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Are male neonates more vulnerable to neonatal abstinence syndrome than female neonates?

Annemarie Unger[1], **Reinhold Jagsch**[2], **Andjela Baewert**[1], **Bernadette Winklbaur**[1], **Klaudia Rohrmeister**[3], **Peter R. Martin**[4], **Mara Coyle**[5], and **Gabriele Fischer**[1]

[1]The Department of Psychiatry and Psychotherapy, Medical University of Vienna, Austria

[2]The Department of Psychology, University of Vienna, Austria

[3]The Department of Paediatrics, University of Vienna, Austria

[4]Addiction Center, Department of Psychiatry, Vanderbilt University School of Medicine, Nashville TN 37212

[5]The Department of Pediatrics, Warren Alpert Medical School of Brown University, Providence, Rhode Island, USA

Abstract

Objective—Prior studies have shown an increased vulnerability among males, to adverse outcomes during the postnatal period. The majority of children exposed to opioids and other medication in utero develop a neonatal abstinence syndrome (NAS), yet individual predisposition for NAS is poorly understood. This investigation examines the role of neonatal sex in the postnatal period, for neonates exposed to standardized opioid maintenance treatment in utero with a focus on the neonatal abstinence syndrome (NAS) regarding severity, medication requirements and duration.

Patients and Methods—This is a secondary analysis of data collected in a prospective randomized, double-blind, double-dummy multi-center trial examining the comparative safety and efficacy of methadone and buprenorphine during pregnancy (Maternal Opioid Treatment: Human Experimental research MOTHER – study). 131 neonates born to opioid-dependent women randomized at six US sites (n=74) and one European site (n=37) were analyzed. Sex-based differences in birth weight, length, head circumference, NAS duration, NAS severity, and treatment parameters of full-term neonates were assessed.

Results—Males had a significantly higher birth weight (p=0.027) and head circumference (p=0.017) than females, with no significant sex difference in rates of preterm delivery. No significant sex-related differences were found for NAS development, severity, duration, or medication administered with non significant differences in concomitant drug consumption during pregnancy (p =0.959).

Corresponding author: Annemarie Unger, Medical University of Vienna, Department of Psychiatry, Währinger Gürtel 18-20, 1090 Vienna, Austria, Tel. +43140400 -3547.

Conflict of interest statement: None to declare.

The ethics committee at the Medical University of Vienna approved the MOTHER trial (INB number 451/1998. All participants signed informed consent.

Conclusions—This unique prospective study shows similar postnatal vulnerability for both sexes, suggesting that factors other than sex are the major determinants of clinically significant NAS.

Keywords

opioid dependence; methadone; buprenorphine; pregnancy; neonatal abstinence syndrome; sex differences

Introduction

Health policy institutions and research funding organizations have been advocating the importance of considering sex as a variable that fundamentally affects health outcomes and disease processes across the lifespan of men and women (1). Sex is a biological determinant of relevance to all human cells and physiological processes. Although the study of sex differences has developed as a science recently, and has become established in some areas, other areas are still lacking, including the study of sex differences of the fetus and neonate (2).

There is considerable evidence to support increased male vulnerability to adverse outcomes during the postnatal period, especially when maternal stress factors are present (3,4). Women carrying male fetuses have a higher incidence of preterm labor, pregnancy-induced hypertension, gestational diabetes mellitus, failure to progress, and caesarean delivery (5). Androgen precursors, such as testosterone and dihydrotestosterone, delay pulmonary maturity and are involved in the production of oestrogen, which may facilitate labor, and therefore pre-term birth (6). Male fetuses have higher rates of fetal distress, lower Apgar scores and higher perinatal mortality, and their mothers have a higher incidence of labor dystocia (7,8).

