



Effect of Maternal Methadone Use on Neonatal Outcomes: Results of a Cohort Study

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Received 2021 September 07; Revised 2021 October 31; Accepted 2021 November 06.

Abstract

Background: Substance abuse treatment is challenging in pregnancy, and methadone maintenance therapy (MMT) is a therapeutic choice. Methadone can cross the placenta and is poorly secreted in breast milk. Given these inconsistent findings of methadone effect on neonatal outcomes, this study was done to investigate the results in neonates of mothers treated with methadone in Mashhad.

Methods: In this retrospective cohort study, mothers referring to two academic hospitals of Mashhad University of Medical Sciences, Mashhad, Iran were studied. Three groups were considered: MMT, other drug abusers, and healthy control. Maternal information, including demographic characteristics, fertility characteristics, and methadone treatment-related characteristics, and neonatal information, including demographic characteristics and neonatal outcomes, were assessed.

Results: Overall, 122 pregnant women with a mean age of 29.14 ± 4.44 years were studied in three groups: control ($n = 59$), MMT ($n = 32$), and other drug abusers ($n = 31$). Baseline characteristics (mothers' age, residence, chronic hypertension, preeclampsia, diabetes, heart disease, thyroid disease, and other diseases) were not different between the three groups. The highest history of miscarriage was seen in other drug abusers (35.5%) ($P = 0.023$). The mean weight, height, and head circumference of neonates in the control group were significantly higher than the MMT group ($P < 0.001$), and in the MMT group was higher than in the other drugs abusers ($P < 0.001$). The highest prevalence of malformations (16.1%) and hospitalization in the NICU (51.6%) was observed in infants of other drug abusers. After adjusting for confounding variables, the odds ratio (OR) of low-birth-weight infants was 13.7 in the MMT group and 19.46 in the other drugs group compared to the healthy control group. The OR of neonates less than 50cm in height was 11.4 in the MMT group and 22.5 in the other drugs. Besides, the OR of neonates less than 35cm was 4.7 in the MMT group and 7.3 in other drugs.

Conclusions: Although the neonates of mothers who used methadone had a higher rate of inappropriate intrauterine growth indices than control group, methadone consumption compared to other drugs had significantly reduced unacceptable outcomes in neonates. Increased gestational age and reduced preterm delivery risk were observed in methadone-treated mothers.

Keywords: Addiction, Methadone, Pregnancy, Neonatal Outcomes

1. Background

Over the past decade, the number of pregnant women addicted to drugs has been increasing. About 90% of drug-abusing women in the United States are of child-bearing age (1), and 80 to 90% of pregnancies in these women are unwanted and unplanned (2). Despite scarce information on drug addiction during pregnancy, among 5,500,000 women referring to the US hospitals for addiction treatment or its complications, 4% are pregnant women (3). Besides, 225,000 neonates are born to mothers who use drugs (4). The situation is similar in developing countries. For example, Iran has progressively

expanded methadone maintenance therapy (MMT) with around 2700 active programs with over 160,000 active participants throughout the country (5). A retrospective cohort study of a five-year period on medical records of pregnant women showed that from 100,620 deliveries, substance abuse was recorded for 519 women giving a prevalence of 0.5% (6). This shows the necessity of implementing prevention and treatment programs for drug users (7, 8).

Drug use should be stopped during pregnancy due to neonatal complications (9); however, despite available treatments and medical care, most of these women resume drug use. Rapid detoxification can lead to maternal

complications due to drug withdrawal syndrome, such as abortion, miscarriage, stillbirth, as well as fetal complications, like intrauterine growth restriction (IUGR), preterm delivery, and fetal death (10). On the other hand, substance abuse treatment, including MMT, has always been associated with many challenges (11, 12). Methadone poses special effects; for example, the patient can perform his or her normal functions without disrupting physical or mental activity. More importantly, methadone destroys the constant cravings in individuals at the risk of drug reuse (13).

