

# ARE INFANTS EXPOSED TO METHADONE *IN UTERO* AT AN INCREASED RISK FOR MORTALITY?

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## ABSTRACT

### Background

The prevalence of opioid abuse is increasing in North America. Opioid abuse during pregnancy can cause medical, obstetric and psychosocial complications. Neonates exposed to opioids *in utero* often develop the neonatal abstinence syndrome. Methadone maintenance therapy is the treatment of choice for maternal opioid dependency. There have been unsupported concerns that infants cared for by mothers treated with methadone have higher mortality rates during the first year of life than in the general population.

### Objectives

To compare the mortality rates of infants exposed to methadone *in utero* to those of general population in Ontario, Canada.

### Methods

We utilized several provincial and national databases including those of the Office of the Chief Coroner of Ontario, the Canadian Institute for Health Information, and the Ontario Infant Mortality Rate Report. Reference organ weights were obtained from the peer reviewed literature.

### Results

The Office of the Chief Coroner of Ontario has reported 8 deaths in children under one associated with *in utero* methadone exposure between January 1, 2006 and December 31, 2010. Over the same period there have been a total of 1103 cases of neonatal abstinence syndrome recorded in the province. The mean infant mortality rate in Ontario for children under the age of 1 year over the same period was 5.2 per 1000 live births. The odds ratio for mortality among children with neonatal abstinence syndrome was not different from that in the general population [OR 1.45 (95% confidence interval 0.471-4.459)] (p=0.56).

### Conclusion

The available data do not support the concerns that children under the age of one year, born to mothers on methadone maintenance therapy (MMT) are at an increased risk for mortality.

**Key Words:** *Methadone, pregnancy, mortality, infant*

The prevalence of opioid dependence amongst women has been on the rise in many North American jurisdictions over the last 5 years.<sup>1</sup> It has been estimated that approximately 90% of drug-abusing women are within childbearing age, and the National Survey

of Drug Use and Health revealed that 5.1% of pregnant women reported using illicit drugs.<sup>2,3</sup> The College of Physicians and Surgeons of Ontario (CPSO) has estimated that oxycodone prescriptions have increased by approximately 850% from 1991-2007 which parallels the rise in

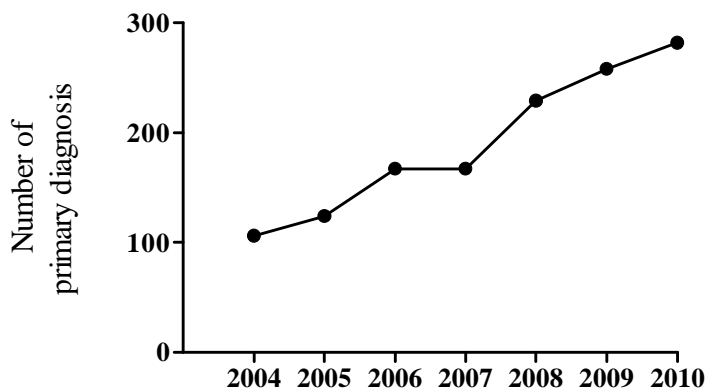
Ontarians requiring methadone maintenance therapy (MMT), from roughly 700 to 16,400 over the same time period<sup>1,4</sup> (MMT has been practiced in North America as the preferred method of treating drug dependency since the 1960s.<sup>4</sup> MMT is generally considered safe and is recommended for opioid-dependent women during pregnancy by the American Academy of Pediatrics and the Centre for Substance Abuse Treatment.<sup>2</sup> The benefits of MMT include improved birth weight, decrease in infant mortality, decreased withdrawal symptoms in both mother and baby, and a

decrease in the dangers associated with maternal drug seeking behaviours.

While crossing the placenta, methadone has not been identified as a human teratogen.<sup>4</sup> Infants exposed to methadone *in utero* commonly display signs of opiate withdrawal after birth. Currently, information regarding the risk of mortality and the long-term effects of *in utero* methadone exposure is scarce.<sup>5</sup> In Ontario, the incidence of neonatal abstinence syndrome (NAS) diagnosis has closely paralleled the increase in rates of known maternal addiction (figure 1).

**FIG. 1** The increasing prevalence of primary NAS diagnosis in Ontario from 2004-2010. This data was extrapolated from the Canadian Institute for Health Information (PCMCH, 2012).

### Prevalence of Primary NAS diagnosis in the Province of Ontario



This increase has been associated with a significant burden on neonatal intensive care units across the province. Approximately 85% of babies exposed to methadone *in utero* develop at least one sign of NAS, however this number has been reported to range between 13-94%.<sup>6-8</sup>

The symptoms of NAS include central nervous system (CNS) hyperirritability, seizures, poor feeding, and metabolic and respiratory disturbances.<sup>7</sup> With the increase in the number of

infants exhibiting signs of NAS<sup>9</sup>, there has been a clinical impression that there may be a higher rate of mortality amongst this group of young methadone exposed infants, than that of the general population. The objective of this investigation was to quantify the rates of infant mortality amongst *in utero* methadone-exposed children younger than one year of age and to compare it to that of the general population in Ontario, Canada.