Opioid-dependent pregnant women represent a highly vulnerable population with numerous stress factors, including a high rate of psychiatric co-morbidity, with prevalence rates ranging between 10% and 73% for those meeting the criteria for a current Axis-I disorder according to DSM-IV (9). Further problems derive from the concomitant use of illicit substances, difficult life circumstances due to poverty and unemployment, and nicotine co-dependence (10,11). Maternal and neonatal outcomes of pregnancies in opioid-dependent women are optimized when women are in opioid agonist maintenance treatment (12,13) with a long-acting synthetic opioid such as methadone or buprenorphine. Nevertheless, the neonatal abstinence syndrome (NAS) of the newborn may develop in the first days after birth in as many as 70% of newborns exposed to opioids in utero (14,15,16). NAS is a condition caused by withdrawal from opioids and is associated with dysfunction of the central and autonomic nervous system, the gastrointestinal tract and the respiratory system (17). Although the type of opioid agonist medication used in pregnancy is a significant determinant of neonatal abstinence, other factors such as prenatal tobacco exposure (10,11,18), the consumption of concomitant illicit substances (15), maternal opioid metabolism as well as postnatal treatment structure also play a role.

The influence of individual risk factors in the development of NAS is not well understood (19). The effect of fetal sex-related hormonal differences, on opioid receptor sensitivity in the developing fetus is still unclear. While some evidence suggests a milder course of NAS in preterm neonates, due to the immaturity of opioid receptors (20), sex differences in NAS intensity have only been investigated in very few prior studies (19, 21). These prior studies on the influence of sex on NAS have provided inconsistent results. While one study (19) showed no significant sex-related differences in a retrospective chart review of 308

methadone-exposed neonates, another; looking at a population of 64 neonates exposed to methadone found a higher vulnerability of males to NAS intensity in the first four days post partum with no sex-specific differences in rates of NAS treatment (21). Based on these prior findings, further exploration of this topic is needed in order to replicate and strengthen prior results. Furthermore, no prior study has looked at sex differences of neonates exposed to buprenorphine in utero, so this cohort offered the unique opportunity to do both.

This purpose of this study was to examine the role of neonatal sex in the postnatal period, for neonates exposed to opioids in utero with a focus on the NAS and birth outcome measurements. This is a secondary analysis of unique data gained through a prospective randomized controlled trial comparing the safety and efficacy of methadone and buprenorphine in pregnancy ("MOTHER study") for which the primary outcomes have recently been reported (22).

Ethics Statement

All sites of the MOTHER study had IRB approval.

Methods

This study is a secondary analysis of data generated in the MOTHER study.

The MOTHER study

The MOTHER study was a multi-center, randomized, double-blind, double-dummy, clinical trial, involving eight sites in North America and Europe, designed to evaluate maternal and neonatal safety, and efficacy of methadone and buprenorphine in opioid-dependent pregnant women (22). Inclusion criteria included opioid dependence, uncomplicated single pregnancy, and enrolment between 6-30 weeks estimated gestational age of pregnancy. Exclusion criteria for women were: other medical conditions, current benzodiazepine use/ abuse, current alcohol use/ abuse, pending legal issues, an acute severe psychiatric condition in need of immediate treatment, and multiple-fetus pregnancies (23, 24). Details of the screening process including enrollment results have been published elsewhere (25). The study duration of over 3 years (May 2005 to October 2008) at seven participating centers (one center participated in screening yet did not randomize any patients) yielded to a sample size of 131 completers (75% of the randomized sample of 175) and their singleton neonates. The 6 US American sites contributed to 72% of the cohort, namely Burlington (University of Vermont, n=26), Philadelphia (Thomas Jefferson University, n=23), Baltimore (Johns Hopkins University, n=17), Nashville (Vanderbilt University, n=13), Detroit (Wayne State University, n=12), Providence (Brown University, n=3) and one European center (28% of the cohort), namely Vienna (Medical University of Vienna, n=37). Further details on recruitment, randomization and induction have already been published elsewhere (22-25). The primary outcome data of the MOTHER trial are publically available as a database [http://Jefferson.edu/jmc/pedicatrics/mother/databases.cfm] and have a user guide [http://www.jefferson.edu/jmc/pediatrics/mother/MOTHER_Users_Guide.pdf]. This analysis focuses on postnatal outcomes so that postnatal procedures of the MOTHER trial are described in more detail below.

