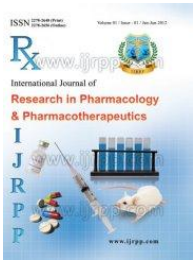
International Journal of Research in Pharmacology & Pharmacotherapeutics



ISSN Print: 2278-2648 ***IJRPP |Vol.6 | Issue 2 | Apr - Jun - 2017***
ISSN Online: 2278-2656 ***Journal Home page: www.ijrpp.com***

Research article ***Open Access***

Longitudinal effects of *in utero* methadone exposure on development using revised norms on the Bayley Scales of Infant Development (BSID)

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ABSTRACT

Much of the scientific justification for using methadone to treat women with heroin use disorders relies on one heavily cited early review of five studies. The review concluded there were no long-term developmental effects directly associated with prenatal methadone exposure because scores for exposed infants on the Psychomotor Development Index (PDI) of the Bayley Scales of Infant Development fell "well within the normal range of development." However, three of the studies reviewed reported significant differences between exposed and control infants on the PDI. The other two did not report scores on the PDI. The PDI is a subscale of the Bayley Scales of Infant Development, which was released with a much more extensive normative sample in 1993. Extrapolating PDI scores from the earlier version to the better 1993 version reveals that methadone-exposed infants were not well within the normal range of development. Given the increasingly higher doses of methadone used to treat pregnant opioid-dependent women, we are concerned about the potential for greater adverse effects in the present era. Beginning with the seminal review, this paper examines subsequent studies for longitudinal outcomes for prenatally exposed infants. We hypothesize that revised BSID-II PDI scores will reveal motor effects for infants born to women with heroin use disorders treated with methadone.

Keywords: Methadone, Longitudinal Outcomes, Prenatal exposure, Bayley Scales

INTRODUCTION

Since the 1960s, methadone maintenance has been used as a treatment for heroin dependency in women with heroin use disorders. Maternal methadone treatment is thought to provide an intrauterine environment for the fetus that is free from repeated cycles of withdrawal due to fluctuations in heroin levels. During methadone treatment, the mother's nutritional status is likely to improve and she may experience fewer obstetrical complications than if she continued to use heroin. Additionally, mothers in methadone treatment may be better able to care for their infants after delivery [1, 2]. Although methadone exposed infants endure neonatal opioid abstinence syndrome at birth, this is considered a medically manageable condition [3]. It is now widely accepted that administering methadone

to pregnant women poses little risk to infants from prenatal exposure.

Apart from literature on neonatal abstinence syndrome, the seminal study on the effects of prenatal methadone exposure was the first review of five longitudinal studies by Kaltenbach and Finnegan [4]. According to that review,

"The results of these studies suggest that no long term developmental sequelae are directly associated with methadone exposure in utero. Although differences were often found between methadone exposed infants and comparison infants on the Bayley Scales of Infant Development, scores for the methadone exposed infants were well within the normal range of development (p.271)."

We revisited the studies included in the review by Kaltenbach and Finnegan and found the suggestion there were no adverse effects from prenatal methadone exposure to be unwarranted. One of the studies reviewed lacked a control group and another did not report Psychomotor Development Index (PDI) scores for the Bayley Scales of Infant Development. Three of the studies on which the seminal review was based reported statistically significant differences between exposed and control infants on the PDI. This difference does not justify the reviewers conclusion that, "during the first two years of life, children exposed to methadone *in utero* do not exhibit any demonstrable developmental sequelae" (p. 271). Kaltenbach and Finnegan apparently dismissed the importance of the motor differences because exposed infants appeared to score within the normal range of development on the PDI, although the exposed infants scored significantly lower than carefully matched controls. The Bayley, first published in 1969, was the instrument used to assess the infants in the three earliest longitudinal studies. The instrument itself was revised in 1993 and published with more extensive and adequate norms.

We present here a summary of the three original longitudinal studies of methadone-exposed infants that served as the basis for the seminal and influential 1984 review. Additionally, with the help of the statisticians at Pearson, we provide scores extrapolated from the 1969 Bayley to the 1993 Bayley Scales of Infant Development (BSID). Item directions and scoring criteria changed on the 1993 edition, improving the instrument by reducing ambiguity and increasing scoring accuracy. The floor and ceiling of the 1993 version were greater to provide children with more opportunity to display variability in performance. The average difference between the 1969 and 1993 version was about 10 points for the PDI in the middle of the distribution, it can be as much as 13 points at the extremes of the distribution.

