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MATERNAL METHAMPHETAMINE USE DURING
PREGNANCY AND SUBSEQUENT
NEURODEVELOPMENTAL AND PSYCHOLOGICAL
SEQUELAE IN THE CHILD-
A CAPE TOWN EXPERIENCE

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A dissertation that is based on independent research performed by the candidate to partially fulfil the requirements for the Master in Medicine (MMed) in Paediatrics, at the University of Cape Town.

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DECLARATION

I, *Jessie Grace van Dyk* hereby declare that the work on which this dissertation is based is original research (unless acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

Signed by candidate

Jessie Grace van Dyk

2011 . 8 . 28

Date

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LIST OF ABBREVIATIONS

ADH	Attention Deficit/ Hyperactivity
CBCL	Child Behaviour Checklist
DAT	Dopamine Transporter
DEA	Drug Enforcement Agency
GMDS	Griffiths Mental Developmental Scales
GQ	General Quotient
HIV	Human Immunodeficiency Virus
IUGR	Intra-uterine growth restriction
MA	Methamphetamine
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
NICU	Neonatal Intensive Care Unit
PET	Positron Emission Tomography
SGA	Small for gestational age
UCT	University of Cape Town

PROTOCOL

**MATERNAL METHAMPHETAMINE USE DURING PREGNANCY AND SUBSEQUENT LONGTERM
NEURODEVELOPMENTAL AND PSYCHOLOGICAL SEQUELAE IN THE CHILD: A CAPE TOWN
EXPERIENCE**

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BACKGROUND

Methamphetamine, part of the amphetamine group of drugs, was first discovered in Japan in 1919. It has been clandestinely manufactured in the United States since the 1960s, and is still legally produced there as a nasal inhalant, as treatment for Attention Deficit Disorder and exogenous obesity, as well as off-label treatment for narcolepsy. (1)

It is a cheap (about R15-30 per 'straw'), easily obtainable, odourless, white powder which has a bitter taste, but dissolves easily in water or alcohol. Known as, amongst others, 'speed', 'ice', 'crystal', 'chalk', 'glass', 'crank', and locally, 'tik', it can be smoked, snorted, orally ingested, injected intravenously or even administered anally. In South Africa the preferred method consists of placing the powder or crystal in a light bulb (from which the metal threading has been removed) and inhaling the fumes produced while heating the bulb from below with a lighter.(2)

The use of methamphetamine has risen sharply globally over the last decade, used by 26 million people worldwide by 2007, more than heroin and cocaine combined, according to the United Nations Office on Drugs and Crime. This has been ascribed to many interlocking reasons: it is cheap, easily obtainable, easy to use without the need for needles or other special 'equipment', and it produces in the user a characteristic 'rush'. This feeling of confidence, power and heightened sexual levels, of feeling 'on top of the world' has made it especially popular amongst teenagers and young adults. (3)

According to an article in the Wall Street Journal of May 21 2007, South Africa has become attractive both as a market and trade hub for recreational drugs, especially methamphetamine (4). Reasons cited include the fact that incomes are higher than most of the rest of Africa, banking and transport systems resemble that of a developed nation, with direct flights to any destination in the world as well as efficient seaports and reliable telephone and internet service. These factors, combined with an overwhelmed justice system has led to the perception of South Africa being a drug trafficker's paradise.

According to figures obtained via the Medical Research Council's South African Community Epidemiology Network on Drug Use there has been a sharp rise in patients presenting with Methamphetamine-related problems since 2002. (2)

Table 1 shows the proportions of patients presenting with methamphetamine as primary or secondary substance of abuse since January 2002 (this period has been divided into six month periods where 2002a refers to January – June 2002 and 2002b to July – December 2002 and so forth). The figures quoted under 'total patients' refer to the total number of patients treated at over 25 specialist treatment centres or programmes for all substances (including methamphetamine, Mandrax, heroin, cocaine, alcohol, cannabis etc).

Figure 1 provides a graphic illustration of these numbers. (Illustrations used courtesy of MRC fact sheet on methamphetamine)(2)

Table 1: Patients with methamphetamine as primary or secondary substance of abuse

	2002b		2003a		2003b		2004a		2004b		2005a		2005b		2006a		2006b		2007a		2007b	
	n	%	n	%	n	%	n	%	n	%	N	%	N	%	N	%	N	%	N	%	N	%
Primary	13	0.8	38	2.2	38	2.3	241	10.7	445	19.3	644	26.1	739	34.7	990	37.2	1184	42.3	1166	40.7	1103	36.1
Secondary	19	1.2	43	2.5	83	5.0	188	8.3	223	9.6	240	9.7	213	10.0	242	9.1	267	9.6	247	8.6	253	8.3
Overall*	32	2.1	81	4.7	121	7.3	429	19.0	668	28.9	884	35.8	952	44.7	1232	46.3	1451	51.9	1413	49.4	1356	44.3
Total patients	1551		1724		1659		2255		2308		2468		2131		2660		2798		2862		3058	

* Patients who have methamphetamine as primary OR secondary substance of abuse

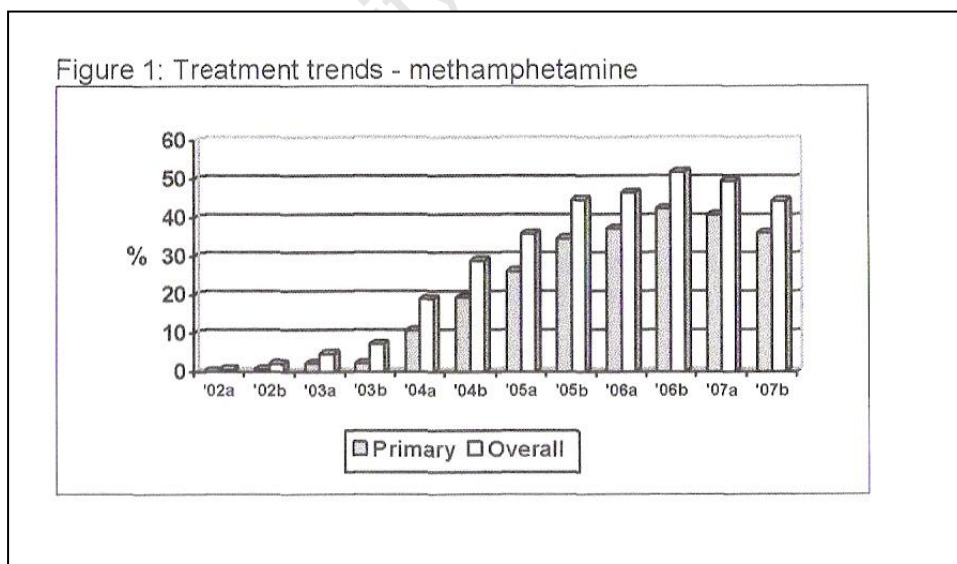
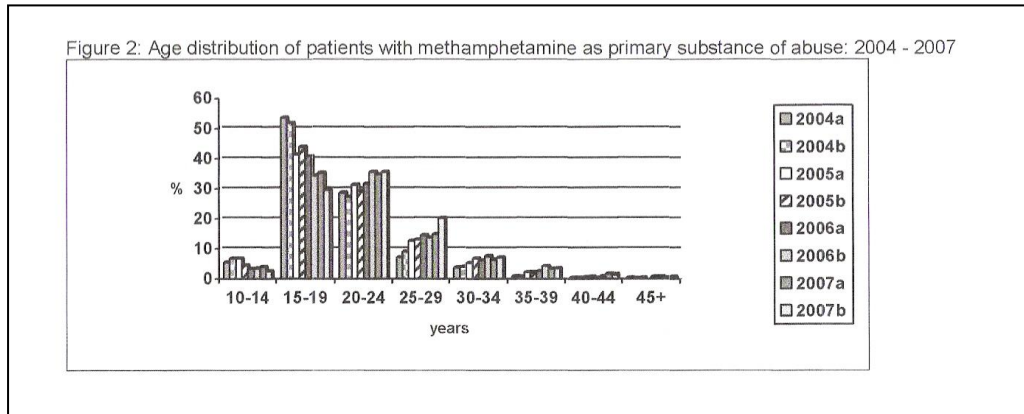


Figure 2 shows the distribution of ages of patients who reported Methamphetamine as their primary substance of abuse- in the second half of 2007 the average age was 23 years and 73% of these were male. Most were coloured (87%), 10% were white, 1% Indian/ Asian and 3% Black/ African.



