MATERNAL METHAMPHETAMINE USE IN PREGNANCY AND LONG-TERM NEURODEVELOPMENTAL AND BEHAVIORAL DEFICITS IN CHILDREN

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ABSTRACT

Aim
To describe neurodevelopmental and/or behavioral findings among a cohort of South African children exposed to maternal methamphetamine (MA) use during pregnancy.

Methods
Developmental assessments with the Griffiths Mental Developmental Scales (GMDS) were completed on a pilot cohort of 15 toddlers aged 2-4 years with a known history of maternal MA use during pregnancy. These were compared to a matched cohort of 21 toddlers without a history of maternal MA use. Each child underwent formal auditory testing and vision screen. The Child Behavior Checklist (CBCL) was completed by a parent or caregiver. Cohorts were matched for age, gestational age at birth, socio-economic status and geographic distribution.

Results
Baseline characteristics were similar between the two groups. Most significant areas of poorer performance on GMDS in the Methamphetamine-exposed cohort was noted on the Personal-Social Ability Subscale ($p<0.0001$) and on the Hand and Eye Co-ordination Subscale ($p=0.0002$), while lower scores were also obtained on General Quotients ($p=0.022$). There were also significant concerns regarding aggressive behavior and attention deficit/hyperactivity on the CBCL for the exposed group, although this did not reach statistical significance.

Conclusion
Among children exposed to maternal MA use during pregnancy, specific developmental and behavioral deficits were increased when compared to controls. This correlates well with available literature. Larger sample sizes would help further support these findings and more definitively distinguish behavioral deficits.

Key Words: *Prenatal exposure, methamphetamine, neurodevelopment, behavior*

Methamphetamine (MA) use has risen sharply worldwide over the last decade[1], with increasing numbers of newborns delivered daily with known maternal MA use during pregnancy. In Cape Town and surrounding areas, admission trends to substance abuse treatment centres, with MA as either the primary or secondary drug of abuse, had risen from less than 1% in 2002 to 51% by 2006[2] and continues to rise.

The effects of prenatal MA use on maternal and fetal well-being have been well documented and include maternal anorexia and hypertension, placental abruption and insufficiency and intra-uterine growth retardation. Preterm delivery and neonatal mortality rates are increased and Apgar scores frequently lower.[3,4] Its effects on the developing brain, however, are less well defined. Animal literature has raised

concerns of structural defects such as retinal defects, cleft lip and palate, rib malformations, poor growth and delayed motor development.[5] Reviews have also suggested deficits in visual system development, an increased incidence of microgyri, impaired spatial learning, sensory-motor coordination and postural motor movements (up to a second generation), and increased startle reflexes.[6-11] Human studies, with varying methodologies, have begun to postulate certain neuroradiological and neurodevelopmental sequelae may be associated with prenatal maternal MA exposure.[12-18] Magnetic Resonance Imaging (MRI) has shown a decrease in size of certain brain structures, while Magnetic Resonance Spectroscopy (MRS) has identified a difference in brain metabolite levels between MA-exposed and non-exposed children.[18] Language delays[19], a delay in mathematics skills[20], autistic characteristics and other language difficulties[15], as well as increased aggressive behavior[16] have been among the specific developmental and behavioural difficulties identified in MA-exposed children.

Thus far minimal research has been done to delineate specific developmental and behavioral deficits in the pre-school child exposed to MA antenatally. Previous attempts at answering the multitude of questions surrounding this topic have utilized varying methods and assessment tools and a wide range of age groups. The absence of a control group or matched cohort without exposure to antenatal maternal MA use also makes it difficult to establish an association between drug exposure and eventual developmental outcome. Additional confounding effects such as lifestyle, socio-economic status and other drug exposures have therefore not been adequately addressed.

By comparing the children in this South African cohort to a group matched as closely as possible for the identified important confounders and by using standardized assessment tools, our study set out to answer the question of specific neurodevelopmental and behavioural sequelae noticeable in the pre-school child due to antenatal MA exposure, thereby providing better support and intervention for this vulnerable population.

