Maternal alcohol and drug use during pregnancy affects the motor behaviour and general movements of infants aged 3-4 months

T. Fjørtoft^{a,b,*}, M. Brandal^a, A.M. Brubakkb,^c, L. Adde^{a,b}, T. Ustad^{a,b}, R. Vågen^a,

K.A.I. Evensen^{b,d,e,f}

a Clinic of Clinical Services, St. Olav's Hospital, Trondheim University Hospital, Trondheim, Norway

b Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway

c Department of Pediatrics, St. Olav's Hospital, Trondheim University Hospital, Norway

d Department of Public Health and Nursing, Norwegian University of Science and Technology, Norway

e Unit for Physiotherapy Services, Trondheim Municipality, Norway

f Department of Physiotherapy, Oslo Metropolitan University, Oslo, Norway

* Corresponding author at: Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology, Box 8905, 7491 Trondheim, Norway.

E-mail address: toril.fjortoft@ntnu.no (T. Fjørtoft).

Abstract

Background: Exposure of alcohol and/or other addictive drugs in pregnancy is a documented risk factor for later neurological impairment.

Aims: The aim of the study was to determine whether infants suffering from prenatal exposure to addictive drugs and alcohol develop an abnormal motor behaviour at three to four months of age.

Study design: Controlled cohort study of infants exposed to alcohol and/or other addictive drugs in pregnancy who were recruited from a hospital follow-up programme. The control group consisted of healthy, unexposed infants.

Subjects: The study group of 108 infants exposed to alcohol and/or addictive drugs in pregnancy were enrolled based on referrals from primary health care. The control group included 106 infants who had not been exposed to the aforementioned substances.

Outcome measures: We assessed the general movements (Prechtl's General-Movement-Assessment, GMA), the motor repertoire (Assessment-of-Motor-Repertoire, AMR), and the Alberta-Infant Motor-Scale (AIMS) in all infants at three to four months of age.

Results: None of the infants in either group had absent fidgety movements (FMs). In the study group 5(5%) had exaggerated FMs and 5(5%) had sporadic FMs; and 68(63%) infants in the study group displayed an abnormal movement character, compared to 23(22%) in the control group (p<0.001). On the AIMS, 46(44%) infants in the study group scored below the 10th percentile, compared to 2(3%) controls (p<0.001).

Conclusion: The study describes an abnormal movement character of infants exposed to alcohol and/or addictive drugs in pregnancy when their motor repertoire was assessed at three to four months of age. The AIMS also showed negative effects on their motor behaviour.

Keywords Infants Prenatal exposure to alcohol or other addictive drugs AIMS General movements Motor repertoire

1. Introduction

Developmental disturbances and later disabilities in children exposed to alcohol, opiates, methamphetamine and/or other addictive substances during pregnancy are a major global issue. The global prevalence of fetal alcohol spectrum disorders (FASD) has been reported to be 7.7 per 1000 population, with the highest rate in Europe at 19.8 per 1000 population [1].

Numerous studies confirm the adverse effects of prenatal alcohol exposure. These studies constitute the basis of international clinical guidelines for diagnosing FASD [2]. In addition to characteristic dysmorphic features, impairment includes social, cognitive and behavioural disorders [2]. Motor developmental disorders have not been emphasised in recent clinical guidelines for FASD [2]. In a meta-analysis, pooled results revealed a significant association between moderate to heavy prenatal alcohol exposure and impaired motor functions like balance, coordination, and ball skills [3]. Alcohol abuse is often combined with abuse of opiates and/or other addictive substances or psychoactive drugs [4]. A study of six-year-old children who had been exposed to intoxicants previous to birth revealed that most of them had been exposed to three or more intoxicants rather than just one. Substances included amphetamine, heroin, benzodiazepines, cocaine and alcohol [5]. The study shows that 19 % of the children had behavioural and concentration problems and 18% received extra help in school. Most of the children received support from child protection services [5]. Cognitive and behavioural difficulties have also been described in older children who had been exposed to prenatal amphetamine abuse [6]. A high rate of attention deficit hyperactivity disorder (ADHD) has been reported in 5- to 12-year-old children who had been exposed to heroin before birth [7]. Prenatal exposure to methamphetamine was observed to have a negative but transient effect on the fine motor performance of one-year-olds [8]. In another study, a group of two-year-old children who had suffered from prenatal cocaine exposure showed significantly poorer fine and gross motor skills than the controls [9]. On the other hand, a study of one- to three-year-old children with a history of prenatal exposure to cocaine and opiates showed no motor deficits after controlling for birth weight and environmental risks [10]. According to a systematic review of studies discussed in MEDLINE and Psychological Abstracts between 1984 and October 2000, there is no convincing evidence of a correlation between prenatal cocaine exposure and developmental impairments in children aged six years or younger [11]. While the long-term effects of cocaine, opioids and methylamphetamine remain to be studied in more detail, research has gathered some findings on the effect of alcohol abuse [2].