Besides the initial feeling of euphoria, increased confidence and heightened libido experienced after taking methamphetamines, these drugs have a number of adverse effects. **They** trigger release of neurotransmitters epinephrine, norepinephrine and dopamine in the sympathetic nervous system. (2) Release of these substances cause euphoria, increased energy and self-confidence, insomnia, restlessness, irritability and tremors, and heightened libido. Other systems outside the central nervous system are also affected. Respiratory effects include tachypnoea, pulmonary hypertension and pulmonary oedema as well as decreased lung capacity, while its effect on the cardiovascular system include tachycardia, hypertension and/or arrhythmias. Overdose can lead to dehydration, hyperthermia, seizures, renal failure, stroke and myocardial infarction. Long-term use of tik leads to severe weight loss due to decreased appetite, severe dermatological problems, increased risk of seizures as well as uncontrollable rage, violent behaviour and personality changes.

Women referred to the Alcohol Drug and Pregnancy Team (ADAPT) at National Women's Hospital in New Zealand showed high rates of psychological, social and health problems related to their drug use. (5)

See figure 3 for a summary of these problems.

Figure 3: Psychosocial and health factors in patients

Psychosocial and Health factors	N= 34
Multiple drug use, incl cigarettes (33), marijuana (14), alcohol (10), opiates (6)	33
History of not keeping appointments for antenatal check-ups	14
Mental health problems, incl psychotic behaviour and attempted suicide	10
Referrals to Child, Young Persons and Family Service	10
Custody issues due to unstable home environment	7
Legal proceedings pending for mother or imprisonment	5
Medical complications prenatally	4
Known history of overdose	2

Thus far, much of what is known about methamphetamine use in pregnancy and its effect on the fetus, newborn and child has come from animal studies, human studies (with varying methodologies) and information and literature on cocaine use in pregnancy. All illicit drugs are known to cross the placenta and therefore reach the growing fetus (6,7), causing direct effects on the fetus, or secondary to changes in the fetal environment. Methamphetamine has been shown to have vasoconstrictive effects leading to decreased uteroplacental perfusion, with subsequent restriction of nutrition and oxygen supply to the fetus and fetal hypoxia, and its anorexic effects on the mother may result in intrauterine growth retardation. The drug can also permeate the placenta itself and lead to prenatal stroke and other organ damage. Increased maternal blood pressure and heart rate substantially raises the likelihood of miscarriage and premature delivery (8). Associated unstable home circumstances, use of other drugs and potential dangerous sexual behaviour add to the risk of immediate complications and long-term sequelae in the unborn child.

Animal studies done on rats and their offspring have found a number of physical, motor, neurotransmitter and behavioural effects after exposure to methamphetamine (9-14). Amongst these effects were increased maternal and child mortality and

structural defects such as retinal defects (9-11), cleft palate and rib malformations. Decreased growth and delayed motor development (10, 12) have also been demonstrated, as well as neurochemical alterations in the central nervous system secondary to neurotoxic effects of methamphetamine on serotonergic neurons (9, 12, 14, 15). These neurochemical alterations seem to be associated with learning impairment (9), increased motor activity (10), behavioural disturbances (14) and enhanced conditioned avoidance responses (12).

The few human studies reported to date have shown similar patterns to those done in animals. Methamphetamine use seems to be associated with increased risk of premature delivery and placental abruption (16, 17), as well as clefting, cardiac anomalies and fetal growth retardation (18). One study, which used MRI to assess global brain volumes and regional brain structures, showed a definite correlation between methamphetamine use in pregnancy and smaller subcortical volumes and cognitive deficits in children exposed to prenatal methamphetamine (19).

Maturation of the brain and central nervous system requires a sequence of events and processes more complex than that of any other system or organ, making it especially vulnerable to prenatal environmental influences (20, 21). The blood-brain barrier of the fetus and young infant is much more permeable than that of the older child and adult, and the fetus lacks efficient drug-metabolising detoxification capacities (22). Toxins associated with in utero growth retardation and maturational delay should be suspected of causing functional developmental toxicity. Therefore any substance or compound that causes retardation of intrauterine somatic growth should be considered a potential neurobehavioural teratogen (23). Methamphetamine complies with all these characteristics, and therefore warrants closer evaluation.

Identification of specific neurodevelopmental and neurobehavioural deficits in children prenatally exposed to methamphetamine would enable a primary health care provider as well as the multidisciplinary team at all levels to be vigilant of

potential problems and provide early, prophylactic care to the exposed child, thereby limiting long-term developmental and cognitive sequelae. Large areas of South Africa remain underserved by medical and social services, and lower socio-economic status leave these children especially vulnerable.

SCREENING FOR DEVELOPMENTAL DELAY AND LEARNING DISABILITIES

The most reliable measure of neurodevelopment remains serial neuropsychological testing, but developmental delay and other specific disabilities can be identified using specific neurological and developmental observations and assessments as well as parental reports.

The optimal selection of tools for any such research would be those that tap into the specific areas known to be affected by the compound under investigation. However, this assumes that information already exists on the effect of that substance on the developing nervous system. Where such information is non-existent or scanty, it is necessary to use a wider spectrum of assessment tools.

Complete evaluation of any child with a potential neurodevelopmental delay or learning disability should commence with a thorough physical examination, especially searching for other, identifiable syndromes associated with these delays, as well as a thorough neurological exam, vision and hearing assessment, head circumference and growth parameters . Developmental examination should ideally be performed with the help of a formal battery of psychoeducational tests administered by an appropriately trained individual and should focus on processing, recall, integration and output of auditory and visual information.

Such comprehensive testing includes (70):

- A reliable, stable and valid measure of intellectual ability
- Measures of aural, motor and visual processing
- Measures of vocabulary and language development
- Measures of academic achievement
- Measures of attention regulation
- Assessment of social skills and emotional stability

AIM OF THIS STUDY

To determine whether specific neurodevelopmental or neurobehavioural deficits can be identified in a cohort of South African children known to be antenatally exposed to methamphetamine, as compared to a matched cohort of children.

METHODS

Study design

This is a descriptive case control study

Subjects

Children to be included in the study will be those born at New Somerset Hospital, Groote Schuur Hospital and Mowbray Maternity Hospital during the period January 2004 to June 2007, whose mothers had disclosed at the time of delivery that they had been taking methamphetamine during their pregnancy. Occasionally this information had been noted in the Neonatal Intensive Care Unit (NICU) admission book, but referrals by the NICU or obstetric service to a social worker for methamphetamine use during pregnancy will also be used as a source of recruitment. History of other drug or alcohol use or cigarette smoking during pregnancy will be obtained from reviewing NICU charts as well as parental interview at the time of testing. Parental consent will be taken before inclusion into the study.

Approximately 15 such children are known at present through disclosure of mothers at the time of delivery and the noting thereof in the newborn's folder at the New Somerset Hospital. Unfortunately, to date, no official database exists in South Africa of methamphetamine-exposed children to ease identification of these children for a study such as this.

Children will be excluded from the study if there is 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 or another syndrome with known developmental delay; or if parental consent is denied. Infants of all gestations will be included, as premature delivery is a known complication of methamphetamine use in pregnancy. All folders will be reviewed carefully as part of the study, to add information and to carefully screen for other pathology. A detailed medical history will also be taken at commencement of the study - of the child, family and mother before and during pregnancy. We will also indicate in our findings whether any of our index cases have been or are currently in foster or other protected care.

A control group of children matched to the previous group for age, sex, and as far as possible, background, birth circumstance, gestation and schooling, will also be evaluated. These children will be identified from records of babies born at New Somerset Hospital, Groote Schuur Hospital and Mowbray Maternity Hospital within six months age of index cases with all attempts made to minimise vast differences in background, schooling and socioeconomic status, since the hospital has quite specific drainage areas. **Attempts will be made to match index cases to controls 1:2, to increase the power of any positive findings. Controls will be included pending parental consent and the same exclusion criteria as the first group.**

In an attempt to boost numbers and increase the power of any findings, data from control cases from another study (investigating the neurodevelopmental outcomes of children whose mothers were HIV positive) will also be added. These controls had been selected from exactly the same geographical area, had the same exclusion criteria, ages, socioeconomic background and educational possibilities as our control group. Ethics approval had been obtained for the other study and permission obtained from the study executive to use the data.

Inclusion of control cases are subject to parental consent and the same exclusion criteria.

Ethical considerations

Consent will be obtained from the parents of all test and control subjects before inclusion into the study. It will take the form of a verbal explanation by one of the investigators (with the help of an interpreter where necessary to make information accessible to the parent in their first language) as well as written material provided to both families of patients (Appendix A) and controls (Appendix B). The consent form to be signed by the parent will also be available in the family's first language (All current potential subjects have either Afrikaans or English as first language, but the consent form and all information will be translated into other languages such as Xhosa, should the need arise.)

