women, rural pregnant women were significantly more likely to endorse illicit opiate use (OR 8.4, 95% CI 1.8–38.9), intravenous drug use (OR 5.9, 95% CI 1.2–29.4), illicit sedative/benzodiazepine use (OR 3.3, 95% CI 1.1–9.6), and polysubstance use (OR 2.8, 95% CI 1.0–7.8). Pregnant women entering detoxification may not be representative of the general population of rural, substance-using pregnant women and this may limit the generalizability of these findings.

Shaw et al conducted a prospective cohort study of 773 women enrolled in a parent–child assistance program (PCAP) in order to identify and characterize rural women accessing PCAP services.[26] A total of 96 women were identified as living in a rural area. Compared to urban women, rural women were younger, they were more likely to identify as Native American or Alaska Native, and they were more likely to have stable housing. In terms of patterns of substance use, rural women were more likely to binge drink and use marijuana compared to urban women but less likely to use methamphetamines and heroin. Rates of opiate use other than heroin were similar between both groups. Compared to urban women, rural women were less likely to make use of addiction and mental health services. The study reported a high attrition rate of participants over the 10 years of data collection, which may introduce bias in the results.

Comprehensive care in rural settings. Three programs were identified during the review that directly respond to the rising rates of opioid dependence in rural communities. These programs go beyond simply characterizing the nature and impact of opioid dependence in rural settings and attempt to address geographic, socioeconomic, and cultural factors that may impact treatment. Each program uses a different model of care, ranging from a case management program in New South Wales, Australia[27] to an opioid detoxification program serving remote communities in Ontario, Canada[28–30] to a program of coordinated prenatal and addiction care in rural Vermont, USA.[31] Passey et al prospectively evaluated a case management system for substance-using women living in rural communities in New South Wales, Australia.[27] Fifty-five women enrolled in the program, of whom 27 were in a methadone substitution program and five were pregnant. Structured interviews administered at baseline and then at three and six months after enrollment showed that polysubstance use was common (91%) as was the use of cannabis (84%), opiates (25%), and tranquilizers (25%). Women also reported multiple chronic conditions on enrollment. For the 21 women who completed the interview at six months, there were significant improvements in their psychological well-being and self-esteem. However, the program had a high attrition rate and a relatively short follow-up time, which limits the ability to understand if case management has a positive impact on long-term outcomes in this population. Furthermore, no data were given regarding the women who left the pilot study prior to completion or the reasons why they left the study.

Kelly et al and Dooley et al describe an integrated program of prenatal care and opioid detoxification at a rural hospital with 400 deliveries per year that serves a large population of Aboriginal women in Ontario, Canada.[28–30] Over the course of the study, the incidence of opioid use during pregnancy rose from 8.4% in 2009 to 17.2% in 2010[28] to 28.6% in 2013.[29] During this time, the frequency of opioid use also changed from occasional use to daily use.[29] Although up to one third of women administered opioids intravenously in 2013, hepatitis C remained relatively rare.[29] No cases of HIV were reported.[29] The goal of the program is to reduce the incidence of NAS, and as such the primary treatment modality is narcotic tapering with long-acting morphine. Nine percent of women were able to stop using opioids[30] and 82.6% of women achieved a dose reduction by the time of delivery. However, illicit opioid use remained high with positive urine drug screens in 46.7% of women at the time of delivery.[30] Despite this, the program was able to achieve a reduction in NAS from 30% to 18% over the course of the study as well as a reduction in transfers to tertiary care facilities for NAS.[28,29] No long-term outcome data were provided for the women who achieved abstinence or for the women who achieved dose reduction.

Meyer et al evaluated the implementation of a coordinated opioid substitution therapy and prenatal care program in rural Vermont.[31] The program addressed barriers to providing community-based care for pregnant opioid-dependent women living in rural Vermont including access to and options for opioid substitution therapy; lack of experience caring for opioid-dependent pregnant women; and limited resources to provide care for opioid-exposed infants in small community hospitals.[32] Additional capacity to treat 585 patients was developed – two-thirds of treatment positions were for buprenorphine substitution therapy.[31] Over the course of the six-year study, there was a 3.5-fold increase in pregnant women receiving opioid substitution therapy, and women initiated prenatal care earlier.[31] Furthermore, more infants were discharged home to be in the care of the mother and remained in the mother's care untill one year of age.[31] Over time, prenatal care, delivery, and management of neonatal abstinence syndrome have shifted from a tertiary referral center back to the community. Limitations of this study include the absence of data for women who did not continue opioid substitution therapy. Bias may be present, as only women who were actively seeking treatment were included in the study.