For this reason, maintenance therapy is a long-term treatment for illicit opioid use (such as heroin and opioid derivatives) (14). The effectiveness of MMT has been validated (15, 16). MMT reduces and often eliminates the use of non-prescription opioids, reduces illegal and criminal activities associated with illicit opioid abuse, and ultimately, decreases the prevalence of HIV; however, some studies have suggested that more than 50% of the patients continued heroin use during MMT (17).

Although methadone crosses the placenta and is poorly secreted in breast milk, some studies have found that MMT in mothers is associated with the increased risk of preterm birth, IUGR, microcephaly, longer hospital stays, and the need to treat neonatal withdrawal syndrome. Some studies have relied on the confounding effects of adverse maternal lifestyle on some of these outcomes (18-20). Breastfeeding has been found safe for methadone-treated mothers (18).

2. Objectives

This study aimed at evaluating the neonatal outcomes in neonates in mothers treated with methadone compared to mothers using other drugs and a control group.

3. Methods

This retrospective cohort study was performed in Imam Reza and Ghaem hospitals in Mashhad in 2017-2018. We evaluated the type of delivery and neonatal outcomes in neonates of mothers treated with methadone (32 mothers) and mothers abusing other drugs (31 mothers). All ethical issues were observed following the guidelines of the Helsinki Declaration. This study was also approved by the Ethics Committee of Mashhad University of Medical Sciences (IR.MUMS.fm.REC.1395.436).

The studied population included the infants referring to the neonatal intensive care unit (NICU). According to Woudes and Woodward (19), as well as the formula for comparing two ratios of a qualitative variable from two independent groups, considering an alpha of 10% and a

test power of 80%, based on the NICU referral rates in neonates of the MMT group (52%) and neonates in the normal population (10%), a sample size of 30 was calculated for each group. Due to the difficulty of finding mothers undergoing MMT or abusing other drugs, this sample size was doubled in the control group (60 mothers). The third group included 30 mothers who reported using other drugs, and the final sample size included 120 mothers. Since there were no multiple gestations in our sample, pregnant women were considered proxies for sample recruitment.

Inclusion criteria were mothers referring to the two studied hospitals in Mashhad for delivery and those undergoing MMT in the specialized addiction recovery centers (MMT group). Exclusion criteria were no consent to participate in the study and a history of psychosis or previous mental disorders.

Maternal information, including demographic characteristics (age, education, and place of residence), fertility characteristics (gravidity, parity, type of delivery, history of abortion, chronic hypertension, preeclampsia, diabetes, heart disease, and thyroid disease), and MMT features and also neonatal information, including demographic characteristics (gender, birth weight and height, head circumference at birth, and gestational age) and neonatal outcomes (malformations, prematurity, and being admitted to the NICU) were recorded. In this study, the birth weight of fewer than 1500 g was considered as low birth weight, 1500 to 3500 g as normal birth weight, and greater than 3500 g as high birth weight.

The MMT group was under the supervision of dedicated methadone clinics. Iran has many methadone maintenance programs, and substance abusers are encouraged to enroll in methadone treatment. In the healthy control group (i.e., with no reported history of drug abuse in their life), who were matched for age and gravidity, selected from the maternity wards of the studied hospitals at the same period, the sample size was about twice as large as the two case groups (59 mothers) due to the availability of non-opiate mothers. The above-mentioned information was also recorded for this group.

Data were analyzed by SPSS 16.0 (Chicago, SPSS Inc; 2007). The obtained data were described using descriptive statistics (mean and median), measures of dispersion (standard deviation and range), and frequency distribution tables. Data were compared, and subgroup analysis was performed using the chi-square test, t-test, and analysis of variance (ANOVA) or nonparametric equivalents. Logistic regression was performed using the Enter method, and an odds ratio with a 95% confidence interval was reported. The model's goodness of fit was reported using Cox & Snell R-squared index. All tests were two-tailed, and a P-

value < 0.05 was considered statistically significant.