Where possible and appropriate, verbal assent will be sought from children themselves.

Information will be treated as strictly confidential and family's privacy protected as far as possible.

This study protocol will also be submitted to the Red Cross Children's Hospital Research Committee and the University of Cape Town Research Ethics Committee for approval.

Funding

At present all expenses incurred in the completion of this study will be carried by the principal investigator. There are currently no outside sponsors and therefore no possible conflict of interests. An application will be submitted to the School of Child and Adolescent Health Research Fund for assistance in covering expenses incurred during the execution of the study.

Measures of testing

A battery of tests will be performed on both children known to have been exposed to methamphetamine in pregnancy, as well as the control group. Every attempt will be made to keep testing times as short as possible, especially for smaller children, and to provide resting time and snacks in between to prevent fatigue from influencing test results.

Full confidentiality will be observed with respect to results of testing as well as personal information received from families, especially considering the sensitive nature of the exposure. This will also be clearly indicated in the consent form.

Screens to be used:

1. Griffiths Mental Developmental Scales (appropriate for ages 3-7 years) (57, 58, 59, 60, 61)
2. The Achenbach Parent Questionnaire (67)

The Griffiths Mental Development Scales will be performed on all subjects. All parents and guardians will be asked to complete the Achenbach Parent Questionnaire.

Parents or legal guardians will also be requested to complete a short questionnaire regarding amongst other factors income, housing, marital status, highest level of education of the mother (or main caregiver in the event of an absent mother) to assist in comparing background and socio-economic factors that may affect development.

Testing will be performed at the Red Cross Children's Hospital's Developmental Service at times when the consulting rooms are not in use for established clinics.

Testing will where possible be performed only by Dr Jessie van Dyk, under supervision and with assistance by Dr Kirsten Donald. Families will be provided with monetary remuneration for transport costs, meals and snacks for the day of testing.

Note: study protocol amended to remove neurodevelopmental assessments previously planned (Test of Reception of Grammar, Beery Buktenika Test of Visual Motor Integration and Goodenough Draw-A-Man Test had previously been included in study protocol but made the assessment too long for children of 2-4 years to complete successfully)

Predicted project duration

Commencement of testing (pending ethical and research committee approval):

February 2009

Completion: April 2010

Data analysis

Initial patient data and testing results will be written onto case report forms, where after it will be entered into a computer database and analysed with the help of standard statistical methods. The process of final analysis will be done under the supervision of a qualified medical statistician, to ensure that all conclusions drawn from this study is scientifically justifiable.

Follow-up

Upon completion of testing the parent or primary caregiver will receive a copy of the report of neurodevelopmental and neurocognitive testing. Direct feedback to the child's school or pre-school will also be done in cases where problems are identified (with parental consent). Every effort will also be made to assist the child and family

as far as possible in finding assistance with other medical, behavioural, as well as social problems identified during this study.

This applies to the control group as well as the groups of known exposed children.

OUTCOMES

Identifying possible specific developmental and neurobehavioural problem areas in children exposed to methamphetamine during pregnancy will 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.

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LITERATURE REVIEW

Methamphetamine use in pregnancy and subsequent neurodevelopmental sequelae in the child: a review of the literature

The objective of this structured review of the available literature was to identify potential neurodevelopmental and psychological effects in children exposed to methamphetamine during pregnancy.

Literature search strategy

The following four databases were searched **up to June 21, 2011**: OVID MEDLINE from 1948, EMBASE from 1980, PsycINFO from 1967 and Cochrane Central Register of Controlled Trials from second quarter 2011. The strategy used terms customized for the database derivations of the terms methamphetamine AND pregnancy AND neurocognitive or developmental outcomes. Reference lists of all retrieved manuscripts were searched for all articles not previously identified. A total of **617** references were retrieved from all 4 databases. All references were then saved in an EndNote library used to identify the **116** duplicates. The remaining **501** unique references were then reviewed against my inclusion criteria. See **Appendix J** for exact search strategy outlines.

Methods of the review

Published literature identified by the above search as potentially relevant to the topic being investigated, were then retrieved and individually scrutinized. Due to the relative paucity of material on the topic under review, different types of publications had to be included. Other literature reviews, original research including retrospective cohort studies and even case studies were assessed in an attempt to identify the type and presentation of potential neurodevelopmental, behavioural and psychological effects that could be expected in children exposed to methamphetamine in pregnancy. In a further attempt to identify potential effects, literature on structural defects and defects identified on neuroimaging of children

exposed to antenatal methamphetamine use, as well as animal studies identifying potential structural and developmental effects of antenatal methamphetamine exposure were also included.

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DISCUSSION

Background

Methamphetamine belongs to the amphetamine family of drugs, and was first synthesized in 1893, 6 years after the first member of this group of compounds, amphetamine, in 1887 (1). Clandestinely manufactured in the United States since the 1960s, it is still legally produced there to treat Attention Deficit Disorder and as short-term treatment of exogenous obesity, as a nasal inhalant, and as off-label treatment for narcolepsy (2). It is classified by the Drug Enforcement Agency (DEA) as Schedule II (having acceptable medical uses but requiring tight control due to their potential abuse leading to significant psychological and physiological dependence). Amphetamines cause their psychostimulant effects and characteristic 'rush' by increasing synaptic biogenic amine levels, including dopamine, norepinephrine and serotonin (1). This feeling of increased confidence, power and libido has made it especially popular among teenagers and young adults (3). When compared to cocaine, both drugs reverse monoamine transporter action and increase the release of dopamine, norepinephrine and serotonin in the synaptic cleft, as well as blocking the reuptake and breakdown of these neurotransmitters, further increasing their availability in the synaptic cleft. Methamphetamine, though, has an added methyl group, which makes it more readily absorbable through lipid-permeable membranes.

Besides the initial euphoria brought on by the drug's stimulant effects, there are also a vast array of short and long term adverse effects due to the increase in neurotransmitter release. These include insomnia, restlessness, irritability and tremors. Other systems outside the central nervous system are also frequently affected leading to respiratory effects (tachypnoea, pulmonary hypertension and pulmonary oedema as well as decreased lung capacity), cardiovascular effects (tachycardia, hypertension and/or arrhythmias), long-term complications such as severe weight loss due to decreased appetite, severe dermatological problems, increased seizure risk, as well as behavioural changes such as uncontrollable rage, violent and aggressive behaviour and personality changes. Both hemorrhagic strokes (including intracerebral and subarachnoid haemorrhages) and ischemic strokes have been linked to the use of amphetamine derivatives (4). Chronic drug

users also often suffer from nutritional deficiencies, are prone to serious traumatic injuries (5) and are more likely to be affected by infectious diseases such as sexually transmitted diseases and HIV (6).

Signs of methamphetamine overdose include hyperthermia (historically referred to as 'Saturday Night Fever'), rhabdomyolysis, cardiomyopathy, dehydration, renal failure, disseminated intravascular coagulation, seizures, stroke, psychosis and myocardial infarction (7).

Methamphetamine (known locally in South Africa as, amongst others, 'speed', 'ice', 'crystal', 'chalk', 'glass', 'crank', and especially 'tik'), is cheap, easily obtainable, odourless and can be taken in by various methods (smoking, snorting, oral ingestion, intravenous injection and by placing the powder in a light bulb and inhaling the fumes while it is heated from below) (8).

Methamphetamine use has been increasing steadily over the last decade, the last estimate being 26 million people worldwide (more than the estimates for heroin and cocaine use combined) according to the United Nations Office on Drugs and Crime.

In South Africa methamphetamine use has seen a steady marked increase over the last ten years. Pluddeman *et al* investigated the trends of treatment demands for substance abuse, with methamphetamine as primary or secondary drug of abuse, at treatment centres in the Western Cape province of South Africa, and found that the numbers had risen from less than 1% in 2002 to 51% by 2006 (9). A fact sheet published by the Medical Research Council of South Africa demonstrated the same trends with a steady rise still observed by 2008 (7).

When analysing referrals to the Alcohol Drug and Pregnancy Team (ADAPT) at National Women's Hospital in New Zealand, female clients showed high rates of psychological, social and health problems related to their drug use. (9) See Table 1 for a summary of these problems.