Course of pregnancy, Delivery and Perinatal Care—The stringent study protocol required daily, supervised medication intake, thrice weekly supervised urine drug screens, standardized ultrasound monitoring, and delivery at the site hospital. Neonates remained hospitalized for one to ten days postpartum, and a standardized NAS rating was performed by trained nursing staff every four hours while in hospital. All staff, except the local site pharmacist, remained blinded to the type of medication exposure throughout the course of

the study. If a neonate was discharged from hospital before day 10, it was expected that s/he and the mother would remain in a residential setting, where NAS observation by trained staff could be continued until day 10, with NAS scores collected twice daily and consecutive treatment, at least eight hours apart) (22).

Outcome Measurements—For the present analysis on sex differences, the following parameters were compared between male and female full-term neonates: head circumference in cm, birth weight in grams, length in cm, birth mode (vaginal, primary or repeat caesarean section), estimated gestational age in weeks, intensive care unit (yes/no), preterm births (defined as an estimated gestational. age less than 37 weeks at time of delivery), Apgar scores at one and five minutes and NAS outcome parameters (see "NAS assessment" below) (22).

Neonatal Abstinence Syndrome (NAS) assessment—NAS was assessed by trained nurses (blinded for intra-uterine medication exposure) every four hours, using a validated modified version of the Finnegan scale (17,26), comprised of 19 opioid-withdrawal signs (i.e. excessive high pitched crying, sweating, sneezing, nasal stuffiness, tachypnoea, hyperactive Moro reflex, tremors, reductions in sleep duration after feeding) to determine the need for treatment. The following NAS outcome variables were compared: Peak MOTHER-NAS-Score (the daily peak NAS scores were summed up to provide a total NAS score), Morphine dose total in mg (the amount of medication administered over the entire course of NAS treatment was totaled), NAS treatment duration (the number of days NAS medication was received by the infant) and Morphine dose / day (total amount of morphine given to infant divided by total number of days treated for NAS) (22).

NAS treatment protocol—NAS was treated with morphine drops (0.4 mg/ml or 0.05% Morphine HCl) dosed according to the total NAS score. Treatment was initiated when the NAS score was equal to or greater than 9, with morphine doses (in parentheses) selected according to the NAS score as follows: 0-8 (0.04 mg/dose), 9-12 (0.04 mg/dose), 13-16 (0.08 mg/dose), 17-20 (0.12 mg/dose), 21-24 (0.16 mg/dose), ≥ 25 (0.20 mg/dose) (22).

Statistics

Statistical analysis was conducted using SPSS 16.0 for Windows. Chi-square tests or Fisher's exact tests were used for categorical data, the latter in cases of four-field schemes if at least one cell showed an expected value of five or less. In case of significance, the direction of the standardized residuals was used to help interpret the results. Comparisons of means between two groups were performed using t-tests for independent samples. Social and demographical variables which differed significantly between the drugs studied were used as potential covariates for further analyses. In the case of neonatal outcome variables, two-way analysis of variance (ANOVA) was employed, with the two factors in the design being study drug (methadone or buprenorphine) and neonatal sex. P-values are provided for the two main effects, as well as for the interaction between study drug and sex of neonate. For analytic purposes, an alpha of $p<0.05$ was considered significant. In case of significant results, values for effect sizes (partial eta-squared values) and observed power were added. The data used for this secondary analysis was NAS data collected for the MOTHER study (22). This data included the following variables: number of infants requiring treatment, number of days medicated for NAS, total NAS score (sum of peak daily NAS scores), and total amount of medication for NAS were determined. Beside the factor site, four maternal variables (maternal age, number of cigarettes smoked in the last 24h before delivery, number of cigarettes smoked on a typical day, duration of heroin consumption) were used as possible covariates for analyzing sex-specific aspects of neonates. As data concerning

cigarettes smoked 24 hours before delivery were rather sparse this variable was dropped as a covariate because a second variable concerning cigarette smoking was available.

