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A Pilot Study of the Nutritional Status of Opiate Abusing Pregnant Women on Methadone Maintenance Therapy

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Abstract

Pregnant women in methadone maintenance therapy may have poor nutrition during pregnancy. In 2006–2008, methadone treated pregnant women (n = 22) were recruited at an urban academic medical center and compared with non-drug using pregnant women (n = 119) at 20–35 weeks gestation. We measured adiposity using pre-pregnancy body mass index (BMI), dietary intake using a food frequency questionnaire, and micronutrient and essential fatty acid status using biomarkers. Methadone treated women had lower BMI, consumed more calories, had lower serum carotenoid concentrations and higher plasma homocysteine concentrations than controls. The study's limitations and implications for future research are discussed.

Keywords

methadone; pregnancy; nutrition; obesity; dietary intake; nutritional biomarkers

Introduction

Opiate abuse during pregnancy can be detrimental to the health of both mother and child. National estimates of opiate use during pregnancy are limited because few pregnant women self-report opiate use (Havens, Simmons, Shannon, & Hansen, 2009; van Gelder et al., 2010); however, screening studies have estimated that 1.0–2.6% of pregnant women abuse opiates (Azadi & Dildy, 2008; Lester et al., 2001; Pegues, Engelgau, & Woernle, 1994). Whether due to substance use, socioeconomic, mental health, or other lifestyle factors (Schempf & Strobino, 2008), women with pregnancies complicated by opiate addiction have higher rates of preterm birth (Almario, Seligman, Dysart, Berghella, & Baxter, 2009), low birth weight (Hulse, Milne, English, & Holman, 1997; Visscher, Feder, Burns, Brady, & Bray, 2003), reduced head circumference (Jacobson et al., 1994) and neonatal withdrawal

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Declaration of Interest

Authors have no conflicts of interest to declare

symptoms (Fajemirokun-Oduyei et al., 2006; Zuckerman, Frank, & Brown, 1995). Opiate addicted pregnant women are encouraged to enroll in a methadone maintenance therapy program to prevent adverse birth outcomes. Methadone maintenance therapy is an effective treatment for opiate dependence (Mattick, Breen, Kimber, & Davoli, 2009), and is the current standard of care for pregnant women (National Consensus Development Panel on Effective Medical Treatment of Opiate Addiction, 1998).

Women who are underweight before pregnancy or do not have adequate energy intake during pregnancy are at increased risk for adverse pregnancy outcomes (IOM, 1990). Maternal micronutrient deficiencies are also detrimental to pregnancy. For example, folate deficiency in the periconceptional period increases the risk for development of neural tube defects (Czeizel & Dudas, 1992; MRC vitamin study research group, 1991). EFA deficiency adversely affects offspring neurological development and function (Uauy, Hoffman, Peirano, Birch, & Birch, 2001), and deficiencies of vitamins C, E, A, and iron have also been associated with preterm birth and intrauterine growth restriction (IOM, 1990).

Poor nutrition among opiate abusing mothers may contribute to adverse pregnancy outcomes. Opiates have direct negative impacts on nutrition by disrupting the gastrointestinal system (Wood & Galligan, 2004) and may affect a mother's ability to adhere to adequate dietary intake and a prenatal vitamin supplement regimen. Little is known about the nutritional status of opiate users, and even less is known about the status of pregnant users. Previous studies have suggested that non-pregnant opiate users entering methadone programs have low body mass index (BMI) (Himmelgreen et al., 1998; Saeland et al., 2011; Szpanowska-Wohn, Kolarzyk, Kroch, & Janik, 2000) and consume an excess of carbohydrates, specifically sweets (Nolan & Scagnelli, 2007; Saeland, et al., 2011; Szpanowska-Wohn, Dluzniewska, Groszek, & Lang-Mlynarska, 2000; Zador, Lyons Wall, & Webster, 1996). Substance users (including opiate users) are likely to have poorer micronutrient status than non-drug users, specifically α -tocopherol, ascorbic acid, and retinol (Nazrul Islam, Jahangir Hossain, & Ahsan, 2001) and low micronutrient intake (Saeland, et al., 2011). Based on evidence in non-pregnant populations, opiate abusing pregnant women may be at high risk poor nutrition.