Table 1: ADAPT referral trends for female clients at National Women’s Hospital, New Zealand

1.0 Psychosocial and Health factors	2.0 N= 34
Multiple drug use, incl cigarettes (33), marijuana (14), alcohol (10), opiates (6)	33
History of not keeping appointments for antenatal check-ups	14
Mental health problems, incl psychotic behaviour and attempted suicide	10
Referrals to Child, Young Persons and Family Service	10
Custody issues due to unstable home environment	7
Legal proceedings pending for mother or imprisonment	5
Medical complications prenatally	4
Known history of overdose	2

Current knowledge of the effects of antenatal methamphetamine exposure

Thus far, much of what is known about methamphetamine use in pregnancy and how it affects the fetus, newborn and child has come from animal studies, a few human studies (with varying methodologies) and literature on cocaine use in pregnancy. All illicit drugs are known to cross the placenta and therefore reach the developing fetus (11, 12), affecting it either directly or secondary to changes in the fetal environment. Methamphetamine has been associated with placental abruption (8), and has also been shown to have vasoconstrictive effects leading to decreased uteroplacental perfusion, with subsequent restriction of nutrition and oxygen supply to the fetus and fetal hypoxia. Maternal effects such as hypertension and anorexia may potentially lead to miscarriage, premature delivery and intrauterine growth retardation. The drug can also permeate the placenta itself, leading to other complications such as prenatal stroke and other organ damage secondary to hypoxia and hypoperfusion. One cohort study looking at factors significantly associated with methamphetamine identified, amongst others, low Apgar scores (6% compared with 1-2% in controls), need for caesarean section (29% compared with 23%), preterm delivery (52% compared with 17%) and neonatal mortality (4% compared with 1%) (13). Another study also showed that pregnant women who were

using methamphetamine during pregnancy were more likely to be younger, have poorer general health, living without a partner, have a lower income, be less educated and be less likely to receive good prenatal care. Add to this the unstable home circumstances, risky sexual behaviour and potential use of other substances and immediate complications and long-term developmental sequelae in the developing fetus become logical outcomes. Apart from the apparent prenatal effects of methamphetamine use, breast milk amphetamine levels have also been shown to be up to seven times higher than that of maternal plasma levels (14).

Findings from animal research

Animal studies have identified a number of effects after exposure to methamphetamine (15-20), including increased maternal and child mortality, retinal defects, cleft lip and palate, rib malformations, poor growth and delayed motor development. One review also suggested lower birth weights, deficits in visual system development, an increased incidence of microgyri, impaired spatial learning, sensory-motor coordination and postural motor movements, and increased startle reflexes. An interesting observation of the same study was that the impaired sensory-motor coordination appeared to be transmitted to the next generation of offspring as well, even without subsequent methamphetamine exposure (21).

Research done in monkeys found hyperaemia, hemorrhage and glial proliferation after exposure to high doses of amphetamines, while in cats the same exposure lead to enlarged chromatolytic medullary neurons (1). Rodents exposed to parenteral doses of amphetamines showed reduced dopaminergic terminals, decreased serotonin levels and swollen or reduced dopaminergic terminals. The mechanism behind amphetamine-induced neurotoxicity remains somewhat unclear, but the theory seems to be that the high levels of cytoplasmic dopamine produced by the disruption of vesicular storage eventually produces accumulation of reactive oxygen species and subsequent severe oxidative stress (22, 23).

Data from human research literature

The few available human studies have identified similar patterns, demonstrating an increased risk of premature delivery and placental abruption (24, 25), cleft lip and palate, cardiac anomalies and intrauterine growth restriction (26). The Infant Development, Environment and Lifestyle Study (IDEAL) showed that methamphetamine/ cocaine-exposed neonates consistently had lower birth weights and smaller head circumferences than non-exposed neonates and were more likely to be small for gestational age (SGA) as calculated by Alexander's algorithm (27). Actual immediate withdrawal symptoms due to exposure to these stimulants are usually less severe than that of opiate withdrawal in the neonatal period, but one study described that up to 49 percent of neonates exposed to methamphetamine antenatally exhibited signs such as abnormal sleep patterns, tremors, hypertonia and poor feeding, although only 4 percent of exposed neonates required medication for withdrawal (8). A review published by Thompson *et al* linked methamphetamine and amphetamine exposure during fetal development with low birth weight, decreased arousal during the neonatal period, increased stress responses, and later: movement disturbances and decreased scholastic achievement (21). These same children demonstrated poorer performance on sustained-attention, long-term spatial and verbal memory, and visual motor-integration tests, although the wide age range in this last study (3-16 years) make the findings harder to interpret.

Brain and central nervous system development and maturation requires a carefully patterned sequence of events and processes more complex than that of any other system or organ, making it particularly vulnerable to prenatal environmental influences (28, 29). The blood-brain barrier of the developing fetus is much more permeable than that of the older child and adult, and the fetus lacks efficient drug-metabolising detoxification capacities (30). Also, there should always be concern regarding any toxin associated with in utero growth retardation and delay of maturation causing functional developmental toxicity, and therefore these toxins should be considered potential neurobehavioural teratogens (31). Methamphetamine has consistently been shown to have negative effects on the growth and maturation

of the growing fetus and its milieu as evidenced above, and therefore merits closer evaluation.

Neurodevelopmental findings on assessment of methamphetamine-exposed children

Few studies have looked at long-term neurocognitive effects of antenatal methamphetamine exposure. Of the small number of publications available, even fewer have examined the pre-school population. Prospective studies following methamphetamine-exposed children up to 15 years of age had found an increase in aggressive behaviour (32) and delays in language, performance in physical fitness activities and mathematics (33). These studies had several limitations, especially the earlier study, including concomitant antenatal alcohol and cigarette exposure, as well as the absence of a control group. Socio-economic status and its effect on the findings in these studies were also never investigated.

Another group of researchers followed children exposed to amphetamine during pregnancy and reported the following: by age 1 these children were exhibiting emotional characteristics of autism, speech difficulties and stranger wariness (34); by age 4, when compared with the norm for Swedish children, their IQ's were lower (32); by age 8 they exhibited more aggressive behaviour and problems with peers (35) and by age 14 they showed significant problems with school advancement (especially due to delays in mathematics and language) and physical fitness activities (33).

Abnormal neuro-imaging findings thought to be associated with antenatal methamphetamine exposure

Older studies looking at cranial ultrasound in children with prenatal methamphetamine and cocaine exposure showed an increased incidence of intraventricular hemorrhage and white matter densities (36). Neuroimaging studies have demonstrated abnormalities in brain structure and chemistry (37). In children with prenatal methamphetamine exposure Magnetic Resonance Imaging (MRI)

showed smaller striatal structures, while Magnetic Resonance Spectroscopy (MRS) demonstrated elevated total creatine levels, possibly a reflection of mitochondrial or glial cell dysfunction. Positron Emission Tomography (PET) in adult methamphetamine users have also shown reduced dopamine transporter (DAT) density and decreased dopamine D2 receptors in the striatum. Similar studies investigating the effect of repeated exposure to methamphetamine in rodents proved toxic effects on dopaminergic and serotonergic neurons (38, 39). Since chronic dopamine D2 receptor blockade could potentially lead to increased striatal trophic activity during fetal development, a decreased basal ganglia volume found in children with antenatal methamphetamine-exposure suggests deficient dopamine function (40).

One study compared global brain volumes and regional brain structures on MRI, as well as performance in neurocognitive assessment of children exposed to methamphetamine antenatally with unexposed controls (41). MRI showed comparable whole brain volumes in both groups, but smaller putamen bilaterally (-17.7%), smaller globus pallidus (left -27%, right -30%), smaller hippocampus volumes (left -19%, right -20%) and a trend towards smaller caudate bilaterally (-13%) in children with antenatal methamphetamine exposure. No difference was seen in volumes for the thalamus, midbrain or cerebellum. The changes seen on MRI correlated with lower scores on measure of visual motor integration, attention, verbal memory and long-term spatial memory in the methamphetamine-exposed group. Another study found evidence that damage to the fronto-striatal circuit in children exposed antenatally to methamphetamine, was associated with suppression of activation in those brain regions involved in performing working memory tasks (42).

One study examining children aged 7-15years by functional MRI while performing a verbal paired associate learning task showed that methamphetamine-exposed children activated more diffuse brain regions, including regions in the medial temporal area bilaterally, known to be essential to memory, when compared to children exposed to only alcohol prenatally and children with no known drug exposure in pregnancy (43). These findings suggest an attempt to recruit compensatory systems to support a weaker verbal memory network. Other possible extrapolations are that children with antenatal methamphetamine exposure activate different networks or pathways for processing cognitive tasks.

Chang et al compared MRS and neurocognitive testing in methamphetamine-exposed children matched with non-exposed children (44). The methamphetamine-exposed group were found to have higher total creatine, N-acetyl compounds, total creatine and glutamate+glutamine concentrations in the frontal white matter (suggesting higher neuronal density or cellular compactness in the white matter), but lower myoinositol and myoinositol/total creatine concentrations in the thalamus (suggesting a lower glial content and corresponding with poorer performance on a visual motor integration task), even when matched for head circumference, parental education, intelligence, global cognitive function and socio-economic status.