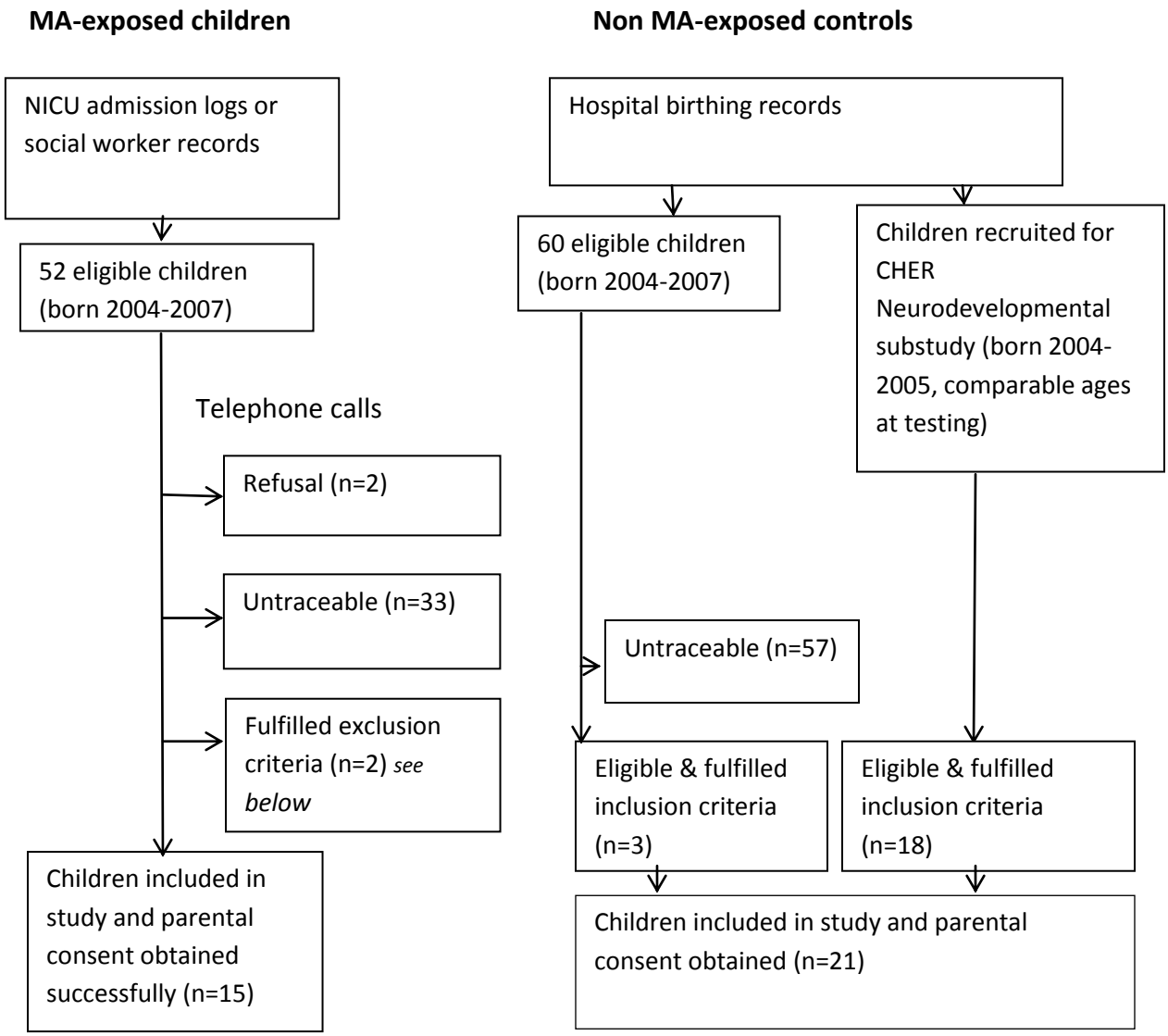
METHODS

This is a prospective matched cohort study.

Children included in the study were those born at New Somerset, Groote Schuur and Mowbray Maternity Hospitals in Cape Town, South Africa over a 2 and a half year period (2004-2007) whose mothers had disclosed regular MA use during pregnancy (more than two occasions during the pregnancy). This information was found either in neonatal intensive care unit (NICU) admission logs or by records of referrals to a social worker. Data on the quantity of use during pregnancy was not available. History of other drug or alcohol use or cigarette smoking during pregnancy was obtained through reviewing NICU charts as well as parental interview at the time of developmental assessment. Participants were excluded for other illicit drug use during pregnancy (by parental report), but not for cigarette smoking or alcohol use during pregnancy. Parental consent was obtained before inclusion into the study.

Of the 52 eligible children 15 were contactable and recruited into the study. See figure 1 for further clarification.

FIG. 1 Flow diagram of inclusion and exclusion of subjects and controls



Exclusion criteria:

- *Presence of other pathology that would impact on their neurocognitive functioning, for instance: serious head injury, severe bacterial meningitis, or pre- or postnatal insults such as hypoxic ischaemic encephalopathy or severe neonatal hypoglycaemia*
- *Maternal use of drugs illicit drugs other than alcohol and nicotine during pregnancy*
- *Presence of another syndrome with known developmental delay;*
- *Parental consent is denied.*

Infants born at all gestational ages were included, as preterm delivery is a known complication of MA use in pregnancy. Secondary chart review was completed by the principal investigator on available medical records. Detailed family history as well as medical history of child and mother was also taken at the first interview and compared to the available chart information. It was also indicated whether children were in foster or other protected care at the time of the interview.