Discussion

Prescription opioids have had the biggest impact on substance use in rural communities and they are now the most frequent drugs of abuse in rural pregnant women. A challenge in selecting and analyzing the studies included in the review was defining what it means to be "rural." Indeed, no accepted definition of rural emerges in the literature. For example, the majority of studies on opioid dependence during pregnancy have been conducted in three countries: the United States, Australia, and Canada. In the United States, the census definition of rural is a community with fewer than 2,500 people[33], whereas in Australia, rural denotes a community with fewer than 1,000 people.[34] In contrast, the Canadian Medical Association defines rural as an area in which physicians have high call requirements, there are long distances to secondary and tertiary care centers, there is lack of specialist care, and there are insufficient health care providers.[35]

The MOTHER trial clearly illustrates the difficulties in defining a rural population. This trial classified three sites as rural: Burlington, Vermont; Providence, Rhode Island; and Nashville, Tennessee. Burlington has a population of just over 40,000 people,[36] Providence has a population of close to 200,000 people[37] and Nashville has a population in excess of 600,000 people.[38] None of these sites fits the census definition of rural, and outside of this study, each of the sites would be considered urban. However, one can infer from the study data that each site represents a tertiary referral center whose catchment area includes a large rural population. In the case of Nashville, for example, the area served includes parts of Appalachia, a rural area with some of the highest rates of opioid abuse in the United States.[39]

Following the publication of the MOTHER trial, buprenorphine has become more widely used in the management of opioid dependence during pregnancy in rural settings. Several factors are likely responsible for this transition, including a better safety profile compared to methadone and less severe NAS symptoms.[19] In addition, unlike methadone, a special license is not required to prescribe buprenorphine. This has led to increased provision of buprenorphine substitution therapy by family physicians who provide the majority of addiction and mental health care in rural parts of the United States.[40] Overall however, there remains a shortage of addiction medicine providers in rural settings, which has resulted in long waitlists for treatment.[41] This has been identified as a barrier to receiving care by opioid-using pregnant women.[18] Furthermore, there is a paucity of literature addressing non-pharmacologic, mental health, and addiction treatment during pregnancy in rural settings.

Understanding the ways in which rural, opioid-dependent pregnant women access health care is likely more important than the size of the community in which the women live. Studies presented in this review identify the need to travel to appointments as an important barrier to accessing treatment for rural, opioid-dependent pregnant women.[26,27,31,32] When services are provided in an accessible location for rural, opioid-dependent pregnant women, it was found that they were more interested to avail and utilize these services.[21,28–32] Although socioeconomic and cultural factors are often thought to create additional barriers to accessing treatment for opioid dependence during pregnancy, rural locations were found to have more of an impact.[25,26–30] That being said, addressing cultural factors in health and social service programing may improve

acceptability of treatment to women and further increase utilization of these services.[25,26–30]

Currently, studies show that rural, opioid-dependent pregnant women often require lower doses of opiate-substitution therapy compared to their urban counterparts.[19,24] This difference is attributed to the relatively younger age of rural, opioid-using pregnant women, the use of prescription opioids rather than heroin, and possibly stabilizing factors such as employment and marriage, which are implied as surrogates for less severe opioid use.[21–24] However, changing patterns of opioid use and routes of administration are now being observed in rural pregnant women,[28–30] and these changes follow trends observed in the rural population more generally. Recent federal drug policy changes in the United States and Canada have limited the availability of the most frequently abused prescription opioid and may have indirectly contributed to emerging heroin and intravenous drug use in rural areas. This is a significant public health concern particularly during pregnancy. Another recurrent issue that emerged in this review was polysubstance abuse. Most rural pregnant women smoke cigarettes in addition to using opioids and to a lesser extent use marijuana, benzodiazepines, or cocaine.[14,15,19–31] The discussion on polysubstance use was largely descriptive, with no articles addressing treatment.

Very few articles address gender issues that affect rural, substance-using pregnant women. Stigma surrounding substance use during pregnancy was identified by women as one of the limiting factors to receiving treatment.[18] Understanding the role and sources of stigma, for example, on the part of providers, family, partner, and society in general, may increase acceptability of treatment in women. Childcare and family responsibilities were also identified as barriers to accessing treatment among rural, opioid-using pregnant women.[18] The role of the woman's partner in substance-use behavior and treatment and intimate partner violence were only touched upon briefly.[16,18,28–30,42] Further work needs to be done to better understand the complex interaction of gender, substance use, and treatment.

Conclusions

This review has shown that the nature, impact, and treatment of opioid use during pregnancy in rural settings differ from those in urban centers. Because the majority of studies included in this review were observational, it is not possible to draw strong conclusions based on the findings. One exception is the use of buprenorphine for the treatment of opioid dependence during pregnancy in rural settings, which is supported by strong evidence. That being said, several themes did emerge. Accessibility and availability were identified as the two biggest barriers to receiving treatment among rural, opioid-using pregnant women. Rural, community-based programs that addressed these two issues reported increased enrollment in treatment programs and keeping birth in communities. Research into these types of concerted health systems responses, particularly with long-term follow-up and attention to gender issues, may provide valuable insight into the management of rural, substance-using pregnant women.

Author Contributions

Conceived the concepts: NAJ. Analyzed the data: NAJ. Wrote the first draft of the manuscript: NAJ. Developed the structure and arguments for the paper: NAJ. Made critical revisions: NAJ. The author reviewed and approved of the final manuscript.

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