Alterations in white matter maturation have also been suggested in children exposed to methamphetamine during fetal life, as demonstrated by lower diffusion on diffusion tensor imaging (DTI) (45). This finding was thought to reflect more compact axon density or higher dendritic or spine density.

Expansion of studies such as these to exactly delineate the full spectrum of neurocognitive effects and how they manifest in the learning environment would be valuable in providing educational and social support to this growing population.

The effects of methamphetamine exposure on adult users are well documented and overwhelming evidence shows that methamphetamine exposure during pregnancy has significant effects on the pregnant mother and subsequently on the growing fetus' developmental milieu antenatally, as well as it's environment and therefore development post-natally. Although not fully characterised, particular structural defects of the brain and central nervous system, amongst others, have been shown in animal literature and suggested in human subjects (15-21, 24-27). By reviewing the available literature specific areas of developmental and behavioural concern have been identified, including aggressive behaviour (29), delays in language, performance in physical fitness activities and mathematics, emotional characteristics of autism, speech difficulties and stranger wariness (34); and significant problems with school advancement (again especially due to delays in mathematics and language) (33). Exposed children demonstrated lower scores on measures of visual motor integration, attention, verbal memory and long-term spatial memory.

Increased complication rates, number of admissions to neonatal intensive care units and nurseries, as well as demands on social and legal services mean increased

costs to all government support systems. In the era of preventative health care knowing which problems to anticipate would benefit society as well as the child and its family. Identifying specific neurodevelopmental and neurobehavioural deficits in children exposed to methamphetamine prenatally would enable the child's primary health care provider as well as the interprofessional team at all levels to be vigilant of potential problems and provide early, directed care to the exposed child, thereby limiting long-term developmental and cognitive sequelae.

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Maternal methamphetamine use in pregnancy and subsequent long-term neurodevelopmental and behavioural sequelae in a cohort of children in Cape Town

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Abstract

Aim: To identify neurodevelopmental or behavioural deficits among children exposed to maternal methamphetamine (MA) use during pregnancy.

Methods: Griffiths Mental Developmental Scales assessments were completed on 15 toddlers aged 2-4 years with a known history of maternal methamphetamine use during pregnancy. These were compared to 21 controls without a history of maternal methamphetamine use. Each child also had a hearing test, vision screen and Child Behaviour Checklist completed by a parent or caregiver. Cases and controls were matched for age, gestational age at birth, socio-economic status and geographic distribution.

Results: Fifteen toddlers were assessed and compared to twenty-one controls. Baseline comparison revealed no significant difference between age at testing, gestational age, socio-economic status or geographic distribution. Methamphetamine-exposed children obtained lower scores on General Quotients ($p=0.0220$), but significantly poorer performance was noted specifically on the Personal-Social Ability Subscale ($p<0.0001$) and on the Hand and Eye Co-ordination Subscale ($p=0.0002$). There were also concerns regarding aggressive behaviour and attention deficit/hyperactivity on the CBCL for the exposed group, although this did not reach statistical significance.

Conclusion: Among children exposed to maternal methamphetamine use during pregnancy, specific developmental and behavioural deficits were increased when compared to controls.

INTRODUCTION

Methamphetamine (MA) use has risen sharply in South Africa over the last decade (1), with increasing numbers of newborns delivered daily with known maternal methamphetamine use during pregnancy. In Cape Town and surrounds, admission trends to substance abuse treatment centres, with methamphetamine as primary or secondary drug of abuse, had risen from less than 1% in 2002 to 51% by 2006 (1) and continues to rise. The effects of prenatal methamphetamine use on maternal and fetal well-being have been well documented, including maternal anorexia and hypertension, placental abruption and poor function and intra-uterine growth retardation. Preterm delivery and neonatal mortality rates are increased and Apgar scores frequently lower (2, 3, 4). Its effects on the developing brain, however, are less well defined. Animal literature has raised concerns of certain structural defects such as retinal defects, cleft lip and palate, rib malformations, poor growth and delayed motor development. 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 (5-10). Human studies, with varying methodologies, have begun to postulate certain neuroradiological and neurodevelopmental sequelae that could be expected with prenatal maternal methamphetamine exposure (11-19). 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 methamphetamine-exposed and non-exposed children (19). Language delays (20), a delay in mathematics skills (21), autistic characteristics and other speech difficulties (22), as well as increased aggressive behaviour (23) have been among the specific developmental and behavioural difficulties identified in methamphetamine-exposed children.

METHODS

STUDY DESIGN

This is a descriptive case control pilot study

SUBJECTS

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 methamphetamine use during pregnancy. This information was found either in neonatal intensive care unit (NICU) admission logs or by records of referrals to a social worker. History of other drug use or cigarette smoking during pregnancy was obtained through reviewing NICU charts as well as parental interview at the time of testing. Parental consent was taken before inclusion into the study.

Of the 52 eligible children only 15 could be found and recruited into the study. Reasons for exclusion included:

- 1) Refusal (2 children)
- 2) Untraceable families (34 children)
- 3) History of other pathology that might impact on their neurocognitive functioning (serious head injury, bacterial meningitis, or pre- or postnatal insults such as hypoxic ischaemic encephalopathy or severe neonatal hypoglycaemia or another syndrome with known developmental delay) (1 child with head injury).

Infants born at all gestational ages were included, as premature delivery is a known complication of methamphetamine use in pregnancy. Available hospital charts were reviewed carefully by the principal investigator, to add information and screen for other pathology. A detailed medical history was also taken at the first interview - of the child, family and mother before and during pregnancy. We also indicated whether children were in foster or other protected care at the time of the interview.

A control group of children, matched for age, sex, background, socioeconomic background, birth circumstance and gestation to the MA group were also evaluated. These children were identified from records of babies born at the same institutions and of within six months of the age of index cases in an attempt to minimise differences. Data from control cases from another study were also added to increase the power of any findings. These controls were drawn from the same geographical area, had the same exclusion criteria, ages and socioeconomic background. Ethics approval was obtained to incorporate data from these controls into our own study.

Inclusion of control cases were subject to parental consent and the same exclusion criteria.

Maternal alcohol use during pregnancy amongst the mothers was also documented. Alcohol use during pregnancy as reported by mothers in the exposed and control groups was present in approximately equal numbers (see Table 1).

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 study protocol was approved by the University of Cape Town Human Research Ethics Committee. (REC REF: 235/2009. Updated 18/04/2011).

MEASURES

Demographic data

This included a questionnaire completed by parents or primary caregivers on social circumstances (family income), medical history, educational history (highest level of schooling obtained by parents of caregivers), current occupation, marital status. A detailed birth and perinatal history was also obtained. It was 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 methamphetamine-exposed as well as the control group. The *Griffiths Mental Developmental Scales (GMDS)* was administered by the principal investigator or co-supervisor, Dr Kirsten Donald.

The GMDS assesses comprehensively the different aspects of normal infant and child development. It has been validated (but not yet standardised) for use in children of different language groups (English, Afrikaans and Xhosa) in South Africa (24). The GMDS measures areas, or 'sub-scales' of development under the categories Locomotor Subscale, Personal-Social Subscale, Hearing and Speech, Eye and Hand Co-ordination Subscale, Performance Subscale 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 intellectual ability), or percentile equivalents. (25, 26, 27, 28, 29).

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

The *Child Behaviour Checklist (CBCL)* (30, 31) is completed by parents or guardians and is designed to assess behavioural problems and social competencies in children. It has been extensively validated across widely differing socioeconomic and cultural spectrums (32).

In addition to arranging the results of scores in 7 syndrome categories (eg Emotionally Reactive, Anxious/ Depressed), it provides 3 more general scores: a total score, a score on internalising behaviours (anxious and inhibited) and externalising behaviours (aggressive and under-controlled). The questionnaire also classifies behavioural scores according to more familiar Diagnostic Statistical Manual-IV (DSM-IV) related categories (Affective Problems, Anxiety Problems, Attention Deficit/ Hyperactivity Problems). The recommended t-score transformation of the raw behaviour scores was used. A t-score of >63 in the general scores or t-score of >69 on the individual syndrome subscales represents clinically meaningful symptoms (32). In this study we used the 18 month to 5 year age version.

Testing occurred in the Developmental Paediatrics Outpatient Clinic consulting rooms at the Red Cross Children's Hospital. Families received transport money for each visit.

STATISTICAL ANALYSIS

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 Griffiths Mental Developmental Scales and t-scores and percentiles in the case of the Child Behaviour Checklist. 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.)