A cohort of children, matched for age, sex, ethnic background, socioeconomic background (by neighbourhood of residence and level of employment), birth circumstance and gestation to the MA group were also evaluated. These children were drawn from the same geographical area, had the same exclusion criteria, ages and socioeconomic background and underwent identical developmental and behavioural assessments. They were identified through birth records from local hospitals as well as through recruitment for a sister study assessing neurodevelopmental outcome of infants born to mothers infected with the Human Immunodeficiency Virus (HIV). Ethics approval was obtained to incorporate data from these controls into our own study.

Inclusion of children to the matched cohort was subject to parental consent and the same exclusion criteria. Maternal alcohol use during pregnancy was also documented. Alcohol use during pregnancy as reported by mothers in the exposed and unexposed groups was present in approximately equal numbers (see Table 1).

TABLE 1 Baseline characteristics of the study population

	Methamphetamine n=15	**Controls n=21**	**p-value**
Child age at testing (mean) (range)	33.8months (25-46.5 mo)	35.6months (27-50 mo)	
Parent/foster care			
Parent(s)	n=4 (27%)	n=21 (100%)	0.00035
Foster (all grandmother)	n=11(73%)	n=0	0.00035
Alcohol use in pregnancy			
	n=3 (20%)	n=2 (10%)	0.41055
Gender			
Male	n=9 (60%)	n=14 (66.7%)	0.68610
Gestational age			
Preterm	n=4 (27%) (28, 30, 35, 36 wks)	n=3 (14%) (34, 34, 35 wks)	0.34747
Home language			
Afrikaans	n=10 (66.7%)	n=21 (100%)	
English	n=1 (6.7%)	n=0	
Afrikaans/English	n=4 (26.6%)	n=0	

Ethical Considerations and Consent

Consent was obtained from the parents or primary caregivers of all subjects before inclusion. Where literacy was questionable, information was read to parents or caregivers and explained by one of the investigators. As all the parents, caregivers and children were either English or Afrikaans first language speakers, an interpreter was not required. Written material was also provided to families.

Information was treated confidentially and family's privacy protected as far as possible. Where families requested further assistance by a social worker or other supportive services, their consent was obtained to share relevant information with these services. Where problems were identified during our assessments, parents and caregivers were offered the option of re-testing and follow-up in the Developmental Paediatrics Outpatient Clinic at Red Cross Children's Hospital. The aims and purposes of the study were made clear to all participants, as well as the fact that participation was voluntary and would not influence any form of government financial support guardians or parents were receiving at the time. Maternal identities and history of drug use was recorded for the purposes of this study only and identifiers destroyed as soon as relevant information had been recorded.

The study protocol was approved by the University of Cape Town Human Research Ethics Committee.

OUTCOME

The aim of this study was to identify specific developmental and neurobehavioral deficits in children exposed to methamphetamine during pregnancy. Knowledge of these deficits would assist doctors and other members of the multidisciplinary team involved in the care of the child to be vigilant of these potential problems, provide early, more intensive developmental care and educational support to these children, and thereby improve their final educational outcome, their ability to function optimally and their quality of life. It would also assist healthcare workers in counselling parents, other primary caregivers as well as adoptive parents in cases of antenatal methamphetamine exposure.

MEASURES

Children in both groups were assessed between the ages of 2-4 years. The following information was collected.

Demographic Data

A questionnaire on social circumstances (family income at time of assessment), medical history, educational history (highest level of schooling obtained by parents of caregivers), current occupation and employment, marital status was completed by parents or caregivers. A detailed birth and perinatal history was also obtained. All of the exposed children were admitted to a Neonatal Intensive Care Unit (NICU) initially for a short observation for possible withdrawal only, but were otherwise healthy at birth. Neonatal morbidity data was collected and corrected for as necessary. It was also noted whether the child was in the care of his/ her parents, other family members or other protective care.

Cognitive and Behavioural Tools

Developmental testing was performed on each child in the MA-exposed and unexposed groups. The Griffiths Mental Developmental Scales (GMDS) was administered by the principal investigator (JD) or co-investigator (KD). Children were identified by exposure and assessed prospectively.

The GMDS assesses comprehensively the different aspects of normal infant and child development. It has been validated for use in children of different language groups (English, Afrikaans and Xhosa) in South Africa.[21] The GMDS is age-standardized and measures areas, or 'sub-scales' of development under the following subscales: locomotor, personal-social abilities, hearing and speech, eye and hand co-ordination, performance and practical reasoning.

Raw scores from all the separate sub-scales are added to obtain a total raw score that can be converted and evaluated as either age equivalents, sub-quotients and general quotients

(the GQ or general developmental ability), or percentile equivalents.[21,22]

The GMDS was administered in each child's home language (Afrikaans or English). No external translator was required.