Early detection of motor impairment in affected children is a prerequisite for early and focused intervention [12]. Studies on motor performance in early infancy after prenatal drug exposure have applied a variety of methods [13, 14]. The Prechtl General Movement Assessment (GMA) is based on observation and analysis of the spontaneous movement pattern of infants at three months of age [12, 15, 16]. Several studies confirm that GMA can predict cerebral palsy [12, 16, 17]. A review about the use of GMA in high risk infant reports that spontaneous motor behaviour in the young infant may presage later cognitive dysfunction in children without cerebral palsy [18], and another review including 10 studies concludes that fidgety movements may not predict cognitive development, but concurrent movements and posture do [19]. A 2012 study on children exposed to opiates in pregnancy showed that abnormal spontaneous movements in infancy pose a high risk of later neurological difficulties [20]. All children in the study were also exposed to, but not necessarily infected with, the human immunodeficiency virus and presented other risk factors like low birth weight, moderate prematurity and perinatal events.

The aim of the present study was to determine whether children with no other risk factors than prenatal exposure to alcohol or other addictive substances present absence of normal fidgety movements and/or an impaired motor maturation at three to four months of age, as compared with a control group. To assess these movements the Prechtl group developed the "Assessment of Motor Repertoire – 3 to 5 months" (AMR) [15] which will be used here along with the Alberta Infant Motor Scale (AIMS) [21]. Based on studies reporting negative effects of prenatal alcohol or drug abuse on infants and abnormal motor findings in other groups at risk for neurological impairments [19, 22], we hypothesised that prenatal alcohol and drug exposure would lead to abnormal motor behaviour by three to four months of age.

2. Methods

2.1 Study design

The present study was a controlled cohort study within the follow-up programme for infants at risk for impaired development at St. Olav's Hospital, Trondheim University Hospital, Norway, between 6 December 2014 and 5 May 2019. Infants who had been exposed to prenatal abuse of illegal addictive drugs and/or alcohol, often in combination with legal, addictive psychoactive drugs, were enrolled consecutively. The control group consisted of healthy infants recruited from the maternity ward between March 2018 and March 2019.

2.2 Participants

Study group

All infants recruited to the study group had been referred for follow-up by the local primary health care, which serves a population of approximately 200,000. The mothers had participated in the Norwegian follow up program for pregnant women and had been identified by the primary health care and social services as substance abusers during pregnancy. This follow up program in primary health care includes close to 100% of the pregnant women in the local community. Social services have a similar follow up program for all known substance abusers. The biological or foster parents of 112 infants were invited to participate in the study when the infants were three to four months old. Because four biological parents refused to give their written informed consent, 108 infants (63 boys and 45 girls) were included in the study. At the time of referral, 11 infants were resident in foster homes; the other infants were being raised by one or both biological parents under guidance of local child protection services. The mothers of 65 (60%) of the infants participating in the study had reported alcohol, benzodiazepines, cannabis or amphetamine abuse during the first months of or throughout the pregnancy when included in the follow up program. Sixteen of these mothers reported additional use of prescription drugs, some for treatment, others because of addiction; 36 (33.3%) mothers had used only prescription drugs for reasons of treatment or addiction; 3 (2.7%) mothers reported no use of drugs or alcohol whatsoever but were regarded as active abusers by primary health care and social services and therefore included in the study; only 4(3.7%) mothers were undergoing a mandatory opioid replacement therapy with buprenorphine or methadone in a strict national follow-up programme. Toxicology screens were not used routinely in primary health care as this requires informed and consent. Information regarding abuse was given by the mothers to the primary healthcare services and reported when admitted to the follow up team at the hospital. All participating parents and foster parents gave their written consent.

Information about gestational age, birth weight, head circumference and birth length was retrieved from hospital journals and/or biological parents or foster parents in the study group and from the parents in the control group (Table 1).

Control group

The control group was recruited consecutively from the Maternity Department at the Women's Clinic of St. Olav's Hospital in Trondheim between February and December 2018. While still in the maternity ward, 152 parents were invited to participate. The parents of 106 three- to four-

month-old, healthy, full-term infants (42 boys, 64 girls) with normal birth weight, uncomplicated delivery and neonatal period gave their written consent for their children, all of whom were singletons, to participate in the control group.