No adjustments were done for multiple tests. 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. Figure 1 and 2 describe some of the differences between groups on these measures.

RESULTS

DEMOGRAPHIC DETAILS

Table 1: Background characteristics of cases and controls

	Meth n=15	Controls n=21
Child age at testing (mean) (range)	33.8months (25-46.5 mo)	35.6months (27-50 mo)
Ethnic Background		
African	n=0	n=0
Mixed	n=15	n=21
European	n=0	n=0
Parental education		
Mother		
<Gr 7	n=2	n=0
Gr 8-11	n=10	n=1
Gr 12	n=2	n=2
>Gr 12	n=0	n=0
Unknown	n=1	n=18
Father		
<Gr 7	n=3	n=0
Gr 8-11	n=1	n=1
Gr 12	n=1	n=1
>Gr 12	n=0	n=0
Unknown	n=10	n=19
Guardian		
<Gr 7	n=6	n=0
Gr 8-10	n=4	n=0
Gr 12	n=0	n=0
>Gr 12	n=0	n=0
Unknown	n=1	n=0
Parent/foster care		
Parent(s)	n=4	n=21
Foster (all grandmother)	n=11	n=0
Alcohol use in pregnancy		
	n=3	n=2
Gender		
Male	n=9	n=14
Female	n=6	n=7
Gestational age		
Term	n=11	n=18
Preterm	n=4	n=3

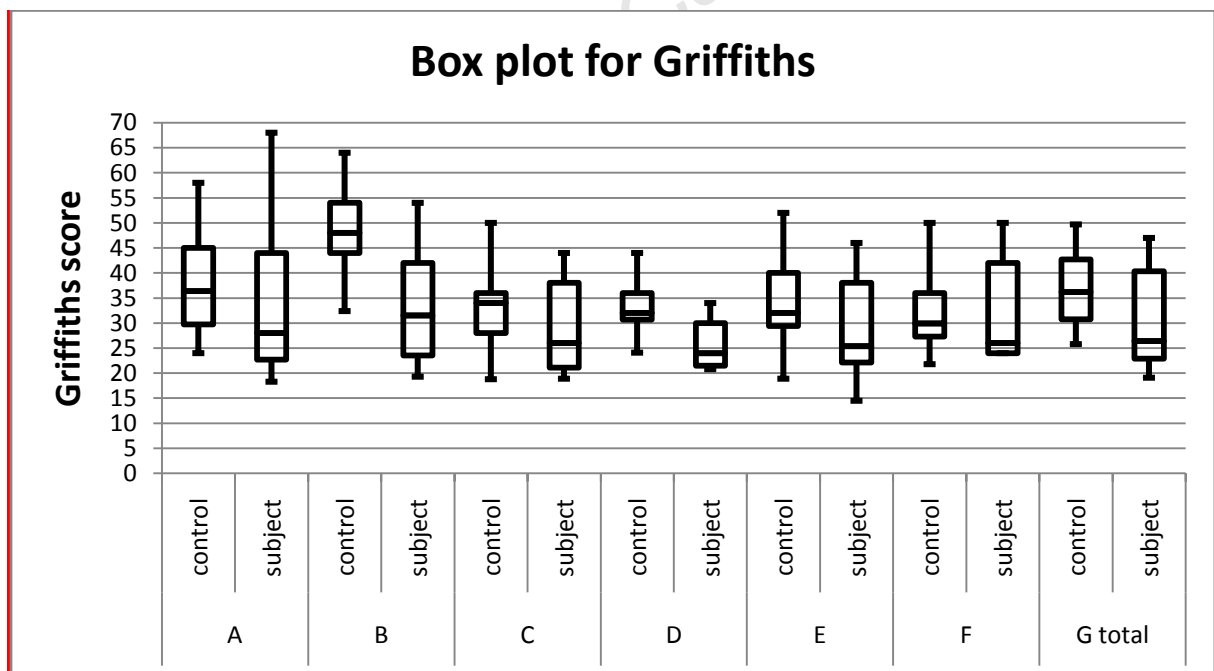
	(28, 30, 35, 36 wks)	(34, 34, 35 wks)
Mode of delivery		
NVD	n=8	n=15
C/section	n=4	n=2
Unknown	n=3	n=4
Home language		
Afrikaans	n=10	n=21
English	n=1	n=0
Afrikaans/English	n=4	n=0

There was no known intra- or extra-uterine growth retardation in either group.

All 15 methamphetamine-exposed children and 21 non-exposed controls had a completed GMDS and CBCL.

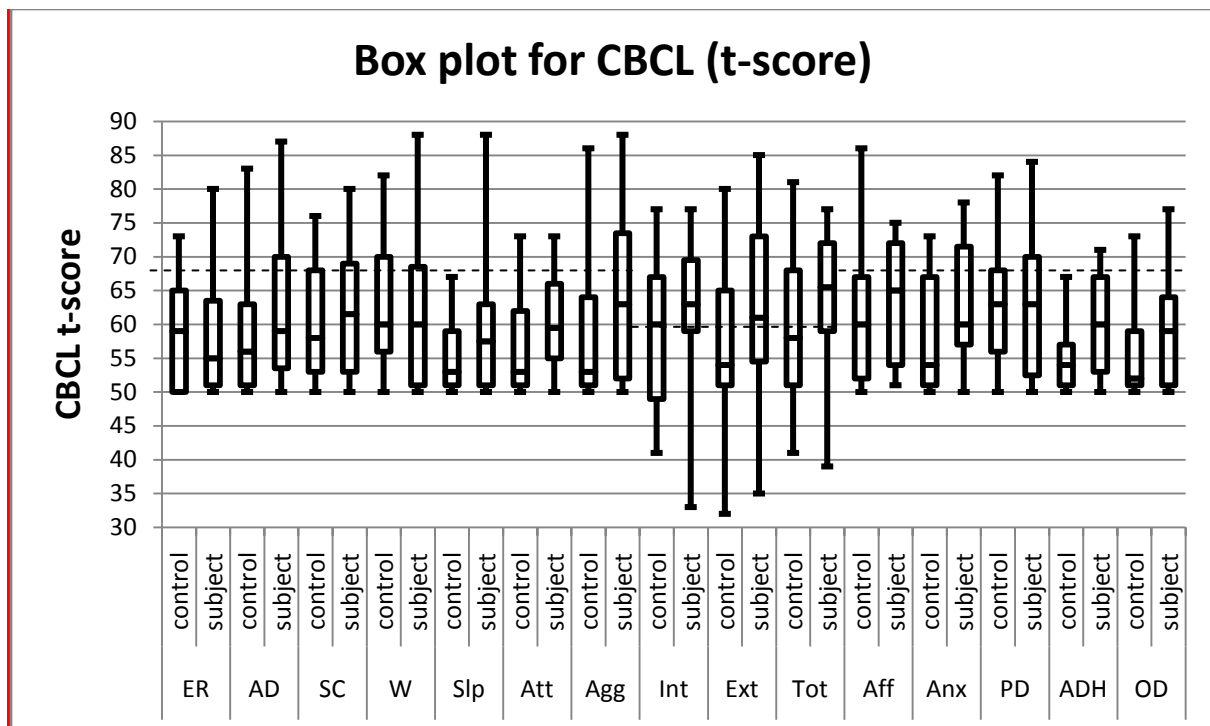
NEURODEVELOPMENTAL ASSESSMENT

Figure 1: Box plot characterising results for GMDS assessment in methamphetamine-exposed children vs controls (using raw scores)



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

Figure 2: Box plot characterising results for CBCL assessment in methamphetamine-exposed children vs controls



Legend: ER – Emotionally Reactive, AD – Anxious / Depressed, SC – Somatic complaints, W – Withdrawn, Slp – Sleep problems, Att – Attention problems, Agg – Aggressive behaviour, Int – Internalising problems, Ext – Externalising problems, Tot – Total problems, Aff – Affective problems, Anx – Anxiety problems, PD – Pervasive Developmental problems, ADH – Attention Deficit/Hyperactivity problems, OD – Oppositional Defiant problems

Differences between the groups on general performance was statistically significant, where Mean age equivalent for methamphetamine-exposed children (M_{METH})= 30.3; Mean age equivalent for control group (M_{CONT})= 36.8; $p = 0.0220$.

There were also statistically significant differences between groups on some of the individual subscales, including performances in the Personal & Social subscale, where $M_{METH} = 33.4$; $M_{CONT} = 48.4$; $p < 0.0001$ and in the Eye and Hand Coordination subscale, where $M_{METH} = 26.5$; $M_{CONT} = 33.6$; $p = 0.0002$.