We conducted a pilot study to describe the nutritional status of a cohort of methadone treated, opiate dependent pregnant women compared with a cohort of non-drug using pregnant women.

Methods

A pilot study of methadone-maintained pregnant women was conducted at Magee-Womens Hospital in Pittsburgh, PA from 2006–2008. Pregnant women (20–35 weeks gestation) who were attending a methadone treatment program were eligible to participate if they were compliant with their methadone treatment, HIV negative, intended to maintain the pregnancy, not place their baby for adoption, and deliver at Magee-Womens Hospital. After providing informed, written consent, women were measured for height and reported their pre-pregnant weight during the third trimester. They also completed a food frequency questionnaire (FFQ) to report their usual dietary intake in the past three months, and provided blood samples for biomarkers of nutrition. A total of 51 methadone treated mothers were approached, 41 were eligible and 30 (73%) agreed to participate. Of these women, 22 (73%) contributed BMI and dietary intake data and 21 (70%) women contributed nutritional biomarker data. Fat soluble vitamins were assayed in 17 (57%) women. The University of Pittsburgh Institutional Review Board approved the study.

For this analysis, the reference population was a group of non-drug using pregnant women enrolled in the Antidepressant Use During Pregnancy (ADUP) Study (Wisner et al., 2009). We chose to use this population as our reference group because of the high rates of depression and mood disorders in the methadone population. Our study of methadone treated women was planned in conjunction with the ADUP study so that measures of nutritional status were congruent. The ADUP protocol and methods have been previously published (Wisner, et al., 2009). Briefly, women in ADUP were recruited at or before 20 weeks gestation, when they reported their height and pre-pregnancy weight. At a second study visit at 30 weeks gestation, women completed the FFQ, and provided a blood sample. After the addition of the nutritional protocol, a total of 289 non-drug using pregnant women were assessed for eligibility, 195 were eligible and chose to participate, 177 contributed data at 30 weeks gestation, and 119 contributed complete BMI, dietary intake, and biomarker data.

Pre-pregnancy adiposity

Pre-pregnancy BMI, $\text{weight (kg)/height (m)}^2$, was based on pre-pregnancy weight and height. BMI categories were underweight (<18.5), normal weight ($18.5\text{--}24.9$), overweight ($25.0\text{--}29.9$), and obese (≥ 30) (NHLBI, 1998).

Dietary intake

A semi-quantitative modified Block98 FFQ, validated in many populations (Block, Thompson, Hartman, Larkin, & Guire, 1992; Block, Woods, Potosky, & Clifford, 1990), was self-administered at 30 weeks gestation in both cohorts. The Block98 FFQ assesses 51 nutrients and 7 food groups from approximately 120 food/beverage items and was modified to focus on a 3-month time period (Block, Coyle, Hartman, & Scoppa, 1994; Block et al., 1986). An individual portion size is asked for each food, and pictures are provided to enhance accuracy of quantification. Completed questionnaires were sent to Block Dietary Data Systems (Berkeley, CA) for optical scanning and nutrient analysis using software developed at the National Cancer Institute. The software used for nutrient analysis produces estimates of usual intake for a wide array of nutrients, calculates the frequency of daily intake, total daily grams of food consumed for each food item, and provides the gram weight for each serving size. Nutrient values were calculated by multiplying the nutrient content of the food by the gram weight and frequency, and summing across all food items. The nutrient values were updated based on the USDA 1994–1996 Continuing Survey of Food Intake by Individuals for women ages 19–44 years and updated folate values for fortified foods from the USDA 1998 nutrient database (USDA, 1998). Folate values were adjusted for increased bioavailability of fortified folate. For foods without added folic acid, micrograms of dietary folate equivalents (DFEs) were equal to the micrograms of naturally occurring food folate. For foods with added folic acid, DFEs were calculated using the following formula: $\text{micrograms of naturally occurring food folate} + (\text{micrograms of added folic acid} \times 1.7)$ (IOM, 1998). Because this FFQ is semi-quantitative, it provides a projection of the amount of nutrients consumed. Nutrient intake was energy-adjusted using the nutrient density method (Willett, 1998).