4. Results

In this study, 122 pregnant women with a mean age of 29.14 ± 4.44 years (range, 19 to 44 years) were studied in three groups of control ($n = 59$), MMT ($n = 32$), and other drugs ($n = 31$). The third group consisted of mothers mostly using opiate or heroin. There was no significant difference in the mean age of mothers between the three studied groups (Table 1). However, the mean gestational age in mothers who abused other drugs was significantly lower than the other two groups ($P < 0.001$). The median of gravidity in the control group was significantly lower than the other two groups ($P = 0.001$). The median of parity was significantly lower in the control and MMT groups compared to mothers using other drugs ($P = 0.001$). The history of abortion in mothers using other drugs (35.5%) was significantly higher than mothers in control (13.6%) and MMT groups (12.5%) ($P = 0.023$).

The mean weight, height, and head circumference of the neonates in the control group were significantly larger than the other two groups ($P < 0.001$). Also, the prevalence of malformations ($P = 0.015$) and NICU stay ($P < 0.001$) was significantly lower in the control group than in the other two groups (Table 2; online Appendices 1 and 2).

Logistic regression showed that after adjusting for maternal age, gravidity, and gestational age, the odds ratio of low-birthweight infants was 13.7 times higher in the MMT group and 1,946 times higher in the mothers using other drugs compared to the control group ($R^2 = 52\%$). The odds ratio of delivering neonates lower than 50 cm in height was 11.4 and 22.5 times more in the MMT group and mothers using other drugs compared to the control group ($R^2 = 51\%$). The odds ratio of delivering infants with a head circumference of less than 35 cm was 4.7 and 7.3 times higher in the MMT group and mothers using other drugs compared to the control group ($R^2 = 32\%$; Table 3).

5. Discussion

The results of this study showed that although neonates of MMT mothers had higher rates of inadequate intrauterine growth indices compared to the healthy mothers, MMT significantly reduced the neonatal adverse outcomes compared to mothers who abused other drugs.

In the present study, the mean gestational age was higher in the control group compared to mothers in the other two groups, while mothers of the MMT group had a higher gestational age compared to mothers using other drugs. Similarly, Dryden et al. reported that the gestational

age of pregnant mothers undergoing MMT was 37.8 weeks (21). In the study by Holloman et al., gestational age was 38.4 weeks in the MMT group and 36.2 weeks in mothers using other drugs (heroin or cocaine). Also, the prevalence of preterm birth was 15% in the MMT group and 53% in mothers using other drugs. There was a significant difference between gestational age and preterm delivery in these two groups (22), which indicates that MMT in pregnant women compared to abusing other drugs can increase the gestational age and decrease the risk of preterm birth (23, 24).

The mean weight, height, and head circumference of neonates in the control group were significantly higher in the control group, MMT group, and mothers using other drugs, respectively. The reasons for this decline in growth criteria can be due to several factors, including the side effects of the drug, factors related to the lifestyle of the drug abuser, such as dietary habits and quality of nutrition during pregnancy, frequent infections, especially genital infections, as well as following fewer healthy recommendations during pregnancy. The drug dosage can also have an inverse impact on the growth criteria. The relationship between lower gestational age at delivery and lower birth weight has been previously studied (25), which confirms a significant difference between mothers using other drugs and the other two groups in the present study. Derakhshan et al. also showed that low birth weight was more frequent in the opium-exposed neonates compared to the control group neonates (26). Holloman et al. reported that the birth weight of neonates of mothers receiving MMT and mothers using other drugs was 3,037 and 2,747 g, respectively (22). Like our findings, Hayes et al. (27) and Greig et al. (28) revealed a reduced head circumference in neonates of mothers receiving MMT.

In this study, a natural vaginal delivery was not different between the three groups. In the study by Holloman et al., there was also no significant difference between having a cesarean section in healthy and MMT groups (22); however, Richard showed a significant increase in cesarean section in drug-abusing mothers (29). These different findings can open a new horizon for further investigations.