## METHODS

Several provincial and national databases were employed to retrieve the required data for this investigation:

1) Information was obtained on all cases of child fatalities in Ontario identified as exposed to methadone *in utero* from January 2006 to December 2010. These data are recorded at the Office of the Chief Coroner of Ontario (OCC). A paediatric death investigation was completed for all cases in accordance with the OCC's policy, which included the Protocol for the Investigation of Sudden and Unexpected Deaths in Children Under Five Years of Age. The information collected included; demographics, drugs of exposure, post-mortem reports, toxicology screens, and diagnosed causes of death.

2) The number of cases of NAS diagnosis in Ontario was obtained from the Canadian Institute for Health Information (CIHI).<sup>10</sup> CIHI data are collected in accordance with the Standards for Management Information Systems in Canadian Health Service Organizations (MIS standards) and were reported by the Provincial Council for Maternal and Child Health.<sup>9,10</sup> MIS standards are a set of national guidelines for gathering and processing data, reporting financial and statistical data on the day-to-day operations of a health service organization. They also provide a framework for integrating clinical, financial and statistical data when recipient costing is done.<sup>10</sup>

3) The Ontario Infant Mortality Rate (IMR) report which includes data on deaths of children up to one year of age was obtained from Statistics Canada.<sup>11</sup> This value is presented as rates per 1000 live births in a given year. The IMR used for the present study was the latest available, from 2007<sup>11</sup>, and it follows the International Statistical Classification of Diseases and Related Health Problems (ICD) Revision No.10.<sup>12</sup>

The published reference values for age-adjusted normal organ weights were obtained from Coppoletta & Wolbach, which is based on analysis of 2287 autopsy records at children's and infants' hospitals in the United States.<sup>13</sup> Only those organs with no demonstrated pathological changes and no diseases or abnormalities noted were included in our analysis. Confidence intervals using regression equations for the original Coppoletta & Wolbach data were later published by Shankle et al in 1983.<sup>14</sup> These values were compared with the organ weights obtained from the fatal cases associated with *in utero* methadone exposure in Ontario.

### Statistical Analysis

Odds ratio (OR) and 95% confidence interval was calculated to compare the mortality risk of infants <1 year of age exposed in utero to methadone and experiencing NAS to the risk in the general population of Ontario; Reference weights were compared to methadone cases using age at the time of death (months) and Fisher Exact analysis.

## RESULTS

Between January 1, 2006 and December 31, 2010, the Office of the Coroner of Ontario identified 8 deaths of children younger than one year whose drug dependent mothers were on on MMT. Upon investigation by the Office of the Chief Coroner and a Pediatric Death Under Five investigation, six of the eight deaths were classified as Sudden Unexpected Death Syndrome (SUDS), all of whom had evidence of unsafe sleeping environments, three of which also included bed sharing. One fatality was determined to be hypoxic ischemia encephalopathy due to bathtub drowning, and the cause of one death was unascertained. Comparison of organ weights at the time of autopsy with published age-specific reference organ weights showed a significant increase in both right and left lung weight ( $p = 0.035$ ,  $p = 0.007$  respectively) (table 1). A non-significant trend toward s increased liver, brain and heart weights compared to reference values was demonstrated.

**TABLE 1** Organ weights in comparison to normal values

CASE:	Right Lung (g)	RL REF	Left Lung (g)	LL REF	Heart (g)	HR REF	Liver (g)	LV REF	Brain (g)	BR	Right Kidney (g)	RK REF	Left Kidney (g)	LK REF
#1	128	55	105	50	42	40	225	225	895	875	23	32	25	33
#2	36	45	N/A	N/A	40.5	30	223	175	740	630	23.6	26	22.3	25
#3	50.9	32	40.2	29	28.3	24	198.3	140	509.9	425	19.2	20	19.5	20
#4	97	55	70	50	41	40	324	225	1001	875	25	32	34	33
#5	49.85	45	49.85	40	30.8	30	240	175	760	630	18.8	26	18.8	25
#6	56.5	32	51	29	21.5	24	176.5	140	442	425	23	20	25	20
#7	81.8	47	70.4	43	43	33	360	200	950	675	28.1	27	31.2	23
#8	59	32	66	29	25.6	24	148.3	140	557	425	15.8	20	19.7	20
p value =	0.035		0.007		0.368		0.054		0.252		0.310		0.788	

There were four female and four male children with a median age at the time of death of 6 months (range 1.4-11). No deaths were reported in the neonatal period (first 28 days). The median maternal age was 27 years (range 23-32) with a median gestational age at birth of 35 weeks (range 32-39). Only three mothers (37.5%) reported initiating breastfeeding. Seven of the eight (87.5%) infants were monitored by the Children's Aid Society. In this cohort, 38% (3/8) of mothers reported concomitant use of oxycodone and 50% (4/8) reported cocaine use during pregnancy. Post-mortem blood toxicology tests using gas chromatography and mass spectrometry did not detect morphine, methadone, alcohol, cannabinoids, or cocaine in any of the eight cases. In one case opiates, cocaine and cocaine metabolites were detected in the child's hair. In another case therapeutic levels of acetaminophen and pseudoephedrine (<50mg/L) were identified in the blood of an infant who had been given common cold medications. There were no othertoxicologically-relevant compounds identified by immunoassay or gas chromatography-mass spectrometry.