2.3 Video recordings and the "Assessment of Motor Repertoire – 3 to 5 months", version the GM Trust 2001

The "Assessment of Motor Repertoire – 3 to 5 months" (AMR) [15] is a method for observing, characterising and analysing the spontaneous movement patterns of infants at the age of three to five months. AMR is based on the scores for five movement subcategories [15]. The first three subcategories are "Fidgety movements" (12 points max.), "Repertoire of co-existent other movements" (4 points max.), and "Quality of other movements" (4 points max.). The fourth subcategory, "Posture" (4 points max.) is based on the observation of "Postural pattern". The fifth subcategory, "Movement character", classifies the overall movement character as smooth and fluent (4 points); abnormal, but not cramped-synchronised (2 points); or abnormal and cramped-synchronised (1 point). The scores of the five subcategories then add up to the motor optimality score (MOS), with a total of 5 to 28 points. Fidgety movements (FMs) are a continuous stream of small, elegant movements observed in the whole body [15, 16, 23]. They appear and disappear between 46 and 58 weeks postmenstrual age. FMs are interspersed with pauses. According to the duration of these pauses, the temporal organisation of fidgety movements can be classified as continual (F++), intermittent (F+), or sporadic (F+/-) [15]. The FMs can also be greatly exaggerated (FA). Continual and intermittent fidgety movements score 12 points, exaggerated fidgety movements score 4 points, and sporadic or absent fidgety movements score 1 point in the AMR subcategory "Fidgety movements". In addition to fidgety movements, a number of other, co-occurring other movements such as hand-hand, hand-mouth and foot-foot contacts are also observed and analysed. Fidgety movements can predict reasonably well whether or not a child is likely to develop cerebral palsy (CP) [12]. The quality assessment of other subcategories of spontaneous movements that co-occur with fidgety movements has also been used to study the relationship between spontaneous movements and motor and cognitive outcomes [18, 19, 24-26]. In our study, the infants' spontaneous movements were video recorded at a mean post-term age of 52.6 (SD 4.1) weeks in the study group, and a mean postterm age of 53.6 (SD 1.3) weeks in the control group.

In compliance with the procedure described by Prechtl and co-workers videos were recorded of infants in the study and the control groups to assess their spontaneous movements [15, 27]. Blinded assessments were performed by four GMA-certified, experienced paediatric physiotherapists. All testers had completed the General Movements Trust advanced course. The videos of both groups were de-identified, mixed and assessed along with videos of other infants recorded for routine clinical purposes. The testers evaluated the footage separately, and the project coordinator administered videos to a third observer if the first two observers disagreed.

2.4 Alberta Infant Motor Scale (AIMS)

The AIMS assesses the motor maturation of infants from term (40 weeks post conception) through the age of independent walking (0 to18 months). It is a normative, execution- and observation-based tool that describes the development of postural control in various positions (prone, supine, sitting and standing) [21]. A chart indicates which percentile the child is on as compared to a normative, age-matched control sample. The construct and content validity of AIMS has been established [28]. Inter-test studies with two unblinded testers revealed correlation coefficients of r = 0.96 to 0.99, depending on the children's age. The AIMS test was conducted at the same visit and at the same age as the GMA.

2.5 Statistical analyses

Data were analysed using SPSS Statistics, version 25 (IBM SPSS Statistics Chicago, IL, USA). Differences in motor repertoire items between groups were analysed using the Chi-square test, and differences in non-parametric data were analysed by means of the Mann-Whitney U test. An odds ratio of 95% CI was calculated as an estimate of the risk for infants in the study group of having abnormal fidgety movements (absent, sporadic or abnormal), an abnormal movement character (monotonous, stiff and jerky), and of performing in a low AIMS percentile group ($<10^{th}$, $<15^{th}$, $<25^{th}$ percentile) as compared with the control group.

The study was approved by the Regional Ethics Committee (project number: 2017/2369). All parents in the study gave their written informed consent after having been informed in detail about the research project. All assessments were observational and non-intrusive to the infants.

3. RESULTS

3.1 Clinical characteristics

There were significant differences between the study and the control groups in mean birth weight, length, and gestational age, but no differences in head circumference (Table 1). There were 63 boys (58%) in the study group and 42 (40%) in the controls. Two infants in the study group had been admitted to the neonatal intensive care unit for observation because of withdrawal symptoms. Apart from the gestational drug and/or alcohol exposure in the study group, no risk factors for neurological impairment were established in either group.