Results

The sex distribution among methadone and buprenorphine exposed neonates was similar (p=0.800). Due to the fact that the number of pre-term deliveries was not balanced between the sexes (6 male and 12 female of 18 pre-terms), the final analysis of sex differences excluded the preterm neonates (original N= 131 minus 18 pre-terms yielded to N=113).

Characteristics of preterm deliveries

Of the complete sample of 131 neonates delivered in this study, 18 neonates (13.7%) were born preterm (EGA week < 37). In contrast to a nearly equal number of male (n = 60, 53%) and female (n = 53, 47%) infants reaching full term, 33% (n = 6) of the infants delivered pre-term were male and 67% (n=12) were female, a non-significant difference (p=0.119). Although full-term neonates received higher Apgar scores, these were not significantly different from preterm neonates (p=0.291 and p<0.312, respectively).

Even though the differences in the peak NAS score and the NAS-treatment variables between the full term and preterm infants (treatment dose total (p = 0.610), adjusted dose per day (p=0.694), and number of treatment days (p=0.460) were not significant, preterm deliveries were excluded from further sex-specific analyses, because of the potential confounding effect of gestational age on outcomes.

Maternal Characteristics

Mothers of the 113 full term neonates treated with methadone (n=59) and buprenorphine (n=54) did not differ significantly in ethnicity, marital status, education, employment status or BMI (all p > 0.20). No differences were found in poly-substance use, age of first heroin use, drug composite score or money spent for drugs in the last month (all p > 0.20), nor for concomitant drug use during investigated period in pregnancy (all p > 0.10). No significant sex differences were found for type of delivery (vaginal/caesarean), labor complications or sex-related differences in neonatal complications.

Urine toxicology

19,8 % of all women had a drug positive urine screen (opiate, benzodiazepine, cocaine or a combination thereof) four weeks prior to delivery. Irrespective of medication, the rates of concomitant consumption were not significantly different between mothers expecting male or female neonates (p=0.959).

Birth outcome measurements

Male newborns were significantly heavier at delivery (p=0.027, partial eta-squared = 0.045, observed power 0.606) and had larger head circumferences (p=0.017, partial eta-squared = 0.057, observed power = 0.673) compared to females, irrespective of study medication, with no significant differences in birth lengths or Apgar values (see table 2).

Neonatal Abstinence Syndrome (NAS)

Neonatal sex did not affect the main findings with 47 % (61 neonates) not requiring NAS medication - of those 61 neonates, 27 were female (44.3%) and 34 male (55.7%) (p=0.250) (21). No significant sex-specific differences were found in the variables concerning NAS course and treatment variables. (see table 2).

Discussion

This analysis focused on sex-differences in the neonatal outcome and NAS of infants exposed to opioids in utero. Pre-defined neonatal variables were examined, accounting for influencing factors such as nicotine use and concomitant drug use during pregnancy and after delivery. Characteristics of participants were similar to those used in previous trials, doses of maintenance medication (buprenorphine or methadone) at delivery were in a sufficient and comparable range (14-16,27-29); the double-blind, double-dummy procedure which continued until four weeks postpartum led to the omission of artifacts that would otherwise have been generated by individual bias.

Birth outcome measurements

A significant sex-related difference was found for birth weight and head circumference, both of which were higher for male neonates. These results are consistent with prior research in other populations and have been hypothesized to be a result of androgen-mediated action (3,30,31). Another possible explanation for accelerated growth in the male fetus has been that sex-determining genes located on the Y chromosome exert a modulating effect on the insulin-like growth factor (32) and on the sex-specific adaptations of the human placenta (33). However, these findings are not specific to opioid dependent women and do not differ from those found in the general population (34,35).

But overall, with an average birth weight of 3,121 (SD 428.29) grams, fullterm neonates were in the upper range when compared to other high-risk populations with a very low rate of preterm deliveries in this high risk population (36).