The prevalence of malformations in neonates shows a significant difference between the control group and other drug abusers, which is consistent with previous studies (24, 30). Besides, there was a significant difference between the prevalence of NICU admission in neonates of mothers using other drugs and the other two groups. Holloman et al. reported that the prevalence of NICU admission in neonates was significantly higher in the mothers using other drugs (26%) compared to the MMT group (16%) (22). Gargari et al. (6) and Vucinovic et al. (31) also announced similar results. In addition, the main reasons for the NICU admission were prematurity and respiratory

Table 1. Comparison of the Baseline Characteristics of Pregnant Mothers in Three Groups ^{a, b}

	Control Group (N = 59)	MMT Group (N = 32)	Other Drugs (N = 31)	P-Value
Maternal age (y)	28.90 ± 5.48	28.90 ± 5.48	30.29 ± 3.70	0.22
Gestational age (weeks)	38.63 ± 1.03	37.63 ± 1.31	36.19 ± 1.19	< 0.001 ^{c, d, e}
Gravidity	2.32 ± 1.07 (2.0, 2.0 - 3.0)	2.53 ± 0.88 (2.5, 2.0 - 3.0)	3.42 ± 1.15 (3.0, 3.0 - 4.0)	0.001 ^{c, e}
Parity	1.19 ± 0.94 (1.0, 1.0 - 2.0)	1.38 ± 0.79 (1.0, 1.0 - 2.0)	2.0 ± 1.0 (2.0, 1.0 - 3.0)	0.001 ^{c, e}
Educational level				< 0.001
Illiterate	1 (1.7)	2 (6.2)	3 (9.7)	
Primary	21 (35.6)	5 (15.6)	22 (71.0)	
Diploma	29 (49.2)	25 (78.1)	6 (19.4)	
Bachelor	8 (13.6)	0 (0)	0 (0)	
Citizen				0.18
Native (Mashhad)	47 (79.7)	30 (93.8)	27 (87.1)	
Non-native	12 (20.3)	2 (6.2)	4 (12.9)	
Familial relationship				0.91
Yes	13 (22.0)	8 (25.0)	8 (25.8)	
No	46 (78.0)	24 (75.0)	23 (74.2)	
Abortion history				0.023
Yes	8 (13.6)	4 (12.5)	11 (35.5)	
No	51 (86.4)	28 (87.5)	20 (64.5)	
Chronic hypertension				0.076
Yes	5 (8.5)	4 (12.5)	8 (25.8)	
No	54 (91.5)	28 (87.5)	23 (74.2)	
Preeclampsia				0.17
Yes	4 (6.8)	3 (9.4)	6 (19.4)	
No	55 (93.2)	29 (90.6)	25 (80.6)	
Diabetes				0.17
Yes	0 (0)	2 (6.2)	1 (3.2)	
No	59 (100.0)	30 (93.8)	30 (96.8)	
Coronary disease				-
Yes	0 (0)	0 (0)	0 (0)	
No	59 (100.0)	32 (100.0)	31 (100.0)	
Thyroid disorder				0.61
Yes	1 (1.7)	0 (0)	1 (3.2)	
No	58 (98.3)	32 (100.0)	30 (96.8)	
Other diseases				0.58
Yes	1 (1.7)	0 (0)	0 (0)	
No	58 (98.3)	32 (100.0)	31 (100.0)	

^a Data are represented as No. (%) or mean ± standard deviation or median (first quartile-third quartile).^b The statistical tests used to compare the quantitative variables were ANOVA, followed by Kruskal-Wallis (only for gravitational and parity) and chi-squared tests.^c Significant difference between the control and methadone groups.^d Significant difference between the control group and users of other drugs.^e Significant difference between MMT group and users of other drugs.

Table 2. Comparison of the Findings of Neonates in Three Groups ^{a, b}

	Control Group (N = 59)	MMT Group (N = 32)	Other Drugs (N = 31)	P-Value
Gender				0.810
Boy	29 (49.2)	17 (53.1)	14 (45.2)	
Girl	30 (50.8)	15 (46.9)	17 (54.8)	
Weight (kg)	3.24 ± 0.27	2.79 ± 0.22	2.41 ± 0.13	0.001 ^{c, d, e}
Height (cm)	50.71 ± 1.84	48.53 ± 1.22	45.39 ± 1.93	0.001 ^{c, d, e}
Head circumference (cm)	34.85 ± 1.01	33.47 ± 1.05	32.03 ± 1.14	0.001 ^{c, d, e}
Delivery				0.110
NVD	35 (59.3)	25 (78.1)	17 (54.8)	
C/S	24 (40.7)	7 (21.9)	14 (45.2)	
Malformation				0.015
Yes	1 (1.7)	1 (3.1)	5 (16.1)	
No	58 (98.3)	31 (96.9)	26 (83.9)	
NICU admission				< 0.001
Yes	5 (8.5)	3 (9.4)	16 (51.6)	
No	54 (91.5)	29 (90.6)	15 (48.4)	

^aData are represented as No. (%) or mean ± standard deviation or median (first quartile-third quartile).