3.2 "Assessment of Motor Repertoire – 3 to 5 months", version the GM Trust 2001

Table 2 shows the results of the AMR in the study and control groups at three to four months of age. Five infants in the study group had exaggerated FMs, compared to none in the control group. No infant in the study or the control group had absent FM. Continual FMs (F++) or FMs with short pauses were seen in 17 (16%) infants in the study group and in 43 (41%) controls (p<0.001). The number of infants with a smooth and fluent movement character was more than twice as high in the control group (81 [78%] versus 40 [37%]; p<0.001). Almost all detailed aspects of the motor repertoire differed significantly between the groups (Table 2). Hand-to-mouth contact was more frequent in the control group than in the study group (81 [79%] versus 67 [62%]; p<0.008), and the same goes for foot–foot manipulation (58 [57%] versus 44 [41 %]; p<0.019). Fiddling was observed in 41 (38%) infants in the study group and in 60 (59%) controls (p=0.008). The median MOS was 26 points (interquartile range 26–28) in the study group and 28 points (interquartile range 28–28) in the control group (p=0.001).

Sporadic fidgety movements were 2.6 times as frequent (95% CI: 0.8-8.5) in the study group as in the control group (Table 3). Sixty-eight (63%) infants in the study group had an abnormal movement character, compared to 23 (22%) controls (OR: 6.0; 95% CI: 3.3-11.0).

3.3 Alberta Infant Motor Scale (AIMS)

Infants in the study group had a mean total AIMS score of 9.0 (SD2.0), compared to 11.8 (SD1.9) in the control group (p < 0.001). Twenty-one infants (20%) in the study group scored $\leq 5^{\text{th}}$ percentile, compared to none in the control group.

When we calculated the odds ratio for having a low AIMS score we found significant differences in all percentile ranges (Table 3). The risk of achieving an AIMS \leq 10 percentile, which could be regarded as atypical, was almost 40 times higher in the study group (OR 38.5; 95% CI: 9.0-164.4) than in the control group. AIMS tests results were missing for six infants in the control group because AIMS was not included in the protocol when testing of the controls started.

4. Discussion

Our study describes significant differences between the early motor behaviour of a study group of three- to four-month-old infants who had been exposed to addictive drugs and/or alcohol in pregnancy, and that of a control group who had not. Their AMR and AIMS results indicate a negative effect of prenatal exposure to addictive drugs like alcohol on early motor behaviour.

The findings are well in line with a previous study in which abnormal early spontaneous movements were reported to be associated with prenatal exposure to maternal opiate abuse but were also possibly associated with other risk factors such as low birth weight and a low Apgar score [20]. Likewise, based on AIMS, prenatal cocaine exposure has been found to have an unfavourable effect on the motor behaviour of infants assessed at four and seven months, which predicted poor motor scores at 15 months [14].

Our study shows minor differences between the study and control groups with respect to abnormal fidgety movements. However, five infants in the study group and none in the control group had exaggerated FMs. If this difference is significant needs to be addressed in larger studies and in an ongoing follow up study. Significant differences in the movement character and in many aspects of the motor repertoire was found. Previous studies showed these abnormalities to be predictive of later neurological problems [18, 24]. The odds of having an abnormal movement character but normal fidgety movements were much higher in the study group than in the control group. The same phenomenon has been described in extremely low birth weight premature infants (<1000g), who are known to have a high risk for neurodevelopmental impairment [22] and minor neurological dysfunctions [19, 24, 25].

Almost all aspects of motor repertoire differed significantly between the study and the control groups. Similar results have been presented for infants with Zika virus infection [29] and extremely low birth weight infants [22], since both conditions interfere with normal brain development. Interestingly enough, five infants in the study group had exaggerated FMs, compared to none in the control group. It has been described previously that half of the infants with exaggerated FMs developed neurological dysfunctions-[15]. The motor optimality score (MOS), which is part of the "Assessment of Motor Repertoire – 3 to 5 months", was significantly lower in the group exposed to drugs / alcohol. This finding is in line with what has been described in other infants at risk for later motor problems [22, 30]. Even if statistically different from the control group a median MOS of 26 in the study group is regarded as optimal. The apparently minor difference of 2 points between the two groups' median MOS (26 points in the study group, 28 in the controls), though statistically relevant, illustrates that this score is strongly dependent on FMs, which account for 12 out of a total of 28 points, and is related to the fact that the control group was very homogeneous.

Our findings based on AMR are in line with a previous study of motor skills assessed at one month and at four months (applying the NICU Network Neurobehavioral Scale and the Posture and Fine Motor Assessment of Infants, respectively), where infants exposed to prenatal cocaine abuse showed poorer motor skills at one month of age. The study found motor skills to improve significantly over time [13]. Another study determined the discriminative capacity of the Alberta Infant Motor Scale (AIMS) and the Movement Assessment of Infants (MAI) in predicting the gross motor function [14]. It concluded that, unlike AIMS, MAI overidentifies infants with motor problems, and that neither test reliably identifies infants who go on to develop motor problems. It remains unclear what kind of assessment of early motor behaviour is best suited for identifying infants at risk for later developmental impairment related to their mothers' prenatal drug abuse.