Neonatal abstinence syndrome

The main focus of this study was on the neonatal abstinence syndrome, a phenomenon affecting the majority of neonates exposed to opioids in utero (13). A most recently published Cochrane review by Osborne et al. reports between 48 to 94 % of neonates affected by some degree of NAS (37) with more than half requiring treatment. 47 % neonates of our investigated target group did not require treatment for NAS, which was distributed evenly between the sexes without significant differences in the comparison of severity, treatment and duration. The low percentage found in our study may have been a result of multiple factors including the comprehensive multi-professional team approach which included daily clinical contacts, the voucher incentive program, sufficient medication dosing and the standardized structure with adjusted inter-rater reliability in NAS scoring and treatment application in the nurseries.

In contrast to our results, Jansson et al. recently reported about significantly more severe NAS symptoms in males compared to females in the first four days of life, without a significant sex-based difference in the rate of treatment requirement. However, those male neonates that did require treatment had a significantly longer treatment course (21). This study comprised 64 methadone-exposed neonates and specifically looked at cardiac measures (heart rate and cardiac vagal tone) using electrocardiogram data collected on days 1 and 3 of infant life as indicators of autonomic dysregulation, and subsequently found that reductions in vagal tone correlated with a higher intensity of NAS symptoms for neonates independent of sex. A limitation refers to the retrospective nature of the design including the assessment of data on urine toxicologies, as subjects were enrolled upon the birth of their infant. However, the design was nonetheless able to account for concomitant consumption of illegal substances, nicotine and SSRI/SNRI exposure, the last two of these were identified as predictors of NAS intensity.

Another previous investigation of neonatal sex and NAS included the so far largest cohort of 308 infants exposed to methadone found no significant sex differences (19) in need for treatment, amount of medication required to treat and duration of NAS treatment in an observational design. The investigation was based on a retrospective chart review which might be seen as a limitation, however, concomitant consumption and nicotine exposure was also accounted for.

Although opioid-dependent women represent a high-risk population for adverse pregnancy outcomes, this study population had a very low rate of pre-term deliveries with 13,7% prior to week 37 irrespective of infant sex. In the United States, rates of preterm delivery in the general population vary between 8.3% and 16.2%, as found in a retrospective cohort study comprising 46,375,578 women who delivered singleton births from 1989 through 2000 (38). A recent survey of women in a methadone maintenance program, found a rate of pre-term birth (29.1%) nearly three times the national average (11.1%) (39). The rate of pre-term delivery is a major public health care issue worldwide, not only due to the cost of health care interventions arising both short and long term, but also due to the requirements for educational and social support, and the loss of labor market productivity associated with disabilities. Through the provision of high quality standards in prenatal and perinatal care to high-risk groups, such as opioid-dependent pregnant women, this societal and economic burden could effectively be diminished (40).

The major strengths of this analysis lie in the quality of data collected in a unique prospective double-blind, double-dummy, multi-center design, the large number of neonates included, and the standardized approach (blinded for medication) towards NAS assessment. Furthermore, the cohort of the MOTHER trial underwent pregnancy in a homogeneous and structured treatment setting with a multi-professional team approach employing voucher-based incentives for drug-free urine screens, an effective contingency management tool which has previously been shown to increase treatment retention and efficacy (41,42). The results presented were attained in a very homogeneous study population following a stringent scientific protocol.

Limitations

The limitation of this analysis may lie in the number of infants assessed; perhaps an even larger study population would have found significant sex differences in NAS outcomes. Furthermore, some factors that may have played a role in birth measurement outcomes such as nutritional intake during pregnancy were not accounted for. However, for industrialized nations, prior studies have reported little influence of nutrient intake on birth weight (43).