Nutritional biomarkers

To objectively describe micronutrient and EFA status, we used biological markers from maternal blood samples. All samples were analyzed in duplicate and in a blinded fashion. Plasma folate was measured by a quantitative sandwich enzyme immunoassay technique on a 2010 Elecsys auto-immunoanalyzer (Roche Diagnostics, Indianapolis, IN). This assay has an inter-assay coefficient of variation (CV) of 2.0–3.9%. The lowest detection limit of this assay is 0.6 ng/mL. Total plasma homocysteine (Hcy), also a measure of folate status, was determined by an enzymatic assay on a Hitachi 917 analyzer (Roche Diagnostics-

Indianapolis, IN), using reagents and calibrators from Catch Inc. (Seattle, WA). The CV was 2.1–5.3%.

Maternal vitamin D status was assessed using serum 25-hydroxyvitamin D [25(OH)D]. 25(OH)D was measured using a commercial enzyme-linked immunosorbent assay (ELISA) from Immunodiagnostic Systems Limited (IDS, Tyne, United Kingdom) and validated against high-performance liquid chromatography (HPLC) results, as described in detail previously (Bodnar et al., 2007). The ELISA assay can detect concentrations of 25(OH)D between 5–300 nmol/L. The CV was <10.0%.

Plasma ascorbic acid (vitamin C) concentrations were determined by HPLC (Rumelin, Fauth, & Halmagyi, 1999). An aliquot of maternal plasma (0.5ml) was acid-stabilized with an equal volume of cold 10% metaphosphoric acid. Samples were stored in amber vials –80°C until assayed. Maternal plasma ascorbic acid peaks were separated on a Waters (Milford, MA) Atlantis C18 5 μ m, 3.9 $\times$ 150mm column and appropriate guard using isocratic conditions with a mobile phase consisting of 20mM ammonium dihydrogen phosphate with 0.015% (w/v) metaphosphoric acid, pH 3.5 and a flow rate of 1.5ml/min. Twenty microliters (20 μ l) of the prepared sample was injected onto an equilibrated column, ascorbic acid was detected by UV absorption at 245nm and eluted at approximately 3 minutes. The CV was 5.5%.

The quantization of serum carotenoids (β -carotene, lycopene, lutein+zeaxanthin, and β -cryptoxanthin), α -tocopherol (vitamin E), and retinol (vitamin A) were determined by HPLC (Armstrong, 1998). Samples were kept in the dark and in amber vials. Maternal serum (100 μ l) was mixed with an equal volume of 20mg/ml retinol acetate (internal standard) and 60mg/ml butylated hydroxytoluene in ethanol and vortexed. Samples were extracted twice with one ml of hexane and the hexane fractions combined, evaporated to dryness under nitrogen and reconstituted in 220 μ l of mobile phase (60% acetonitrile, 20% methanol, 20% dichloromethane, and 0.77g/L ammonium acetate and 1ml/L of triethylamine). 75 μ l of the prepared sample was injected onto an equilibrated HPLC column (Supleco LC-18, 4.6 $\times$ 150 mm, 5 μ m particle size) with an appropriate guard column. The vitamins were eluted isocratically at a flow rate of 1.5ml/min and detected by photodiode array. Concentrations were detected at these UV wavelengths and approximate elution times: 292nm: α -tocopherol (2–3 minutes); 326nm: retinol (~1.5 minutes); and 452nm: lutein+zeaxanthin, β -cryptoxanthin, lycopene, and β -carotene (1–7 minutes). The CV's were: serum α -tocopherol (6.0%), serum retinol (8%), serum lutein+zeaxanthin (12%), serum β -cryptoxanthin (11%), serum lycopene (9%), serum β -carotene (11%). We adjusted serum α -tocopherol by dividing α -tocopherol by total lipids, calculated as cholesterol plus triglycerides. Serum cholesterol and triglyceride concentrations were determined enzymatically using specific reagents from Pointe Scientific (Canton, MI).