The Child Behavior Checklist (CBCL)[23] was completed by parents or guardians. It is designed to assess social competencies and behavioral problems in children. It has been extensively validated across widely differing socioeconomic and cultural spectrums.[24]

The CBCL clusters responses into a total score, as well as Internalising and Externalising domains. In addition, the CBCL arranges results in more familiar Diagnostic Statistic Manual-IV (DSM-IV) related categories (Affective Problems, Anxiety Problems, Attention Deficit/ Hyperactivity Problems). The recommended t-score transformation of the raw behavior scores was used.[25]

The cut-off for categorising clinical relevance for the categories of internalising-type behavior, externalising–type behavior and total behavior problems is a t-score of ≥63. A t-score of 60-63 is borderline.[24] The cut-off for clinical relevance when categorising the behavioral scores for the different categories, is a t-score of ≥70. A t-score of between 65 and 69 is borderline.[23] In this study the 18 month to 5 year age version was used.

The GMDS and CBCL were chosen as assessment tools as these are the preferred tools for assessment in this institution, as well as in the country in general. They are widely used and frequently utilised for research purposes in South Africa, as well as in Europe, the United Kingdom and Australia.[26,27] Testing occurred in the Developmental Paediatrics Outpatient Clinic consulting rooms at the Red Cross Children's Hospital. Unfortunately, it was not always possible to blind assessors to the exposure status of the participants. Families received transport money for each visit.

Statistical Analysis

Descriptive statistics were used to describe both populations (MA-exposed and unexposed). As no previous data was available to allow calculation of sample size, a predetermined time period was selected. The scores in our dataset were linearly transformed from the original raw data to obtain z-scores, percentiles and age-equivalents in the case of the GMDS and t-scores and percentiles in the case of the CBCL. Raw data was used to do the statistical analysis, though, and as the groups were matched at the onset of the study, only univariate analysis (t-test) was performed. (For the purpose of where an individual falls in the distribution of the general population, z-score is useful, whereas raw data is more appropriate when comparing two groups.)

Because of the small sample size, no further adjustments were made. Minimum and maximum scores, means, medians, upper and lower quartiles were obtained for data in the GMDS and CBCL, and p-values derived to delineate statistical significance of any differences in performance. The level of significance was taken at $p<0.05$.

RESULTS

Demographic Details

Table 1 describes the differences in demographic details between the two cohorts. There was no known intra- or extra-uterine growth retardation in either group. There was no difference in presence of neonatal morbidities between groups. Ethnicity and socio-economic status was also consistent between both groups. Significant differences were seen in the number of children in the care of their biological parents versus foster care, where most of the MA-exposed children were in the care of a grandmother. Alcohol use was slightly higher in the MA-exposed groups when compared with the non-exposed group. Complete educational history for parents and caregivers proved difficult to collect.

Neurodevelopmental and Behavioral Assessments

On the GMDS, differences between the groups on general performance was statistically significant, where mean age equivalent for MA-exposed children (MMETH) was significantly lower at MMETH= 30.3; mean age equivalent for non-exposed group (MCONT) = 36.8 ($p = 0.0220$). MA-exposed children, therefore, performed at an

age equivalent significantly lower than their own age and when compared to the non-exposed group.

Specific differences were also identified in the Personal & Social subscale, where MMETH = 33.4; MCONT = 48.4 (p <0.0001) and in the Eye and Hand Coordination subscale, where MMETH =26.5; MCONT = 33.6 (p = 0.0002).

In addition, there was a tendency for differences in the Hearing & Speech subscale where MMETH =28.4; MCONT = 33.6 (p = 0.0804); in the Performance subscale where MMETH =28.5; MCONT = 34.4 (p = 0.0657). See Table 2 for further clarification of these findings.

Sensitivity analysis was performed, excluding all preterm infants; the resulting p-values remain statistically significant in the same subscales (see table 2).

TABLE 2 GMDS results for exposed and control groups (raw scores)

Group	Scales	N	Mean	Std Dev	Median	Inter quartile range (IQR)
Control (N=21)	**A**	20	37.4	9.8	36.4	29.7- 45
	B	21	48.4	8.9	48	44 - 54
	C	21	33.5	8.2	34	28 - 36
	D	21	33.6	5.1	32	30.7 - 36
	E	21	34.4	8.3	32	29.4 - 40
	F	21	32.9	8.0	29.9	27.3 - 36
	G_tot	21	36.8	7.1	36.2	30.75 - 42.7
Subject (N=15)	**A**	15	34.0	14.9	28	22.7 - 44
	B	15	33.4	10.7	31.5	23.5 - 42
	C	15	28.4	8.5	26	21.1 - 38
	D	15	26.5	5.2	24	21.5 - 30
	E	15	28.5	10.2	25.4	22.1 - 38
	F	15	31.1	8.9	26	24 - 42
	G_tot	15	30.3	9.2	26.4	22.9 - 40.3