Differences between groups in the following subscales approached statistical significance: in the Hearing & Speech subscale where $M_{METH} = 28.4$; $M_{CONT} = 33.6$; $p = 0.0804$; in the Performance subscale where $M_{METH} = 28.5$; $M_{CONT} = 34.4$; $p = 0.0657$. See Table 2 for further clarification of these findings.

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

Group	Scales	N	Mean	Std Dev	Minimum	Lower Quartile	Median	Upper Quartile	Maximum																								
control (N=21)	A	20	37.4	9.8	24	29.7	36.4	45	58																								
	B	21	48.4	8.9	32.4	44	48	54	64																								
	C	21	33.5	8.2	18.8	28	34	36	50																								
	D	21	33.6	5.1	24.1	30.7	32	36	44																								
	E	21	34.4	8.3	18.9	29.4	32	40	52																								
	F	21	32.9	8.0	21.8	27.3	29.9	36	50																								
	G_tot	21	36.8	7.1	25.8	30.75	36.2	42.7	49.7																								
Subject (N=15)	A	15	34.0	14.9	18.3	22.7	28	44	68																								
	B	15	33.4	10.7	19.3	23.5	31.5	42	54																								
	C	15	28.4	8.5	18.9	21.1	26	38	44																								
	D	15	26.5	5.2	20.8	21.5	24	30	34																								
	E	15	28.5	10.2	14.5	22.1	25.4	38	46																								
	F	15	31.1	8.9	24	24	26	42	50																								
	G_tot	15	30.3	9.2	19.1	22.9	26.4	40.3	47																								
<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th>Score</th> <th>A</th> <th>B</th> <th>C</th> <th>D</th> <th>E</th> <th>F</th> <th>G_total</th> </tr> </thead> <tbody> <tr> <td>p-value</td> <td>0.4290</td> <td>< 0.0001</td> <td>0.0804</td> <td>0.0002</td> <td>0.0657</td> <td>0.5274</td> <td>0.0220</td> </tr> <tr> <td>p-value (without preterm infants)</td> <td>0.5973</td> <td>0.0002</td> <td>0.1503</td> <td>0.0005</td> <td>0.0691</td> <td>0.7331</td> <td>0.0421</td> </tr> </tbody> </table>										Score	A	B	C	D	E	F	G_total	p-value	0.4290	< 0.0001	0.0804	0.0002	0.0657	0.5274	0.0220	p-value (without preterm infants)	0.5973	0.0002	0.1503	0.0005	0.0691	0.7331	0.0421
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 G = General performance

Even when correcting for the two preterm infants in the methamphetamine-exposed group, the resulting p-values remain statistically significant in the same subscales (see table 2)

BEHAVIOUR

The cut-off for clinical relevance when categorising the behavioural scores for the different categories, is a t-score of ≥ 70 . A t-score of between 65 and 69 is borderline.

Methamphetamine-exposed children scored much higher in the Sleep Problems category, but this did not reach statistical significance ($p=0.124$). Again, while methamphetamine-exposed children averaged higher scores in most of the other categories (except Attention Problems, Internalising Problems and Affective Problems), this was not statistically significant.

The cut-off for categorising clinical relevance for the categories of *internalising*-type behaviour, *externalising*-type behaviour and *total* behaviour problems is a t-score of ≥ 63 . A t-score of 60- 63 is borderline.

The mean score for *Internalising Behaviours* in the children with methamphetamine 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 which is not clinically relevant. The mean t-score for *Externalising Behaviours* 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) which again is not clinically relevant. The differences between scores on *Internalising vs. Externalising Behaviours* were not shown to be statistically significant, $p = 0.5917$ and $p=0.1187$ respectively.

DISCUSSION

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

There are many factors besides methamphetamine exposure during pregnancy which may influence performance of children in these areas.

NEURODEVELOPMENT AND COGNITION

Reviews have suggested certain developmental problems. Among those identified have been defects in visual system development, impaired spatial learning, sensory-motor coordination and postural motor movements (36).

A review published by Thompson *et al* linked methamphetamine and amphetamine exposure during fetal development with decreased arousal during the neonatal period and increased stress responses. Later in life these children exhibited movement disturbances and decreased scholastic achievement (36), 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 longterm follow-up of older children and adolescents exposed to MA antenatally. They identified an increase in language delays (20), and poorer performance in physical fitness activities and mathematics (21). 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 age 1(22); lower IQ's vs norms by age 4(37); more aggressive behaviour and problems with peers by age 8 (23) and significant problems with school advancement (again

especially due to delays in mathematics and language) and physical fitness activities by age 14 (38).

Very limited data is available on the neurodevelopmental profile of preschool children with antenatal methamphetamine exposure. The majority of literature published on methamphetamine-exposed children was based on neuroradiological findings in children over wide age ranges, with findings that included smaller striatal structures on Magnetic Resonance Imaging (MRI) and elevated total creatine levels on Magnetic Resonance Spectroscopy (MRS), possibly a reflection of mitochondrial or glial cell dysfunction (19). Few studies have focused on intellectual functioning (32-20, 21, 22, 23, 37, 38)

Prior to enrolment, none of the children in our study group had ever been referred to Developmental Paediatrics services, despite parental or caregiver's concerns in most of the methamphetamine-exposed cases. Our test results clearly showed that all the methamphetamine-exposed children met criteria for further developmental follow-up. Although specific problem areas were identified in all of the exposed children, for which they could receive remedial support, none of them at the time of testing were receiving any such assistance and would likely have entered the mainstream schooling environment with significant academic challenges. The above are clear indications of the inadequacy of systems in place to identify and support high risk children such as these in a resource limited environment.

In general, methamphetamine-exposed children obtained lower scores on final 'General Quotients' and performed at an age-equivalent lower than that of controls.

Our findings on neurocognitive testing show that 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 (20), our research also showed diminished performance on language ability. Although this did not reach statistical significance, qualitative comments from individual assessments frequently mentioned poor speech quality and paucity of vocabulary in general. Methamphetamine-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 neuro-cognitive 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.

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 level 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 (33, 34). Poverty, gang and other violence also affect the psychological and cognitive development of young children (35). Learning difficulties, developmental delays and behavioural problems are less likely to be picked up and/or acted upon in these communities. Add recurrent illness, poor nutrition and limited access to preventative primary care and these children face the cumulative burden of particular social stress and greater biological vulnerability.

BEHAVIOUR

Previous literature highlights certain behavioural profiles of concern in children exposed to methamphetamine in utero. These included especially emotional characteristics of autism and stranger wariness (22) and an increase in aggressive behaviour and problems associating with peers (20, 23).

Although our findings did not reach statistical significance, we feel it is clinically relevant that the scores on the Aggressive Behaviour subscale approached significance ($p=0.0972$). This correlates well with available literature.

A trend toward significance was also found between groups on the Attention Deficit/Hyperactivity Problems subscale ($p=0.0775$). Attention deficit/ hyperactivity has not previously been identified as significantly increased in methamphetamine-exposed children. These two areas of behavioural problems would again impact significantly on a child's ability to interact appropriately and meaningfully in the classroom setting.

University of Cape Town

STUDY LIMITATIONS

Methamphetamine 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 more or less equally reported between the two groups, the impact therefore on the developmental profile of each group may be considered similar. There was only one other mother in the subject group with additional use of marijuana during pregnancy.

The nature of drug abuse and the accompanying lifestyle of participants made this a very difficult population to study. In most cases the child's father was not involved, and often the mother was incarcerated or her whereabouts unknown. Addresses were mostly transient and telephone numbers disconnected or incorrect. When the child was eventually found, he or she was likely to be in protected care or fostered by a family member (in all our cases children were placed with a grandmother soon after birth, with variable visitation by parents). Appointments were frequently not kept due to a lack of transport or money, scheduled court appearances or the fact that the parent was still actively using recreational drugs.

Due to the small sample sizes in both the methamphetamine-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.

CBL questionnaires were completed by (mostly) foster parents for the subjects and biological parents (mostly mothers) for the controls. This discrepancy may have lead to some variation in reporting due to different expectations in regards to acceptable or problem behaviours.

Despite these limitations, it remains important to document and further investigate our findings. Little is known about the neurodevelopmental and behavioral effects of methamphetamine 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 methamphetamine is associated with significant neurodevelopmental and behavioural 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 methamphetamine 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.