A revised AMR version was recently performed [31]. By the time the results were published, our study had been approved by the ethical committee and hospital and had already started. In the revised version, some items were merged and various subcategories renamed, but they yield the same number of points. It is highly unlikely, therefore, that adopting the revised version would have substantially altered our conclusions. More specifically, scores in the third subcategory of the revised AMR version ("Age-Adequate Movement Repertoire") were calculated differently from our study, which proceeded according to Bruggink [32].

Strengths and limitations

Primary health care applied strict criteria in composing out study group: all mothers of infants in the study had been abusing alcohol or other addictive substances during pregnancy. It is therefore reasonable to believe that all infants in the study group had been exposed to alcohol or addictive drugs in utero. Self-reported abuse in the group was relatively high (62%), and only three mothers did not report any use of alcohol or other drugs. Self-reports of substance abuse tend to understate the actual prevalence. A study among pregnant women in a substance abuse treatment programme found substantial underreporting for all classes of illicit drugs, and underreporting is believed to be even more frequent in the general population of pregnant women [33]. In an open study among almost 300,000 pregnant women, self-reported prevalence of cannabis use was lower than that of toxic substances, suggesting that cannabis use has been underestimated in self-reported surveys [34]. When assessing drug or alcohol use in pregnancy, timing seems to be a crucial factor. One way of getting a better picture of the actual marijuana or cocaine use might be to ask women about their consumption habits during the preceding month rather than the days prior to conception [35]. This was not considered in the present study, and toxicology reports were available only for a few mothers. A limitation of this study is the heterogeneity of the study population with respect to drug and/or alcohol exposure, which unfortunately made it impossible to differentiate between results according to the type of abuse. Each substance may have different effects on the various aspects of early motor behaviour.

The observed mean difference in birth weight (321 grams) between the study and the control groups could partly due to the difference in gestational age (0.9 weeks) [36]. However, both low birth weight and prematurity have been reported after exposure to alcohol or other drugs in pregnancy [37]. The differences in birth weight, birth length and gestational age between the study group and the controls were so small that they do not qualify as independent risk factors for later impaired motor development. Except for two newborns who needed observation in the Neonatal Intensive Care Unit (NICU) because of withdrawal symptoms, no peri- or neonatal complications were reported. Because the control group were recruited from the same maternity ward and local population as the study group, it seemed safe to neglect differences related to ethnicity and cultural variation.

The discriminative power of the two tests applied in the present study to predict the motor outcome in children exposed to prenatal alcohol/drug abuse remains unclear. Both AMR and

AIMS have been extensively used for describing infant motor behaviour [24, 38, 39]. The validity of AIMS seems to be limited in cultures other than the normative sample's [40]. On average, the AIMS score is higher in the control group than in the normative sample, which indicates that there is a bigger difference between the study and the control groups than the test results of the study group alone suggest.

The long-term negative effects of intrauterine drug/alcohol exposure on early infant motor behaviour need to be further explored. Perhaps prenatal drug exposure does indeed affect the motor repertoire and causes a monotonous movement character in terms of a lack of variation, but loses its negative effects over time, as described in other studies using other methods [13]. Nor did the present study examine to what extent general stimuli or special care during the first three months of age are beneficial to the infants' motor development. These questions remain to be addressed in an ongoing follow-up study. The fact that AIMS, when used between three and four months, has few items could possibly increase the difference between the two groups as each item has a relatively large impact when the total score is converted into centiles

5. Conclusions

The present study uses AMR to describe the poor motor repertoire and poor movement quality in a group of infants exposed to drugs and/or alcohol in pregnancy as compared with a control group of term-born infants at three to four months of age. The study group's risk of abnormal movements was six times higher than the controls'. No significant absence of fidgety movements was found in infants exposed to prenatal drug and/or alcohol abuse, which indicates a good prognosis with respect to later CP. The AIMS suggests negative effects on motor behaviour. The clinical consequences of these findings are yet to be examined in follow-up studies.

Conflict of interest

No disclosures.

Acknowledgements

This study was supported with grants from the Norwegian Fund for Postgraduate Training in Physiotherapy (id number:118325) and from St. Olav's Hospital, Trondheim University

Hospital, Trondheim, Norway. We would like to thank Miha Tavcar (scriptophil) for proofreading the manuscript.

References

1. Lange S, Probst C, Gmel G, Rehm J, Burd L, Popova S. Global Prevalence of Fetal Alcohol Spectrum Disorder Among Children and Youth: A Systematic Review and Meta-analysis. JAMA pediatrics. 2017;171(10):948-56.