Iron status was assessed using serum ferritin and serum soluble transferrin receptor concentrations. Serum ferritin concentrations were analyzed using an immunoradiometric assay with I-125 labeled anti-ferritin antibody in a kit obtained from DPC (catalog # IKFE1, Los Angeles, CA). Serum soluble transferrin receptor (sTfR) levels were measured using an ELISA from by R&D Systems (Minneapolis MN). The CV for serum ferritin was 16.4% and CV for serum sTfR was 8.5–17%.

The EFAs we focused on in this analysis were docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and arachidonic acid (AA). Lipids were extracted from red blood cells (Bligh & Dyer, 1959). The samples plus 1, 2-dinonadecanoyl-sn-glycero-3-phosphocholine (Avanti Polar Lipids, Inc. Alabaster, AL) (50 μ g of 19:0), as an internal standard, were homogenized in four ml of methanol, two ml of chloroform and 1.1 ml of

water. After 15 minutes, two ml of chloroform and two ml of water were added and the samples were vortexed. The tubes were centrifuged at 1200 g for 30 minutes at 16°C and the upper phase discarded. The lower phase was dried under nitrogen and resuspended in 1.5 ml 14% boron trifluoride methanol. The samples were heated at 90°C for 40 minutes and after cooling extracted with 4.0 ml pentane and 1.5 ml water. The mixtures were vortexed and the organic phase recovered (Morrison & Smith, 1964). The extracts were dried under nitrogen, resuspended in 50 µl heptane and two µl injected into a capillary column (SP-2380, 105 m × 53 mm ID, 0.20 µm film thickness). The gas chromatograph was a Perkin Elmer Clarus 500 equipped with a flame ionization detector, an autosampler, a HP Pentium 4 with a data handling system and a HP Laserjet L300. The oven temperatures were 140EC for 35 min; 8EC/min to 220EC, hold for 12 min. Injector and detector temperatures were both at 260EC and helium, the carrier gas, was at 15 psi. Identification of components was by comparison of retention time with those of authentic standards (Sigma). The CVs were: DHA (14.4%), EPA (4.2%), and AA (5.5%).

Covariates

At enrollment, mothers self-reported information on race/ethnicity, parity, education, employment status, marital status, smoking status and symptoms of depression. For marital status, “married” included married or living as married and “other” included single, separated, widowed and divorced. Symptoms of depression were measured using the Edinburgh postnatal depression scale (Cox, Holden, & Sagovsky, 1987).

Statistical Analysis

We used Pearson chi-square tests and Student’s t-tests to determine differences in maternal characteristics. Nonnormal data were log-transformed before statistical tests were performed and geometric means were calculated. Multivariable linear regression models were used to assess the independent associations between methadone treatment status and pre-pregnancy BMI, dietary intake, and nutritional biomarkers. Models were adjusted for maternal age, race/ethnicity, parity, education status, employment status, marital status, smoking status and BMI. Because the ADUP study discontinued use of the EPDS near the end of the study, we could not adjust for depressive symptom scores in the entire cohort. Therefore, we compared results with and without adjustment for EPDS score among women with such data to evaluate it as a confounder. To facilitate interpretation of results from the models of log-transformed dependent variables, we calculated the percent change in the dependant variable between methadone-maintained pregnant women and non-drug using pregnant women as $[\exp(\text{beta coefficient}) - 1] * 100$. Data were analyzed using Stata software version 9.0 (Stata Corp, Austin TX).

Results

Methadone-maintained pregnant women were more likely to be younger, unmarried, unemployed, high-school educated, smokers, and have high depressive symptoms than control women (Table 1). Race and parity were not significantly different between the two groups.