Score	Subscale A	Subscale B	Subscale C	Subscale D	Subscale E	Subscale F	G_total score
p-value	0.4290	**<0.0001**	0.0804	**0.0002**	0.0657	0.5274	**0.0220**
p-value (after excluding preterm infants)	0.5973	**0.0002**	0.1503	**0.0005**	0.0691	0.7331	**0.0421**

In above table: *A = Locomotor ability; B = Personal-Social Ability; C = Language (Hearing and Speech); D = Eye and Hand Co-ordination; E = Performance ability; F = Practical Reasoning ability; G = General performance*

In terms of behavior on the CBCL the following was noted: The mean t-score for Externalising Behaviors in the exposed group is 61.3 (SD 13.2) which falls into the borderline range, compared to a mean score in the control group of 54.7 (SD 11.8). The mean t-score for Internalising Behaviors in the children with MA exposure is 61.4 (SD 11.8), which falls into the borderline range, compared to a mean score of 59.2 (SD 11.9) for the control group. The differences between scores on Internalising vs. Externalising Behaviors were therefore not shown to be statistically significant, p = 0.5917 and p=0.1187 respectively, although this remains

clinically important and deserves further investigation. Please see table 3 for further illustration. There was also a tendency for MA-exposed children to demonstrate more atypical behavior in the domains of: anxious/ depressed behavior, somatic complaints, attention problems, aggressive behavior, affective problems, pervasive developmental problems, attention deficit/ hyperactivity, oppositional defiant problems and sleep problems. It is, however, significant to note that subjects score higher in categories representing externalising behavior than in those representing internalising behaviour.

TABLE 3 Summary of statistical analysis of score for CBCL (controls vs subjects)

Group	Variable	Mean	Std Dev	Median	Inter quartile range (IQR)
Control (N=21)	**ER_t**	57.8	8.2	59	50 - 65
	AD_t	58.0	8.9	56	51 - 63
	SC_t	60.8	9.3	58	53 - 68
	W_t	62.6	10.2	60	56 - 70
	Slp_t	55.1	5.2	53	51 - 59
	Att_t	56.6	7.4	53	51 - 62
	Agg_t	57.4	9.1	53	51 - 64
	Int_t	59.2	11.9	60	49 - 67
	Ext_t	54.7	11.8	54	51 - 65
	Tot_t	59.3	12.4	58	51 - 68
	Aff_t	60.2	9.5	60	52 - 67
	Anx_t	58.2	8.9	54	51 - 67
	PD_t	62.6	9.5	63	56 - 68
	ADH_t	55.7	6.3	54	51 - 57
	OD_t	55.8	6.6	52	51 - 59
Subject (N=16)	**ER_t**	58.2	9.1	55	51 - 63.5
	AD_t	62.4	10.7	59	53.5 - 70
	SC_t	61.6	9.6	61.5	53 - 69
	W_t	61.8	11.4	60	51 - 68.5
	Slp_t	60.4	12.2	57.5	51 - 63
	Att_t	60.4	7.8	59.5	55 - 66
	Agg_t	63.2	11.6	63	52 - 73.5
	Int_t	61.4	11.8	63	59 - 69.5
	Ext_t	61.3	13.2	61	54.5 - 73
	Tot_t	63.4	11.5	65.5	59 - 72
	Aff_t	63.6	8.9	65	54 - 72
	Anx_t	63.1	8.7	60	71.5
	PD_t	62.9	10.0	63	52.5 - 70
	ADH_t	59.8	7.4	60	53 - 67
	OD_t	58.9	8.6	59	51 - 64

P-values from t-test under the assumption of linear transformation (CBCL t-score: control vs. subject)

Score	ER_t	AD_t	SC_t	W_t	Slp_t	Att_t	Agg_t	Int_t
p-value	0.8822	0.1802	0.7839	0.8227	0.1244	0.1443	0.0972	0.5917
Score	**Ext_t**	**Tot_t**	**Aff_t**	**Anx_t**	**PD_t**	**ADH_t**	**OD_t**	
p-value	0.1187	0.3052	0.2700	0.1069	0.9220	0.0775	0.2129	

In the above table abbreviations are:

ER_t = Emotionally Reactive subscale; AD_t = Anxious/Depressed subscale; SC_t = Somatic Complaints subscale; W_t = Withdrawn subscale; Slp_t = Sleep problems subscale; Att_t = Attention problems subscale; Agg_t = Aggressive Behaviour subscale; Int_t = Internalising Problems subscale; Ext_t = Externalising Problems subscale; Tot_t = Total score; Aff_t = Affective Problems subscale; Anx_t = Anxiety Problems subscale PD_t = Pervasive Developmental Problems Subscale; ADH_t = Attention Deficit/ Hyperactivity; OD_t = Oppositional Defiant Problems

DISCUSSION

The main purpose of this study was to identify and describe neurodevelopmental and behavioral profile of a cohort of MA-exposed children in the age bracket 2 to 4 years.