Conclusion

In conclusion, the issue of gender research is of increasing importance in all medical fields, and there is a particular lack of information on fetal and neonatal sex issues. Research needs to begin at an early stage, particularly in light of the tremendous health care costs generated by the morbidities encountered when prenatal care is limited, and substance dependence is an issue (39,44). The need for gender related medical research is warranted, as sex-specific needs and problems can only be addressed through effective interventions when they have been determined by way of clinical research settings.

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Table 1

Sociodemographic and addiction characteristics. (N= 113)

	Methadone (n=59)		Buprenorphine (n=54)			
	mean	**SD**	**mean**	**SD**	***t/Chi²***	***p***
Maternal age (in years)	27.39	5.34	25.41	5.21	1.994	0.049
Ethnicity n (%)					0.267	0.745[a]
Caucasian	53 (90%)		50 (93%)			
Non-Caucasian	6 (10%)		4 (7%)			
Marital status n (%)					1.448	0.229[a]
Unmarried	49 (83%)		49 (91%)			
Married	10 (17%)		5 (9%)			
Employment status n (%)					0.507	0.477[a]
Unemployed	50 (85%)		43 (80%)			
Employed	9 (15%)		11 (20%)			
Education (in years)	11.27	2.08	11.54	1.97	-0.696	0.488
BMI	25.99	6.51	24.65	4.64	1.242	0.217
Number of cigarettes/typical day	12.83	5.75	10.63	5.88	2.008	0.047
Number of cigarettes/day (last 24 hours prior to deliery)	12.21	7.66	8.35	6.64	2.654	0.009
Age at first heroin use	18.08	7.68	20.12	8.18	-1.225	0.224
Duration of heroin consumption (months)	43.41	55.45	25.43	27.40	2.213	0.030
Polysubstance use n (%)					0.185	0.667[a]
No	45 (76%)		43 (80%)			
Yes	14 (24%)		11 (20%)			
Money spent on drug (last 30 days)	760.15	1,435.49	725.93	1,394.38	0.128	0.898
Drug composite score	0.30	0.10	0.28	0.10	1.156	0.250
Concomitant drug use (op, co, am, thc)						all >0.10

[a] by Chi-square test.

Table 2

Sex-related differences in delivery and Neonatal Abstinence Syndrome (NAS) variables in relation to maternal maintenance medication pregnant women were treated with. (N=113, excluding 18 preterm births)

	Methadone				Buprenorphine				Significance		
	Females (n=27)		Males (n=32)		Females (n=26)		Males (n=28)		p_{SD}	p_{Sex}	p_{IA}
	mean	SD	mean	SD	mean	SD	mean	SD			
AGPAR1	8.12	1.35	7.79	1.68	8.38	0.58	8.21	1.37	0.165	0.300	0.736
AGPAR5	8.97	1.02	8.85	1.09	9.14	0.65	9.03	1.09	0.301	0.516	0.973
Weight (in g)	2,961.44	419.93	3,191.17	333.84	3,100.57	434.72	3,213.88	481.13	0.297	0.027	0.447
Length (in cm)	49.30	2.36	49.65	2.00	49.94	1.76	50.19	2.52	0.133	0.435	0.902
Head circumference (in cm)	33.19	1.55	34.11	1.15	33.92	1.20	34.30	1.64	0.089	0.017	0.306
Parity	1.53	1.04	1.61	1.14	1.51	1.33	1.72	1.31	0.811	0.459	0.724
Peak MOTHER-NAS-Score	13.59	5.09	13.10	6.35	11.35	3.15	10.61	3.75	0.011	0.500	0.894
Morphine dose total (in mg)	13.10	34.52	25.83	70.38	4.33	3.71	3.24	2.28	0.041	0.437	0.356
NAS treatment (in days)	11.99	15.58	13.72	20.56	6.55	6.97	4.35	5.63	0.005	0.927	0.440
Morphine dose/day (in mg)	0.45	0.63	0.61	1.05	0.21	0.21	0.15	0.16	0.004	0.667	0.346

p_{SD} Probability Study Drug, p_{Sex} Probability Sex of Neonate, p_{IA} Probability Study Drug × Sex of Neonate.

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