Adiposity

Pre-pregnancy underweight, normal-weight, overweight and obesity were prevalent in 14%, 64%, 14%, and 9% of methadone-maintained pregnant women and 3%, 52%, 20%, and 25% of non-drug using pregnant women, respectively. Mean pre-pregnancy BMI was significantly lower among methadone-maintained pregnant women [22.9 (SD 5.6)] than non-drug using pregnant women [26.4 (SD 6.5), $p = 0.02$]. After adjustment for maternal age, race/ethnicity, parity, education, employment, marital status, and smoking, methadone-

maintained pregnant women had pre-pregnancy BMI values that were 5 kg/m² lower than non-drug using pregnant women [$\beta = -5.0$ (95% CI: $-8.5, -1.4$), $p < 0.01$].

Dietary Intake

Methadone-maintained pregnant women reported a significantly higher energy intake than control women (Table 2). After adjustment for the above confounders as well as pre-pregnancy BMI, methadone-maintained pregnant women reported consuming 34.3% more energy per day than control women. Energy from carbohydrates did not differ between the two groups. However, methadone-maintained pregnant women reported consuming more energy from sweets than control (23.0% vs. 12.9%, $p < 0.01$). In unadjusted analysis, methadone-maintained pregnant women consumed less energy from protein and less fiber than control women. After adjustment for confounders, the results were no longer significant. Also after adjustment, intake of micronutrients and polyunsaturated fatty acids did not differ by methadone-maintained pregnant status.

Nutritional biomarkers

In general, methadone-maintained pregnant women exhibited poorer nutritional status than control women, with lower concentrations of plasma folate, serum lipid-adjusted α -tocopherol, serum lutein+zeanthin and lycopene, red cell DHA and EPA, and higher concentrations of plasma homocysteine (Table 3). After adjustment for confounders, the differences in homocysteine and the carotenoids remained statistically significant. While iron deficiency (serum ferritin < 20 μ g/L) was common in both groups, fewer methadone treated women had iron deficiency (62% vs. 82%, $p < 0.05$).

In sensitivity analysis among all the methadone-maintained pregnant women and the sub-cohort of ADUP with depressive symptom scores, adjustment for EPDS score had no meaningful impact on the results (data not shown).

Discussion

In this pilot study comparing cohorts of methadone-maintained pregnant women and non-drug using pregnant women, our data suggests that methadone treated women were significantly leaner when entering pregnancy than control women, and may be more likely to be underweight. Despite being leaner, methadone treated women may consume significantly more energy per day than control women. We found that methadone treated women may consume more energy from sweets and less energy from protein. Methadone treated women may also be less likely to consume a high-fiber, nutrient-dense diet than control women. But because most of these differences in micronutrient dietary intake were attenuated and not statistically significant after confounder adjustment, these decreases in fiber and micronutrient consumption are likely due to socioeconomic factors and not opiate use alone. Independent of socioeconomic and behavioral factors, methadone treated women exhibited poor serum carotenoid status, indicative of fruit and vegetable consumption, and poor plasma homocysteine, indicative of folate status.

In 1990, the American Dietetic Association stated that “nutrition intervention, planned and provided by a qualified nutrition professional, is an essential component of the treatment and recovery from chemical dependency” (ADA, 1990). Regardless, there has been a paucity of literature describing the nutritional needs of opiate users entering treatment. We are unaware of any other published study to examine the nutritional status of pregnant women prescribed methadone, and because of the physiologic changes that occur during pregnancy, studies of nutrition in non-pregnant populations do not directly translate to populations of pregnant women. Only Zador et al. included 10 pregnant women among their sample of 76 opiate-

using women, and this small group of women was not analyzed separately. Previous studies in non-pregnant populations have shown inconsistent results regarding the adiposity of opiate users. Our results are in agreement with other studies that showed that opiate-users are lean (Saeland, et al., 2011; Szpanowska-Wohn, Kolarzyk, et al., 2000), and that substance-users have lower BMI than their non-drug using counterparts (Himmelgreen, et al., 1998). One other investigative team reported that opiate users have a higher BMI than non-drug users (Nolan & Scagnelli, 2007), but this study was conducted among only 14 methadone patients and 14 non-drug users. Another study reported that the average BMI in a cohort of women was within normal range (20–25 kg/m²), but nearly a quarter of the women in the study were underweight (<20 kg/m²) (Zador, et al., 1996).