MATERIALS AND METHODS

Kaltenbach and Finnegan [4] reviewed all the longitudinal studies for outcomes of prenatal methadone exposure that were available at the time they wrote. We obtained copies of these five papers and describe the three that administered the Psychomotor Development (PDI) scale of the 1969 Bayley and included a control group. These studies provide the scientific foundation for the use of methadone in pregnant women.

Strauss et al. 1976

Strauss and collaborators [5] investigated outcomes on the Mental Development Index (MDI) and Psychomotor Development Index (PDI) at 3, 6, and 12 months of age. Exposed infants in this study were n=60 offspring born to mothers enrolled in a prenatal methadone treatment program in the inner city area of Detroit. Exposed infants were compared to control infants at birth for weight, gestational age, Apgar scores at one and five minutes, obstetric analgesics, obstetrical anesthetics, and prenatal visits. Although attrition was higher for the pregnant mothers with opioid-use disorders than for the controls, this did not appear to systematically bias the sample. Over the course of the study, these authors reported a decline of 16.6 points for psychomotor performance of infants born to women on methadone maintenance.

The decline in psychomotor performance was highly significant [Age x Scale Interaction, F (df = 2, 48), 12.9, $p < .001$]. These authors also reported a significant difference between scale, age, and group, F (df = 2, 98) 3.3, $p < .05$. Methadone doses over the six weeks prior to delivery for women in this study rarely exceeded 40mg/day (M = 16.4). In this study, infants were reported to experience only mild degrees of withdrawal. This study was supported by a grant from NIDA, 00696-01.

Wilson et al., 1981

Wilson and collaborators [6] compared outcomes for infants of methadone treated and untreated drug dependent mothers at Houston's public maternity hospital between August 1974 and July 1977. Their study included 68 narcotic dependent women matched to a drug free control group for age, race, socioeconomic status, marital status, and gestation age at the time prenatal care was initiated. Qualitative urine screening was used to monitor drug use during pregnancy. The psychologist who administered the Bayley was blind to the infant's drug exposure condition. In this study, most of the women in methadone treatment were white, while most of the women who were using heroin were black. Hispanic women comprised about 30 percent of each group. Only three women in the methadone treatment group used no other drugs during the study. The majority of the women in the methadone treatment group continued consuming a variety of both illicit and licit drugs. Seventy percent of women in methadone treatment used heroin during the study, while only ten percent of the heroin group used methadone. In the methadone group, the incidence and severity of neonatal abstinence syndrome required the longest course of treatment ($t = 2.76$, $p < .01$). The mean PDI for the methadone group at 9 months was lower than for the untreated opioid dependent group and significantly lower than that for the drug free controls ($F = 4.16$, $p < .018$). The daily methadone dose for women in this study ranged from 20 to 60mg for 32 of the women in the study, while the dose was less than 20mg for six women, and only one woman received a dose of 90mg/day. The study was supported by a grant from NIDA, 00696-01.

Rosen and Johnson, 1982

Rosen and Johnson [7] began their longitudinal study of infants born to women in methadone maintenance programs in New York in 1977. Their study included 57 infants of mothers in treatment programs. Infants of 31 drug free mothers served as a control group. These infants were enrolled in the study within 24 hours of delivery and matched for race, socioeconomic class, neonatal sex, birth weight, and gestational age to exposed infants. Infants were seen at a follow up clinic at 2, 4, 6, 8, 10, 12, 15, and 18 months of age. Exposed and control groups consisted of mostly black infants. After attrition over the course of the study, groups consisted of 45 methadone exposed infants and 25 controls. Tone discrepancies were noted in the methadone group, both hypertonic and hypotonic, for infants between 6 to 12 months of age, along with delays in motor development. Methadone exposed infants scored significantly lower than controls on the PDI by 12 months of age ($p < .03$). In this study, the average daily dose of methadone was 42.9mg per day. In the methadone treatment group, 56% of women continued to use other drugs during their pregnancies. This study was supported by a grant from NIDA 01663.