Based on CIHI records there were 821 recorded NAS diagnoses in Ontario from 2006-2009. We extrapolated these data by linear regression and estimated approximately 282 NAS diagnoses in 2010 (figure 1). The mortality rate of infants exposed to *in utero* methadone was therefore 8 per 1103 children diagnosed, or 0.725%.

According to Statistics Canada, the Infant Mortality Rate (IMR) in the Province of Ontario for the same time period was 5.2 per every 1000 live births up to one year of age (Statistics Canada, 2011). This yields an odds ratio of 1.45 for mortality in children with NAS (95% confidence interval 0.47-4.46) (p = 0.56).

## DISCUSSION

In evaluating the causes of infant death amongst the eight infants exhibiting NAS at birth, several etiological directions have to be considered. Firstly, only three of eight mothers admitted initiating breastfeeding, as a potential source of continuous methadone exposure. The toxicology screens did not detect any methadone or drugs of

abuse in post-mortem blood samples. The limit of detection for these samples may not have detected low levels. The positive hair test for cocaine identified in one case possibly reflects passive exposure to cocaine smoke in the household, which has not been associated with infant mortality. In all six cases of Sudden Unexpected Death Syndrome, there was evidence of unsafe sleeping environment and three of which included bed sharing. While bed sharing is the social norm in many cultures, its safety and benefits have been the subject of much controversy. Bed sharing has been associated with an increased likelihood of breastfeeding frequency and duration and may strengthen the bonding between the mother and child.<sup>15,16</sup> The dangers of unsafe sleeping environment include an increased risk for accidental asphyxia.<sup>17</sup>

Our study does not detect an apparent increased risk of mortality among infants born with NAS in Ontario. MMT has been recommended for use during pregnancy and has numerous maternal and infant benefits. The addict lifestyle can compromise the ability of a pregnant woman to live in a safe, substance-free environment, receive appropriate prenatal care, and maintain a healthy well-balanced diet. MMT encourages prenatal care, and is associated with an increase in birth weight and a decrease in infant mortality when compared to those addicts who remain untreated.<sup>18</sup>

The increase in lung weights in all 8 fatal cases compared to reference values is likely due to pulmonary congestion and edema. An increase in post-mortem lung weight is consistent with previously established pulmonary pathology associated with methadone related deaths.<sup>19</sup> The trend toward an increased in liver and brain weights in babies exposed to methadone could potentially be explained by hemodynamic perfusion alterations. Increased brain weights have been previously associated with the Sudden Infant Death Syndrome although the mechanism has not fully been described.<sup>20</sup>

There are several limitations to the data used by us which must be considered when examining our analysis. First, CIHI information depends on appropriate recognition of NAS as well as accurate hospital coding. The Finnegan Scale, which is most commonly used to identify and quantify NAS is a partially- subjective,

observation- based scale.<sup>8</sup> Although validated, there still exists the potential that some cases of NAS may go undiagnosed. Furthermore, NAS is commonly diagnosed by confirmation of *in utero* opioid exposure through physical and neurological examination, maternal sampling or reporting. This may leave a group of infants exposed to methadone unaccounted for. It is therefore conceivable that there have been more cases of NAS not captured by CIHI as a primary diagnosis. An increase in this denominator would decrease the estimate of mortality odds ratio towards unity.

Another limitation is the proper identification of neonates and infants who die in the first year of life who were exposed to methadone *in utero* and had the Neonatal Abstinence Syndrome. Unless this information were proffered by the parents at the time of death, or the investigating coroners thought to make the inquiry, the Protocol for the Investigation of Sudden and Unexpected Deaths in Children Under Five Years of Age used in these years did not make a specific inquiry into *in utero* exposure to methadone or NAS. Recently the OCC has undertaken a revision of the death questionnaire for infants who die in the first year of life, which will specifically inquire into maternal methadone use and the Neonatal Abstinence Syndrome, which will improve data collection.

Out of the eight fatalities described here, three of the mothers also reported concomitant oxycodone use and four reported cocaine use during pregnancy. In our study, 67% (4/6) of infant mortalities where ethnicity was known were identified as First Nations. Compared to the rest of Canada (non-aboriginals) the infant mortality rate has been 1.5-4 times higher in First Nations communities.<sup>20</sup> This confounding factor further decreases the relative odds ratio for increased infant mortality associated with *in utero* methadone exposure.

In summary, maternal addiction to opioids does not appear to increase the risk of mortality among infants younger than one year of age in Ontario. While more studies are needed to corroborate these findings in other jurisdictions, it is possible that the calculated non-significant odds ratio of 1.45 is in fact even lower, due to obvious underreporting of maternal addiction during pregnancy.

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