Reviews have suggested certain specific early developmental problems. One review published by Thompson et al linked MA and amphetamine exposure during fetal development with movement disturbances and decreased scholastic achievement[31] later in life, with poorer performance on sustained-attention, long-term spatial and verbal memory, and visual motor-integration tests. The wide age range in this study (3-16 years) limits the ability to extrapolate specific age estimates, though.

Cernerud and colleagues reported on long-term follow-up of older children and adolescents exposed to MA antenatally. They identified an increase in language delays[19], and poorer performance in physical fitness activities and mathematics.[20] Similar areas of concern were identified when researchers followed a cohort of Swedish children exposed to amphetamine during pregnancy: exhibition of emotional characteristics of autism, speech difficulties and stranger wariness by the age of one year[20]; lower IQ's vs norms by age 4[32]; more aggressive behavior and problems with peers by age 8[16] and significant problems with school advancement (again especially due to delays in mathematics and language) and physical fitness activities by age 14.[33]

A recent study of mother-infant pairs in the United States examined the effects of prenatal MA exposure on children through 3 years of age when compared with non-exposed subjects. They found no difference in cognition and modest motor effects at 1 year of age which had mostly resolved by 3 years of age.[34]

When looking specifically at behavioral sequelae of MA-exposure in utero, previous literature highlights certain behavioural profiles of concern in children. These included especially emotional characteristics of autism and stranger wariness[15] and an increase in aggressive behaviour and problems associating with peers.[16,19] Even short-term use of MA in adults has been shown to lead to aggressive behavior, uncontrollable rage, violent behavior and significant personality changes.[4] All amphetamines are known to cross the placenta, thus it is not at all absurd to expect similar effects on the fragile, developing brain.[3] Cocaine, with similar effects in the human body and brain, has in recent literature been linked to a significant increase in aggressive behavior and Attention Deficit/ Hyperactivity Disorder (ADHD) in offspring exposed in utero.[32] Methamphetamine has a longer half-life (12 hours vs 1 hour), a more dramatic increase in Dopamine and more significant effects on the human brain.

Thus limited data is available on the neurodevelopmental profile of preschool children with antenatal MA exposure, but significant trends have emerged: diminished cognitive performance, problems with memory, visual-motor integration, language, aggressive behavior and attention.

In our study, MA-exposed children generally obtained lower scores on final 'General Quotients' (i.e. diminished cognitive performance) and performed at an age-equivalent lower than that of controls.

Our findings on neurocognitive testing show that specific statistically significant problems were identified in personal-social ability and hand-eye co-ordination. These are important areas performance in the school environment. Similar to findings of other studies[19], our research also showed diminished performance on language ability. Although this did not reach statistical significance, qualitative comments from individual assessments frequently mentioned poor articulation, speech quality and diminished ability to communicate in general. MA-exposed children also performed worse than controls on assessments of manipulation skills, speed of working, precision and pattern-recognition (the 'Performance' subscale). Although these scores did not reach statistical significance, they are considered important skills for daily living.

As the number of children in both the subject and control groups in this study is so small, only tentative conclusions can be drawn from our findings on their neurocognitive profile. However, areas of concern have been identified

and that most of these correlate with what is already shown in the available literature regarding general cognitive ability, motor skills and language development. The fact that these could be identified in such a small cohort suggests important concerns that deserve further scrutiny. Although our findings on behavioral profiles of MA-exposed children did not reach statistical significance, we feel it is clinically relevant that the scores on the Aggressive Behavior subscale approached significance. This correlates well with available literature.

A trend toward significance was also found between groups on the Attention Deficit/Hyperactivity Problems subscale. Attention deficit/ hyperactivity has not previously been identified as significantly increased in MA-exposed children. These two areas of behavioral problems would again impact significantly on a child's ability to interact appropriately and meaningfully in the classroom setting.

Environmental risk factors are particularly prevalent in the general South African society, but probably more so in the communities from which these children were drawn. There are high incidences of parental and individual poor health, lower levels of maternal education, possible concomitant maternal depression and other drug or alcohol use, violence, social isolation and poverty. Emotional problems can be both common causes and consequences of cognitive and language disorders.[28,29] Poverty, gang and other violence also affect the psychological and cognitive development of young children.[30] Learning difficulties, developmental delays and behavioural problems are less likely to be picked up and/or acted upon in these communities. In addition, recurrent illness, poor nutrition and limited access to preventative primary care result in these children facing the cumulative burden of particular social stress and greater biological vulnerability.