2. Hoyme HE, Kalberg WO, Elliott AJ, Blankenship J, Buckley D, Marais AS, et al. Updated Clinical Guidelines for Diagnosing Fetal Alcohol Spectrum Disorders. Pediatrics. 2016;138(2).

3. Lucas BR, Latimer J, Pinto RZ, Ferreira ML, Doney R, Lau M, et al. Gross motor deficits in children prenatally exposed to alcohol: a meta-analysis. Pediatrics. 2014;134(1):e192-209.

4. Forray A. Substance use during pregnancy. F1000Research. 2016;5.

5. Topley J, Windsor D, Williams R. Behavioural, developmental and child protection outcomes following exposure to Class A drugs in pregnancy. Child Care Health Dev. 2008;34(1):71-6.

6. Eriksson M, Jonsson B, Steneroth G, Zetterstrom R. Amphetamine abuse during pregnancy: environmental factors and outcome after 14-15 years. Scandinavian journal of public health. 2000;28(2):154-7.

7. Ornoy A, Segal J, Bar-Hamburger R, Greenbaum C. Developmental outcome of school-age children born to mothers with heroin dependency: importance of environmental factors. Dev Med Child Neurol. 2001;43(10):668-75.

8. Smith LM, LaGasse LL, Derauf C, Newman E, Shah R, Haning W, et al. Motor and cognitive outcomes through three years of age in children exposed to prenatal methamphetamine. Neurotoxicol Teratol. 2011;33(1):176-84.

9. Arendt R, Angelopoulos J, Salvator A, Singer L. Motor development of cocaine-exposed children at age two years. Pediatrics. 1999;103(1):86-92.

10. Messinger DS, Bauer CR, Das A, Seifer R, Lester BM, Lagasse LL, et al. The maternal lifestyle study: cognitive, motor, and behavioral outcomes of cocaine-exposed and opiate-exposed infants through three years of age. Pediatrics. 2004;113(6):1677-85.

11. Frank DA, Augustyn M, Knight WG, Pell T, Zuckerman B. Growth, development, and behavior in early childhood following prenatal cocaine exposure: a systematic review. JAMA. 2001;285(12):1613-25.

12. Novak I, Morgan C, Adde L, Blackman J, Boyd RN, Brunstrom-Hernandez J, et al. Early, Accurate Diagnosis and Early Intervention in Cerebral Palsy: Advances in Diagnosis and Treatment. JAMA pediatrics. 2017;171(9):897-907.

13. Miller-Loncar C, Lester BM, Seifer R, Lagasse LL, Bauer CR, Shankaran S, et al. Predictors of motor development in children prenatally exposed to cocaine. Neurotoxicol Teratol. 2005;27(2):213-20.

14. Fetters L, Tronick EZ. Discriminate power of the Alberta Infant Motor Scale and the movement assessment of infants for prediction of Peabody Gross Motor Scale scores of infants exposed in utero to cocaine. Pediatric Physical Therapy. 2000;12(1):16-23.

15. Einspieler C, Prechtl HFR, Bos AF, Ferrari F, Cioni G. Prechtl's method on the qualitative assessment of general movements in preterm, term and young infants. London: Mac Keith Press; 2004.

16. Einspieler C, Prechtl HF. Prechtl's assessment of general movements: a diagnostic tool for the functional assessment of the young nervous system. Mental retardation and developmental disabilities research reviews. 2005;11(1):61-7.

17. Prechtl HF, Einspieler C, Cioni G, Bos AF, Ferrari F, Sontheimer D. An early marker for neurological deficits after perinatal brain lesions. Lancet. 1997;349(9062):1361-3.

18. Peyton C, Einspieler C. General Movements: A Behavioral Biomarker of Later Motor and Cognitive Dysfunction in NICU Graduates. Pediatr Ann. 2018;47(4):e159-e64.

 Einspieler C, Bos AF, Libertus ME, Marschik PB. The General Movement Assessment Helps Us to Identify Preterm Infants at Risk for Cognitive Dysfunction. Frontiers in psychology. 2016;7:406.
 Palchik AB, Einspieler C, Evstafeyeva IV, Talisa VB, Marschik PB. Intra-uterine exposure to maternal opiate abuse and HIV: the impact on the developing nervous system. Early Hum Dev. 2013;89(4):229-35.

21. Piper MC, Darrah J. Motor Assessment of the Developing Infant1994.

22. Fjortoft T, Evensen KA, Oberg GK, Songstad NT, Labori C, Silberg IE, et al. High prevalence of abnormal motor repertoire at 3 months corrected age in extremely preterm infants. European journal of paediatric neurology : EJPN : official journal of the European Paediatric Neurology Society. 2016;20(2):236-42.