Studies of alcohol dependence have suggested that patients require increased nutrition to metabolize drugs, and have a decreased nutrient storage because of damaged livers (Morgan, 1982; Visocan, 1983). Patients with alcohol dependence differ from patients dependent on opiates, but an increased nutritional requirement may be a possible explanation for why we found that methadone-maintained pregnant women had increased energy intake but decreased BMI. Conversely, Zador et al. found that women on methadone had low pregravid BMIs and low energy intake (Zador, et al., 1996). This difference may be due to different dietary intake collection techniques used, as Zador et al. used two 24-hour recalls, and we used a FFQ. Previous studies have consistently reported that opiate users have a high intake of carbohydrates, especially sweets (Himmelgreen, et al., 1998; Kolarzyk, Jenner, Szpanowska-Wohn, Pach, & Szurkowska, 2005; Nolan & Scagnelli, 2007; Saeland, et al., 2011; Szpanowska-Wohn, Dluzniewska, et al., 2000; Zador, et al., 1996), and low intake of fiber and complex carbohydrates (Gambera & Clarke, 1976; Kolarzyk et al., 2005; Kolarzyk, Jenner, et al., 2005; Zador, et al., 1996). Our results are similar for percent of energy from sweets, but we found no difference in percent of energy from carbohydrates between the two groups. Our dietary intake results suggest that methadone-maintained pregnant and control pregnant women have similar micronutrient intake. This was surprising, as previous study has shown substance users to have greater food insecurity than non-drug users (Himmelgreen, et al., 1998) and have limited access to food (Saeland, et al., 2011). But our results are similar to several other assessments, which found that micronutrient intake among opiates users is generally high, with the exception of only one or two micronutrients, most commonly iron, and vitamins A and C (Gambera & Clarke, 1976; Kolarzyk, Chrostek Maj, et al., 2005; Szpanowska-Wohn, Kolarzyk, Pach, & Targosz, 2004). For example, Zador et al. found that opiate using women had a mean micronutrient intake between 70–207% of the Australian recommended dietary intake, with the exception of iron and zinc (55% for both) (Zador, et al., 1996).

The American Dietetic Association hypothesizes that “abuse of drugs accelerates nutritional needs beyond normal, so that even a well balanced diet may be inadequate” (ADA, 1990). Despite having similar intake as control women, we found methadone-maintained pregnant women had significantly poorer status for several micronutrients. Nazrul Islam et al. found that substance-users had significantly poorer α -tocopherol, ascorbic acid and retinol than non-drug users (Nazrul Islam, et al., 2001). Unlike our population, the cohort in Nazrul Islam et al.’s study was Bangladeshi males, mostly employed, who used multiple substances, and was not adjusted for smoking status. Therefore, it is not surprising that our results are not similar. Methadone treated women in our study had less iron deficiency than control women. Pregnancies exposed to methadone are considered “high risk” and may be screened more carefully for iron deficiency and treated earlier. Unfortunately, we lacked data on supplement use to test this hypothesis. This finding may also be due to chance alone.

As is often the case with pilot studies, our study is limited by a small sample size. Additionally, the methadone treated women in our study may be better off than the general

methadone-maintained pregnant population because our study required women to be adherent to their treatment, on stable dosing, and be HIV negative. Although we adjusted for confounders, and race and parity were similar between the groups, socioeconomic and smoking status differed significantly between the two groups. We did not have data to control for all the factors that may have affected nutrition, for example, supplement use, alcohol use, severity of opiate use, other drug use and behavioral health disorders such as anxiety. There is no gold standard for measuring nutrition, and all methods, including ours, have limitations. Assessing dietary intake using FFQ relies on memory and cognitive function and is a measure of average intake over the last three months. FFQs are particularly limited in their ability to measure total energy intake (Subar et al., 2003), so our results may be subject to bias. The nutritional biomarkers we used indicate short- and medium-term nutritional status and are influenced by factors other than dietary intake, including genetic and lifestyle factors (Willett, 1998).