These issues are not unique to the poorer suburbs of Cape Town, though, but may be said about any poor neighbourhood of any large North American city.

Study Limitations

MA use often coincides with the use of other recreational drugs and alcohol. Alcohol use during pregnancy was not considered an exclusion criterion for this study, and as history of alcohol use during pregnancy was reported as similar between the two groups, the impact therefore on the developmental profile of each group may be considered similar also. History of alcohol and nicotine use during pregnancy was through self-report only, potentially affected by recall bias, but interview data was compared to history taken on NICU admission to confirm. A significant limitation was the inability to quantify exact MA drug use during pregnancy, as well as use of other drugs. Maternal report and recollection had to be relied on, and this may introduce bias. There was no alternative; however, as routine drug quantification testing did not exist in the public sector at the time.

The nature of drug abuse and the accompanying lifestyle of participants made this a very difficult population to study, similar to the experience of other researchers. Parental incarceration was frequent, addresses often transient and placement of the child in foster care a common occurrence (in all our cases children were placed with a grandmother soon after birth, with variable visitation by parents). Appointments were frequently missed due to a lack of transport or money, scheduled court appearances or the fact that the parent was still actively using recreational drugs. For these reasons the number of patients finally included in the two groups was small. This will be considered a pilot project, and further research continues. We feel the findings are significant and should be reported.

The fact that almost all MA-exposed children were in foster care, compared to unexposed children being in the care of their biological parents, does provide a measure of internal validation, as drug use in pregnancy was self-reported with no available confirmatory testing.

Due to the small sample sizes in both the MA-exposed group (N = 15) and the control group (N = 21), the analysis lacks power. Therefore, differences that exist between the two groups may be less apparent. It was also not

always possible to blind assessors fully to the exposure status of participants, another factor which may have introduced bias into the analysis.

Despite these limitations, it remains important to document and further investigate our findings. Little is known about the neurodevelopmental and behavioral effects of MA exposure in pregnancy, especially in a resource-poor setting where infants are often exposed to the added risks of low socio-economic status and poverty.

Recommendations

Although our sample size was small in this pilot study, the results do support findings elsewhere in the literature. New trends identified in our research further support the notion that MA is associated with significant neurodevelopmental and behavioral problems, some of which are already identifiable in early childhood and prior to formal school entrance. It would be valuable to continue studying this population formally for specific developmental and neurocognitive difficulties.

Public health drives should target education and prevention of MA abuse in young, pregnant women in known high risk areas. Paediatric services should anticipate problems and aim to target exposed children for more intensive follow-up as early as the neonatal period, with developmental assessment, follow-up and educational and social support as soon as problems are identified, allowing them to achieve their full potential.

Conflict of Interest

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial or non-financial interest in the subject matter or materials discussed in this manuscript.

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REFERENCES

1. World drug report 2012. Vienna (Austria): United Nations Office on Drugs and Crime; 2012
2. Pluddemann A, Myers BJ, Parry CD. Surge in treatment admissions related to methamphetamine use in Cape Town, South Africa: implications for public health. Drug Alcohol Rev 2008; 27: 185-90.
3. DeVane L. Pharmacokinetic correlates of fetal drug exposure. NIDA Res Monograph 1991; 114: 18-36.
4. Winslow BT, Voorhees KI, Pehl KA. Methamphetamine Abuse. Am Fam Physician 2007;76:1169-74,1175-7.
5. Šlamberova R, Pometlova M, Charousova P. Postnatal development of rat pups is altered by prenatal methamphetamine exposure. Prog Neuropsychopharmacol Biol Psych 2006;30 (1):82–88.
6. Acuff-Smith KD, Schilling MA, Fisher JE, Vorhees CV. Stage-specific effects of prenatal d-methamphetamine exposure on behavioural and eye development in rats. Neurotoxicol Teratol 1996;18:199-215.
7. Acuff-Smith KD, George M, Lorens SA, Vorhees CV. Preliminary evidence for methamphetamine-induced behavioural and ocular effects in rat offspring following exposure during early organogenesis. Psychopharmacology 1992;109:255-63.
8. Yamamoto Y, Yamamoto K, Fukui Y, Kurishita A. Teratogenic effects of methamphetamine in mice. Japanese J Legal Med 1992;46:126-31.
9. Cho DH, Lyu HM, Lee HB, et al. Behavioural teratogenicity of methamphetamine. J Toxicol Sci 1991;16 (suppl 1):37-49.
10. Cabrera TM, Levy AD, Li Q, et al. Prenatal methamphetamine attenuates serotonin mediated renin secretion in male and female rat progeny: evidence for long-term dysfunction of serotonin pathways in brain. Synapse 1993;15:198-208.
11. Weissman AD, Caldecott-Hazard S. Developmental neurotoxicity to methamphetamines. Clin Exp Pharmacol Physiol 1995;22:372-4.
12. Thompson BL, Levitt P, Stanwood GD. Prenatal exposure to drugs: effects on brain development