^bThe statistical tests used to compare the quantitative variables were ANOVA, followed by Kruskal-Wallis (only for gravitational and parity) and chi-squared tests.

^cSignificant difference between the control and methadone groups.

^dSignificant difference between the control group and users of other drugs.

^eSignificant difference between the MMT group and users of other drugs.

Table 3. The Odds of Low Birth Weight, Short Stature, and Small Head Circumference in Mothers Using Methadone and Other Substances Compared to the Control Group

	Weight		Height		Head Circumference	
	OR (CI95%)	P-Value	OR (CI95%)	P-Value	OR (CI95%)	P-Value
MMT group	13.79 (1.09 - 173.23)	0.042	11.49 (3.5 - 37.6)	0.001	4.76 (1.55 - 14.5)	0.006
Users of other drugs	1946 (56.1 - 67500)	0.001	22.55 (1.9 - 260.7)	0.013	7.37 (1.06 - 51.0)	0.043
Maternal age	1.17 (0.91 - 1.49)	0.21	0.92 (0.78 - 1.09)	0.37	0.97 (0.86 - 1.10)	0.70
Gravidity	0.20 (0.07 - 0.57)	0.002	1.18 (0.59 - 2.34)	0.62	0.85 (0.50 - 1.46)	0.57
Gestational age	0.59 (0.34 - 1.03)	0.068	0.30 (0.13 - 0.67)	0.003	0.48 (0.28 - 0.82)	0.007

distress (21). Accordingly, the need for NICU admission is lower in the neonates of the mothers receiving MMT than in the mothers addicted to heroin. Therefore, MMT can affect the health of infants at birth and reduce the need for NICU admission, which leads to reduced medical costs imposed on the health system and the infant's family.

Although the results of this case-control study showed that MMT could reduce the inappropriate neonatal outcomes, to confirm the effectiveness of MMT in pregnant women as a treatment protocol, we strongly recommend a comprehensive controlled clinical trial with sufficiently large sample size.

One of the limitations of this study was the inability to evaluate the long-term effects of MMT and abusing other drugs on neonates due to the study design and the limited

time of this process. Besides, we evaluated drug use based on self-reports, and no reliable information was available regarding drug dose dosage. Although we did not document the socio-economic status, this criterion was similar in the MMT group and healthy controls; however, other drug abusers had a lower condition. Since the most frequent abusive drug was opium, we did not perform a stratified analysis. This analysis is suggested in future studies, which include a diverse spectrum of abusive drugs. It should be noted that drug abuse, as a global concern, is also increasing in Iran, and limited studies have been conducted on drug addiction and drug abuse in pregnant women in Iran.

5.1. Conclusions

In general, methadone use during pregnancy as an alternative to other drugs can increase gestational age, neonatal developmental criteria (height, weight, and head circumference) and decrease preterm delivery and NICU admission. Therefore, methadone can be used for maintenance treatment in patients using other types of drugs during pregnancy.

Supplementary Material

Supplementary material(s) is available [here](#) [To read supplementary materials, please refer to the journal website and open PDF/HTML].

Acknowledgments

We highly appreciate the support of the vice-chancellor for research of the Mashhad University of Medical Sciences. This article results from an MD thesis approved by the Mashhad University of Medical Sciences (950864).

Footnotes

Authors' Contribution: Jarahi, Irvani, and Khadem-Rezaian conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Conflict of Interests: There are no conflicts of interests.

Ethical Approval: This study was approved by the Ethics Committee of Mashhad University of Medical Sciences (IR.MUMS.fm.REC.1395.436).

Funding/Support: This study was supported by the Mashhad University of Medical Sciences.

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