The method for extrapolating scores was provided by Zhu [8], statistician at Pearson who had access to the Bayley normative data. To extrapolate scores based on the 1993 BSID norms for groups of infants in these earlier longitudinal studies, it was necessary to make assumptions about when data was collected. Unless otherwise specified by the authors, it was assumed data was collected two years before the date of the publication. Revised scores were computed by subtracting a correction factor of 0.45 points per year between 1993 and the date the data was collected. Scores for the PDI as given in the publications are shown in Table I. An additional study from the same era, not included in the review, found that methadone exposed infants scored significantly below non-exposed controls at the last point of data collection, or at two years of age in this study [9, 10].

RESULTS

In three studies included in the seminal review by Kaltenbach and Finnegan methadone exposed infants scored significantly lower than carefully matched controls on the Psychomotor Development Index (PDI) of the Bayley. Two studies included in their review did not report on motor skills. Methadone exposed infants did not score significantly better than heroin-exposed infants did in the only study that explicitly included a heroin-exposed group. The extrapolated mean PDI score for the combined groups of methadone exposed infants is 87.48 ($n = 105$) compared to an extrapolated mean of 96.5 ($n = 106$) for unexposed controls was significant t ($df = 209$) = - 16.17, $p = .0001$. Methadone exposed infants ($M = 87.48$) scored significantly below the 1993 PDI mean which was 100.4, t ($df = 1\ 04$) = -32.76, $p = 0.0001$.

Table 1: PDI Scores for methadone

	Age months	Methadone Mean/SD	Heroin Mean/SD	Control Mean/SD	PDI	Significance
Strauss et al., 1976	12	102.8 (11) N = 25		110.4(9.8) N = 26		p < .01
Wilson et al., 1981	9	89.9 (12.6) N = 35	92.2(19.2) N = 35	99.0(14.5) N = 55	99.0 14.5	p < .01 Methadone vs Controls
Rosen and Johnson, 1982	18	92.6(2.38) N = 45		105.3(2.21) N = 25	105.3 2.21	p < .05

DISCUSSION

During pregnancy, the primary goal is to stabilize the mother, prevent the fetus from repeated episodes of withdrawal, provide prenatal care, and provide addiction treatment [11]. It follows from this that the fundamental rationale for exposing unborn infants to methadone is a belief that mothers will be able to resist using illicit drugs during pregnancy. Given the very influential role these first longitudinal studies had on public policy, it is remarkable that most of these infants were born to women who continued using other drugs while in methadone treatment programs. In one study, 70 percent of the women were still using heroin[6] and in another study, 56 percent of the women in methadone maintenance continued using drugs [7].

Women in these studies were on very low doses of methadone compared to today's standards, which may explain their continued use of heroin. Pregnant women today routinely receive methadone doses that are four times higher than reported for mothers of infants in the early longitudinal studies of developmental outcomes for prenatal exposure. If methadone adversely affects motor development at lower doses, higher doses may produce more severe adverse effects. Recent studies are now challenging the idea that children prenatally exposed to methadone develop normally. [12, 13]

We are not the first to call for additional research on this problem. Others have brought attention to the fact that methodological flaws and inconsistencies confound interpretation of today's literature [14]. The empirical evidence that exists does not support the conclusion that prenatal methadone exposure has no developmental consequences for children. Prenatal exposure to methadone leads to motor delays for children, at least during the first two years of life, compared to controls. Long-term consequences of exposure are unknown, but a body of literature suggests that children may not outgrow their early motor delays. At least one study of the perceptual motor, educational, and social outcomes for children with documented motor delay at age 5 predicted problems in these domains in adolescents at ages 17-18, including the shortest academic careers of groups studied [15].

Infants from one of the early longitudinal studies were followed to seven years of age. They differed from controls in school behavior, displaying poorer academic achievement, more disruptive behavior, and increased aggression [16].

Progress in neuroscience reveals possible mechanisms by which heroin and methadone may influence the developing brain [17]. When another μ-opioid receptor agonist, buprenorphine, is prenatally administered, rat pups display anomalies in axons and myelin. Myelinated axons in the corpus callosum of the pups are significantly larger in diameter than controls and are surrounded by a proportionately thinner myelin sheath than controls [18]. Altered myelin suggests a neural substrate that could be the mechanism that accounts for the PDI results in the early longitudinal studies. Long-term outcomes for prenatal exposure may not be evident for years following methadone exposure, until the brain completes development late in adolescence.

While it is possible that methadone exposure in the prenatal period has no lasting effects on brain development, or that the effects from methadone are less severe than those from parental heroin exposure, this conclusion cannot be legitimately drawn from the existing literature. A 2008 recent review by Farid [18] still relies on the earliest studies [16,19, 20] Existing literature does not contain truly longitudinal studies of the effects of prenatal methadone exposure, studies which follow children through adolescence until after the brain has finished its development.