23. Einspieler C, Peharz R, Marschik PB. Fidgety movements - tiny in appearance, but huge in impact. J Pediatr (Rio J). 2016;92(3 Suppl 1):S64-70.

24. Fjortoft T, Grunewaldt KH, Lohaugen GC, Morkved S, Skranes J, Evensen KA. Assessment of motor behaviour in high-risk-infants at 3 months predicts motor and cognitive outcomes in 10 years old children. Early Hum Dev. 2013;89(10):787-93.

25. Bruggink JL, Van Braeckel KN, Bos AF. The early motor repertoire of children born preterm is associated with intelligence at school age. Pediatrics. 2010;125(6):e1356-63.

26. Grunewaldt KH, Fjortoft T, Bjuland KJ, Brubakk AM, Eikenes L, Haberg AK, et al. Follow-up at age 10years in ELBW children - Functional outcome, brain morphology and results from motor assessments in infancy. Early Hum Dev. 2014;90(10):571-8.

27. Fjortoft T, Einspieler C, Adde L, Strand LI. Inter-observer reliability of the "Assessment of Motor Repertoire--3 to 5 Months" based on video recordings of infants. Early Hum Dev. 2009;85(5):297-302.

28. Piper MC, Pinnell LE, Darrah J, Maguire T, Byrne PJ. Construction and validation of the Alberta Infant Motor Scale (AIMS). Can J Public Health. 1992;83 Suppl 2:S46-50.

29. Einspieler C, Utsch F, Brasil P, Panvequio Aizawa CY, Peyton C, Hydee Hasue R, et al. Association of Infants Exposed to Prenatal Zika Virus Infection With Their Clinical, Neurologic, and Developmental Status Evaluated via the General Movement Assessment Tool. JAMA network open. 2019;2(1):e187235.

30. Einspieler C, Bos AF, Krieber-Tomantschger M, Alvarado E, Barbosa VM, Bertoncelli N, et al. Cerebral Palsy: Early Markers of Clinical Phenotype and Functional Outcome. Journal of clinical medicine. 2019;8(10).

31. Einspieler C, Bos AF, Krieber-Tomantschger M, Alvarado E, Barbosa VM, Bertoncelli N, et al. Cerebral Palsy: Early Markers of Clinical Phenotype and Functional Outcome. Journal of clinical medicine. 2019;8(10).

32. Bruggink JL, Einspieler C, Butcher PR, Stremmelaar EF, Prechtl HF, Bos AF. Quantitative aspects of the early motor repertoire in preterm infants: do they predict minor neurological dysfunction at school age? Early Hum Dev. 2009;85(1):25-36.

33. Garg M, Garrison L, Leeman L, Hamidovic A, Borrego M, Rayburn WF, et al. Validity of Self-Reported Drug Use Information Among Pregnant Women. Maternal and child health journal. 2016;20(1):41-7.

34. Young-Wolff KC, Tucker LY, Alexeeff S, Armstrong MA, Conway A, Weisner C, et al. Trends in Self-reported and Biochemically Tested Marijuana Use Among Pregnant Females in California From 2009-2016. JAMA. 2017;318(24):2490-1.

 Yonkers KA, Howell HB, Gotman N, Rounsaville BJ. Self-report of illicit substance use versus urine toxicology results from at-risk pregnant women. Journal of substance use. 2011;16(5):372-89.
 Skjærven R, Gjessing HK, Bakketeig LS. Birthweight by gestational age in Norway. Acta Obstet Gynecol Scand. 2000;79(6):440-9.

37. Pinto SM, Dodd S, Walkinshaw SA, Siney C, Kakkar P, Mousa HA. Substance abuse during pregnancy: effect on pregnancy outcomes. Eur J Obstet Gynecol Reprod Biol. 2010;150(2):137-41.

38. Darrah J, Bartlett D, Maguire TO, Avison WR, Lacaze-Masmonteil T. Have infant gross motor abilities changed in 20 years? A re-evaluation of the Alberta Infant Motor Scale normative values. Dev Med Child Neurol. 2014;56(9):877-81.

39. Spittle AJ, Doyle LW, Boyd RN. A systematic review of the clinimetric properties of neuromotor assessments for preterm infants during the first year of life. Dev Med Child Neurol. 2008;50(4):254-66.

40. Mendonça B, Sargent B, Fetters L. Cross-cultural validity of standardized motor development screening and assessment tools: a systematic review. Dev Med Child Neurol. 2016;58(12):1213-22.

	Study group		Control group		p value
	(n=108) *		(n=106)		
	Mean	(SD)	Mean	(SD)	
Gestational age (weeks)	38.8	(2.0)	39.7	(0.9)	< 0.001
Birth weight (g)	3262	(663)	3583	(443)	< 0.001
Head circumference (cm)	34.6	1.9	35.5	1.6	0.218
Length	48.4	2.8	50.2	1.9	< 0.001

Table 1. Clinical characteristics of the study group and control groups at birth.