and implications for policy and education. Neuroscience 2009;10:303-312.
13. Billing L, Eriksson M, Steneroth G, Zetterstrom R. Predictive indicators for adjustment in 4-year old children whose mothers used amphetamine during pregnancy. Child abuse and neglect 1988;12:503-7.
14. Cernerud FX, Eriksson M, Jonsson B, Steneroth G, Zetterstrom R. Amphetamine addiction during pregnancy: 14-year follow-up of growth and school performance. Acta Ped 1996;85:204-8.
15. Billing L, Eriksson M, Larsson G, Zetterstrom R. Amphetamine addiction and pregnancy III. One year follow-up of the children. Psychosocial and pediatric aspects, Acta Paediatr Scand 1980;69:675-680.
16. Billing L, Eriksson M, Jonsson B, Steneroth G, Zatterstrom R. The influence of environmental factors on behavioural problems in 8-year old children exposed to amphetamine during fetal life. Child Abuse Neglect 1994;18:3-9.
17. Dixon SD, Bejar R. Echoencephalographic findings in neonates associated with maternal cocaine and methamphetamine use: incidence and clinical correlates. J of Ped 1989;115(5 Pt 1):770-8.
18. Chang L, Alicata D, Ernst T, Volkow N. Structural and metabolic brain changes in the striatum associated with methamphetamine abuse. Addiction 2007;102 (suppl. 1):16-32.
19. Billing L, Eriksson M, Steneroth G, Zetterstrom R. Predictive indicators for adjustment in 4-year old children whose mothers used amphetamine during pregnancy. Child Abuse and Neglect 1988;12:503-7.
20. Cernerud FX, Eriksson M, Jonsson B, Steneroth G, Zetterstrom R. Amphetamine addiction during pregnancy: 14-year follow-up of growth and school performance. Acta Ped 1996;85:204-8.
21. Allan MM, Luiz DM, Foxcroft CD. The performance of South African Normal Preschool Children on the Griffiths Scales of mental development: a comparative study, University of Port Elizabeth. Presented at the 10th National Congress of the Psychological Association of South Africa, October 1992.
22. Luiz D. Griffiths Scales of Mental Development: South African Studies (Research paper noC25) 1988.
23. Achenbach TM & Edelbrock C. Manual for Child Behaviour Checklist and revised Child Behaviour Profile. Burlington, VC: University of Vermont, Department of Psychiatry (1983).
24. Ivanova M, Achenbach TM, Dumenci L, et al. Testing the 8-syndrome structure of the child behaviour checklist over 30 societies. Journal of Clinical Child and Adolescent Psychology 2007; 36 (3): 405-417.
25. Jensen-Doss A, Osterberg LD, Hickey JS, Crossley T. Agreement between chart diagnoses and standardized instrument ratings of youth psychopathology. Adm Policy Ment Health 2013;40:428-437.
26. Hemels MA, Nijman J, Leemans A et al. Cerebral white matter and neurodevelopment of preterm infants after coagulase-negative staphylococcal sepsis. Pediatr Crit Care Med 2012;13,(6):678-684.
27. Robinson M, Whitehouse AJO, Zubrick SR, et al. Delivery at 37 weeks' gestation is associated with a higher risk for child behavioural problems. Aust N Z J Obstet Gynaecol 2013;53:143-151.
28. Dooling EC. Cognitive disorders in children. Curr Opin Pediatr 1993;5:675-9.
29. Richter L & Grieve KW. Home Environment and Cognitive Development of Black Infants in impoverished South African Families. Infant Mental Health Journal 1991;12 (2):88-102.
30. Donald DR & Dawes A (eds). 1994. Childhood and adversity: Psychological perspectives from South African Research. David Phillip, Cape Town. p136-153.
31. Thompson BL, Levitt P, Stanwood GD. Prenatal exposure to drugs: effects on brain development and implications for policy and education. Neuroscience 2009;10:303-312.
32. Wouldes T, LaGasse L, Sheridan J, Lester B. Maternal methamphetamine use during pregnancy and child outcomes: what do we know? J of NZ Med Ass 2004;117:1206.
33. Plessinger MA. Prenatal exposure to amphetamines. Risks and adverse outcomes in pregnancy. Obstet Gynecol Clin North Am 1998;25:119-38.
34. Smith LM, LaGasse LL, Derauf C, et al. Motor and cognitive outcomes through three years of age in children exposed to prenatal methamphetamine. Neurotox Terat 2011;33:176-184.
35. Levine TP, Lester B, Lagasse L, et al. Psychopathology and special education enrollment in children with prenatal cocaine exposure. J Dev Behav Pediatr 2012;33:377-86.