Poor nutrition is a concern for all opiate users entering treatment, but is especially a concern for pregnant women and their infants. Our pilot study found that methadone maintained pregnant women may be at increased risk of entering pregnancy underweight and with nutrient deficiencies. Larger studies are needed to follow-up on this important finding given the high-risk nature of these pregnancies and the associations between nutrition and poor outcomes of pregnancy.

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Glossary

Methadone Maintenance Therapy	A treatment program used to treat opiate addiction in which patients receive daily doses of methadone, a synthetic agent that prevents opiate cravings and withdrawal
Body Mass Index	A measure of general adiposity that is calculated from a person's weight divided by their height, squared
Dietary Intake	A person's usual consumption of foods and beverages usually averaged over a period of time. There is no gold standard of measuring dietary intake, but common measurement tools include food frequency questionnaires and 24-hour recall interviews
Micronutrient	The vitamins and minerals required, usually in small amounts, for biological function in humans
Essential fatty acid	The fats, primarily polyunsaturated fats and monounsaturated fats, required for human survival

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Table 1

Demographics of methadone exposed and non-exposed pregnant women.

Maternal Characteristic	Methadone treated (N=22)	Control (N=119)	p-value ^I
Maternal age, mean (SD)	27.1 (6.1)	31.3 (5.7)	<0.01
Parity, N (%)			
0	7 (31.8)	50 (42.0)	
1–6	15 (68.2)	69 (58.0)	0.37
Race/ethnicity, N (%)			
White, non-Hispanic	20 (90.9)	96 (80.7)	
Non-white or Hispanic	2 (9.1)	23 (19.3)	0.25
Married ² N (%)			
Married	9 (40.9)	87 (73.1)	
Other	13 (59.1)	32 (26.9)	<0.01
Employment status, N (%)			
Employed	4 (18.2)	67 (56.3)	
Unemployed	18 (81.8)	52 (43.7)	<0.01
Educational status, N (%)			
>High school degree	7 (31.8)	100 (84.0)	
High school degree	15 (68.2)	19 (16.0)	<0.01
Smoker, N (%)			
Non-smoker	6 (27.3)	104 (87.4)	
Currently smokes	16 (72.7)	15 (12.6)	<0.01
Symptoms of depression ³ , N (%)			
EPDS < 12	9 (40.9)	82 (79.6)	
EPDS ≥ 12	13 (59.1)	21 (20.4)	<0.01

^I Student's t-test for maternal age, chi-squared test for other characteristics² Married=married or living as married, Other=single, separated, widowed and divorced³ Scored using the Edinburgh postnatal depression scale (EPDS); 16 control women missing EPDS

Table 2
Mean energy-adjusted maternal nutrient intake in the 3rd trimester by methadone treatment status

Dietary constituent	Methadone treated n=22		Control n=119		p-value ²	p-value ³	Adjusted ⁴ % change	p-value
	Mean ¹	(95% CI)	Mean	(95% CI)				
Energy, kcal/d	3033	(2595–3471)	2172	(2041–2303)	40.6	<0.01	34.3	<0.01
Carbohydrate, % kcal	56.7	(53.0–60.6)	54.4	(52.9–56.0)	4.2	0.27	7.4	0.14
Protein, % kcal	12.0	(11.2–12.8)	13.3	(12.7–13.8)	–9.7	0.03	–5.9	0.28
Fat, % kcal	31.5	(28.6–34.8)	33.0	(31.8–34.3)	–4.4	0.35	–10.0	0.10
Fiber (g/d)	6.2	(5.3–7.2)	8.2	(7.6–8.8)	–24.8	<0.01	–12.6	0.17
Folate (DFE/d)	217.6	(183.0–258.8)	256.3	(242.0–271.4)	–15.1	0.03	–9.6	0.27
Vitamin C (mg/d)	70.5	(55.6–89.3)	90.5	(82.2–99.6)	–22.1	0.04	–7.2	0.64
Vitamin E (aTE/d)	4.0	(3.4–4.6)	4.7	(4.4–5.0)	–15.0	0.05	–5.2	0.60
Vitamin A (IU/d)	3326	(2350–4706)	3818	(3458–4215)	–12.9	0.31	5.4	0.74
Iron (mg/d)	6.8	(5.7–8.0)	7.3	(7.0–7.8)	–8.1	0.26	–5.1	0.56
PUFA (g/d)	7.5	(6.5–8.7)	7.8	(7.3–8.3)	–3.3	0.65	–4.7	0.62

DFE=dietary folate equivalent, aTE=α-tocopherol equivalent, PUFA=polysaturated fatty acids

¹Mean for energy is arithmetic mean; means for other nutrients are geometric means, adjusted for energy intake using the density approach, and presented as intake per 1000 kcal/day.