Acknowledgements

We want to thank Tove Rosen for drawing our attention to this topic and the women who participated in the B.A.B.I.E.S study.

REFERENCES

[1]. Finnegan, L. Treatment issues for opioid dependent women during the perinatal period. *J of Psychoactive Drugs.* 23, 1991, 191-201.

[2]. Kaltenbach K, Silverman N, Wapner, R. Methadone maintenance during pregnancy. In: State Methadone Treatment Guideline. U.S. Department of Health and Human Services. Rockville, MD. 1992, 85-93.

[3]. Joseph H, Stancliff, S, Langrod, J. Methadone maintenance treatment MMT: a review of historical and clinical issues. *Mt Sinai J Med.* 67, 2000, 347-364.

[4]. Kaltenbach,K, Finnegan LP. Developmental outcome of children born to methadone-maintained women: A review of longitudinal studies. *Neurobehav toxicology and teratology.* 6, 1984, 231-275.

[5]. Strauss ME, Starr RH, Ostrea EM, Chavez CJ, Stryker JC. Behavioral concomitants of prenatal addiction to narcotics. *J. Pediatrics.* 89, 1976, 842-846.

[6]. Wilson GS, Desmond MM, Wait RB. Follow up of methadone treated women and their infants: Health, developmental, and social implications. *J. Pediatr.* 98, 1981, 716-722.

[7]. Rosen TS, Johnson HL. Children of methadone maintained mother: follow-up to 18 months of age. *J. Pediatrics.*101, 1982, 192-196.

[8]. Zhu JJ. personal communication. Dr. Zhu was the statistician at Pearson, the company that now sells the Bayley.

[9]. Hans SL. Developmental Consequences of prenatal exposure to methadone. *Ann N Y Acad Sci.* 562, 1989, 195-207.

[10]. Hans SL, Marcus J. Motoric and attentional behavior in infants of methadone-maintained women. *NIDA Res Monogr.* 43, 1983 287-293.

[11]. The American College of Obstetricians and Gynecologists. *Opioid abuse, dependence, and addiction in pregnancy.* Committee on Health Care for underserved women and the American Society of Addiction Medicine. 2012 reaffirmed 2016.

[12]. Hunt RW, Tzioumi D, Collins E, Jeffery HE. Adverse neurodevelopmental outcome of infants exposed to opiate in-utero. *Early Hum Dev.* 84, 2008, 29-35.

[13]. Teraski LS, Gomez J, Schwarz JM. An examination of sex differences in effects of early-life opiate and alcohol exposure. *Phil.Trans. Soc. B.* 371, 2016, 20150123.

[14]. Winklbaur B, Kopf N, Ebner N, Jung E, Thau K, Fischer, G. Treating pregnant women dependent on opioids is not the same as treating pregnancy and opioid dependence: a knowledge synthesis for better treatment for women and neonates. *Addiction.* 103, 2008, 1429-1440.

[15]. Cantell MH, Smyth MM, Ahonen TP. Two distinct pathways for developmental coordination disorder: persistence and resolution**.** *Hum Mov Sci. 22*, 2003, 413-431.

[16]. Rosen TS, Johnson HL. Long-term effects of prenatal methadone maintenance. NIDA Res. Monogr. 59, 1985, 73-83.

[17]. Farid WO, Dunlop, SA, Tait RJ, Hulse GK. The effects of maternally administered methadone, buprenorphine and naltrexone on offspring: review of human and animal data. *Curr Neuropharmacol.* 6, 2008, 125-150.

[18]. Sanchez ES, Bigbee JW, Fobbs W, Robinson, SE, Sato-Bigbee, C. Opioid addiction and pregnancy: perinatal exposure to buprenorphine affects myelination in the developing brain. *Glia.* 56, 2008, 1017-1027.

[19]. Kaltenbach K, Finnegan LP. Perinatal and developmental outcome of infants exposed to methadone in-utero. *Neurotoxicol. Teratol.* 9, 1987, 311-313.

[20]. Strauss ME, Lessen-Firestone JK, Chavez CJ, Stryker, JC. Children of methadone- treated women at five years of age. *Pharmacol. Biochem. Behav.* 11, 1979, 3-6.