 Length
 48.4
 2.8
 50.2
 1.9
 <0.001</th>

 *Missing information for two infants whose foster parents had no information about the infants' clinical characteristics

Motor optimality list	AMR score	Study group (n=108)		Cor	Control (n=105)	
				(n=		
		n	(%)	n	(%)	
1. Fidgety movements	12 = normal	98	(91)	101	(96)	0.091
	4 = abnormal (exaggerated FA)	5	(5)	0	(0)	
	1 = absent or sporadic	5	(5)	4	(4)	-
Quality and temporal organisation of fidgety movements	F++	17	(16)	43	(41)	< 0.001
movements	F+	81	(75)	58	(55)	
	F+/-	5	(5)	4	(4)	_
	F-	0	(0)	0	(0)	-
	FA	5	(5)	0	(0)	-
2. Repertoire of co-existent other movements*	4 = age-adequate	106	(98)	104	(100)	0.163
movements	2 = reduced (5 or 6 movement patterns)	2	(2)	0	(0)	
	1 = absent (<5)	0	(0)	0	(0)	
3. Quality of other movements*	4 = N > A	106	(98)	104	(100)	0.378
	2 = N = A	1	(0.9)	0	(0)	
	1 = A > N	1	(0.9)	0	(0)	
4. Posture*	4 = N > A	92	(85)	100	(96)	0.011
	2 = N = A	5	(5)	3	(3)	
	1 = A > N	11	(10)	1	(1)	
5. Movement character*	4 = smooth and fluent	40	(37)	81	(78)	< 0.001
	2 = abnormal, not cramped- synchronised	68	(62)	23	(22)	
	1 = cramped- synchronised	0	(0)	0	(0)	

Table 2. Results of the assessment of the general movement and motor repertoires at three to four months of age in the study and control groups.

	Median	IQR	Median	IQR	
Motor optimality score					
	26	(26–28)	28	(28–28)	<0
Detailed motor repertoire	n	(%)	n	(%)	
Hand-face/mouth contact	67	(62)	81	(79)	0.
Foot-foot contact	80	(74)	90	(88)	0.
Foot-foot manipulation	44	(41)	58	(57)	0.
Fiddling	41	(38)	60	(59)	0.
Leg lifts, flexion at knees	87	(81)	96	(93)	0.
Leg lifts, extension at knees	38	(36)	50	(49)	0.
Hand-knee contact	18	(17)	32	(31)	0.
Detailed movement character					
Smooth and fluent (N)	39	(36)	82	(79)	<0
Jerky (A)	4	(4)	1	(1)	
Monotonous (A)	61	(57)	20	(19)	
Stiff	1	(0.9)	0		
Predominantly slow-speed	1	(0.9)	0		
Predominantly fast-speed	2	(1.9)	1	(1)	
Predominantly large amplitude	5	(6)	0		
Predominantly small amplitude	0		0		
Detailed posture description	I	1			
Variable finger postures	58	(54)	83	(81)	<0.0
Few finger postures	44	(41)	14	(14)	<0.0
Predominant fisting	17	(21)	9	(10)	1

*Missing information for one infant due to the infant's state

Chi-square test IQR = interquartile range AMR = Assessment of Motor Repertoire – 3 to 5 months N = normalA = abnormal $\begin{array}{l} F = abnormal \\ F++ = continual fidgety movements \\ F+ = intermittent fidgety movements \\ F+/- = sporadic fidgety movements \\ F - = absent fidgety movements \end{array}$

Table 3. Odds ratio (OR) with 95% confidence intervals (95% CI) as an estimate of the relative risk of having abnormal fidgety movements and an abnormal movement character, and of the relative risk of having an AIMS percentile ≤ 25 , ≤ 15 and ≤ 10 in the study group, as compared with the control group.

	Study group n = 108		Control gro	oup n = 106 *		
	n	(%)	n	(%)	OR	(95% CI)
Abnormal fidgety movements (sporadic or exaggerated)	10	(9.3)	4	(3.8)	2.6	0.8-8.5
Abnormal movement character	68	(63)	23	(22.1)	6.0	3.3–11.0
$\begin{array}{l} AIMS \leq 25 th \\ percentile \end{array}$	82	(79)	18	(18)	16.8	8.4–33.6
AIMS ≤ 15th percentile	53	(51)	2	(2)	50.4	11.8–215.3
AIMS ≤ 10th percentile	46	(44)	2	(3)	38.5	9.0–164.4

* AIMS test results missing from six infants

AIMS = Alberta Infant Motor Scale