²Calculated as $[\exp(\beta) - 1] \times 100$. Nutrient values were log transformed before tests were performed.

³Student's t-test.

⁴Adjusted for: maternal age, race/ethnicity, parity, education, employment, marital status, smoking, and BMI

Table 3

Mean maternal micronutrient and EFA status, by methadone maintenance therapy treatment

Nutrient	Methadone treated ¹		Control			
	Mean ² (95% CI) n=21	Mean (95% CI) n=119	% change ³	p-value ⁴	Adjusted ⁵ % change	p-value
Folate (ng/ml)	2.5 (2.3–2.6)	2.7 (2.6–2.8)	–20.0	0.02	–3.0	0.79
Homocysteine (μmol/L)	4.0 (3.3–4.8)	2.4 (2.3–2.7)	63.4	<0.01	62.6	<0.01
25(OH)D (nmol/L)	89.4 (75.1–106.6)	82.9 (76.4–89.9)	7.9	0.47	7.4	0.55
Ascorbic acid (μg/ml)	9.5 (7.3–12.2)	10.7 (9.8–11.6)	–11.3	0.28	10.4	0.47
α-tocopherol (μg/ml)	14.7 (13.1–16.5)	16.6 (15.8–17.4)	–11.3	0.08	–8.7	0.25
α-tocopherol/total lipids	0.021 (0.018–0.024)	0.024 (0.023–0.025)	–13.5	0.01	–9.0	0.16
Retinol (μg/ml)	0.44 (0.36–0.54)	0.44 (0.42–0.46)	1.6	0.83	8.7	0.34
Lutein+zeaxanthin (μg/ml)	0.05 (0.03–0.09)	0.14 (0.12–0.15)	–62.3	<0.01	–59.4	<0.01
β-cryptoxanthin (μg/ml)	0.07 (0.04–0.11)	0.09 (0.07–0.11)	–52.9	0.24	–59.4	0.26
Lycopene (μg/ml)	0.17 (0.13–0.24)	0.29 (0.26–0.31)	–39.7	<0.01	–47.5	<0.01
β-carotene (μg/ml)	0.06 (0.02–0.14)	0.10 (0.08–0.12)	–26.1	0.52	–20.9	0.66
Ferritin (ng/ml)	13.5 (9.2–20.0)	9.5 (8.2–10.9)	60.8	0.16	115.9	0.07
sTfR (nmol/L)	16.9 (13.8–20.6)	18.5 (17.5–19.6)	–9.0	0.23	–16.0	0.06
Docosahexaenoic acid (%)	1.9 (0.9–3.8)	2.3 (1.8–2.9)	–89.7	0.01	–85.0	0.10
Eicosapentaenoic acid (%)	0.14 (0.09–0.23)	0.24 (0.21–0.29)	–42.3	0.02	–3.9	0.89
Arachidonic acid (%)	7.4 (4.9–11.3)	9.2 (8.1–10.5)	–18.9	0.24	9.3	0.69

EFA=essential fatty acid, 25(OH)D=25-hydroxyvitamin D, sTfR=Serum soluble transferrin receptors

¹Methadone mothers: n = 17 for fat-soluble vitamins (α-tocopherol, α-tocopherol/total lipids, retinol, and the carotenoids)²Means for all micronutrients and EFAs are geometric means.³Calculated as $\exp(\beta) \cdot 100$. All micronutrients and EFAs were log transformed before tests were performed.⁴Student's t-test.⁵Adjusted for: maternal age, race/ethnicity, parity, education, employment, marital status, smoking, and BMI