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APPENDIX A

INFORMATION LEAFLET AND CONSENT FORM FOR ANTENATAL METHAMPHETAMINE EXPOSURE STUDY (English)

(to be completed by parents or legal guardians of minors under 18 years)

Trial title: Maternal Methamphetamine use during pregnancy and subsequent longterm neurodevelopmental and psychological sequelae in the child: a Cape Town experience

Principal investigator: Dr Jessie van Dyk
Paediatrician
School of Child and Adolescent Health
Red Cross Children's Hospital
Contact number: 0823329586
Email: jessie.vandyk@doctors.org.uk

Dear Parent

Your child has been invited to take part in a research project. We have compiled some information on exactly why we are doing this study, why we have asked your child to take part, and what will happen during the course of this project. Please take some time to read through the brochure we are providing and then ask the study staff or doctor if you have any questions or concerns. We will need you to provide consent and sign the attached consent form before we can go any further, so it is very important that you fully understand exactly what our project entails and what will be expected of you and your child. Your child's participation is completely voluntary and you can withdraw at any stage even if you agree to take part today. We would ask that, if you are uncomfortable with any of the processes or have concerns at any stage during the study, that you contact myself (Dr van Dyk) or Dr Donald before simply withdrawing, as we do believe that participating could have advantages for your child and your family.

This study has been approved by the Committee for Human Research at the University of Cape Town will be conducted according to the ethical guidelines and principles of the International Declaration of Helsinki, South African Guidelines for Good Clinical Practice and Medical Research Council (MRC) Ethical Guidelines for Research.

Why are we doing this study?

It is well known that using any drug, and even some medicines, in pregnancy can potentially harm the growing fetus (developing baby). In the case of methamphetamine, known as 'tik' locally, there is not much research done on children yet, only some on animals and adults who are using the drugs themselves. We know that it is harmful to animals and adult users,

and because we have some evidence of what it can do to the pregnant mother, the placenta and the growing fetus, we are concerned that there could be development and learning problems in children whose mothers have used 'tik' in their pregnancies. These problems may not be as obvious when the baby is very small, but could progress as he or she gets older, and especially once they are about to, or are already school-going.

We would like to evaluate children where the moms have obviously been concerned enough about the welfare of their babies by telling doctors about their drug use at the time of delivering their babies. If we were able to show that using 'tik' during pregnancy could cause learning, behaviour or developmental problems in the child later in life, then we could be more vigilant, know to do more regular developmental follow-up on these children and so provide early educational support to help ensure that they can lead as productive, full, happy lives as possible and achieve their full potential. . In order for us to make any assessments from such a study, we need to also test a group of non-exposed children and compare their test results with those of the children who are known to have been exposed.

What would taking part in our study involve?

With your permission we would like your child to take part in a few developmental, behaviour and psychometric tests and screens. These tests will help us identify any developmental problems (for instance if your child has not reached a specific milestone that is expected for his or her age), learning difficulties (for instance a problem with language or other areas that would affect his or her schooling) and behaviour problems (for instance Attention Deficit Hyperactivity Disorder). We will also do a full physical exam to make sure there are no other medical problems, and will test hearing and vision. We would also like you to complete questionnaires about aspects of your child's behaviour and development. These tests will take roughly a morning to complete, and will be done at the Red Cross Children's Hospital by Dr Jessie van Dyk, a general paediatrician, with the assistance of Dr Kirsty Donald of the Department of Neurology.

Your child's participation is completely voluntary and deciding not to take part will not have any detrimental effect on further treatment received at our hospital.

What will you benefit from taking part?

Parents or caregivers will have full access to the results of the tests, and should any problems be found, we will try to the best of our capabilities to provide the appropriate care and advice, as well as assist with further arrangements for special educational support and special multidisciplinary referral (such as occupational therapy, physiotherapy and other medical specialities).

Who will have access to the study information and your child's records?

All information obtained from you and collected through testing will be treated as extremely confidential. We understand the sensitive nature of the information disclosed to us and the amount of trust involved in sharing it with us. In the event that information is used for publication or the completion of a thesis, the identities of participants and their family members will remain anonymous. The only people who will have access to the full information collected will be Drs van Dyk and Donald. We will at all times endeavour to

ensure that no discrimination is experienced by participants or their families for any information disclosed.

As part of ensuring the scientific validity of our study, the research records may need to be reviewed by auditors or the Research Ethics Committee.

Will you be paid to take part and are there any costs involved?

You will not be paid to participate in the study, but transport costs will be paid for yourself and your child for visits required during the study. As the testing days can become quite long and tiring, we will also provide snacks for especially your child for that time.

Is there anything else you should know?

If you have any further questions, or concerns about the study at any stage during the period of the study, please don't hesitate to contact Dr Jessie van Dyk on 0823329586 or 0124607900.

You can contact the Committee for Human Research at 021-4066338 (Health Sciences Faculty, Research Ethics Committee, Room E52-24 Groote Schuur Hospital, Old Main Building, Observatory, 7925) if you have any concerns or complaints that have not been satisfactorily addressed by your study doctor.

University of Cape Town

CONSENT

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I declare that:

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3. I have been given a chance to ask questions and have received adequate answers to these questions
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5. I am aware that I may choose to leave the study at any time and will not be penalised or prejudiced in any way if I choose to do so
6. I will receive a copy of this signed document

Signed at (place)

On (date)

Signatures:

Patient:

Printed name

Signature (where child can write)

Date

Mother:

Printed name

Signature

Date

Father:

Printed name

Signature

Date

Legal guardian:

Printed name

Signature

Date

Relationship

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Date

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Signature

Date

Father:

Printed name

Signature

Date

Legal guardian:

Printed name

Signature

Date

Relationship

APPENDIX C

INLIGTINGSBROJSJURE EN TOESTEMMINGSVORM VIR VOORGEBOOR-TELIKE METAMFETAMIEN BLOOTSTELLING STUDIE (AFRIKAANS)

(vir voltooiing deur ouers of wettige voogde van minderjarige kinders onder 18 jaar)

Titel van studie: Moederlike Metamfetamien gebruik tydens swangerskap en daaropvolgende langtermyn neuro-ontwikkelings en sielkundige gevolge vir die kind: 'n Kaapstad ervaring

Hoof navorser: Dr Jessie van Dyk
Kinderarts
School of Child and Adolescent Health
Rooikruis Kinderhospitaal
Kontak telefoon nommer: 0823329586
E-pos: jessie.vandyk@doctors.org.uk

Beste Ouer of Voog

U kind word hiermee vriendelik uitgenooi om deel te neem aan 'n navorsings- projek. Ons het die volgende inligtings-brosjure saamgestel om aan u te verduidelik waarom ons hierdie studie aangepak het, hoekom ons u kind gevra het om daaraan deel te neem en wat presies tydens die verloop hiervan sal gebeur. Neem asseblief 'n oomblik om daardeur te lees en vra dan gerus vir die studie personeel of dokter indien u enige verdere vrae of bekommernisse het. Ons benodig dat u asseblief u toestemming gee en die aangehegte toestemmingsvorm teken voordat ons kan voortgaan met enige toetsing, en daarom is dit uiters belangrik dat u presies verstaan waaroor die studie gaan en wat van u en u kind verwag sal word. U kind se deelname is volkome vrywillig en u kan ten enige tyd u kind onttrek, selfs al stem u vandag in. Ons vra nietemin dat, indien u op enige stadium ongemaklik is met enige van die prosesse of enige kwelling het, dat u dit asseblief onder my aandag (Dr van Dyk), of die van Dr Donald bring voordat u summier onttrek, omdat ons tog glo dat deelname aan die studie sekere voordele vir u kind en familie kan inhou.

Hierdie studie is goedgekeur deur die Komitee vir Menslike Navorsing van die Universiteit van Kaapstad, en sal uitgevoer word volgens die etiese riglyne en beginsels van die Internasionale Helsinki Deklarasie, Suid-Afrikaanse Riglyne vir Goeie Kliniese Praktyke and Mediese Navorsingsraad Etiese Riglyne vir Navorsing.

Waarom doen ons hierdie studie?

Dit is welbekend dat die gebruik van enige middels, en selfs sommige medikasies, tydens swangerskap potensieel skadelik kan wees vir die groeiende fetus (ontwikkelende baba). In die geval van metamfetamien, hier by ons bekend as 'tik', is daar maar min navorsing tot

dusver op kinders, net 'n beperkte hoeveelheid op diere en volwassenes wat self die middel gebruik. Ons weet dat dit skadelike gevolge inhou vir volwasse gebruikers en diere daaraan blootgestel, en omdat ons bewyse het van die potensiele gevare vir die swanger ma, plasenta en die groeiende fetus, is dit ons kommer dat daar moontlik ontwikkelings en leerprobleme mag wees by kinders wie se ma's 'tik' gebruik het tydens hul swangerskappe. Hierdie probleme mag moontlik nie eers sigbaar wees wanneer die baba klein is nie, maar later soos hy of sy ontwikkel en gereed maak om skool toe te gaan na vore kom.

Ons wil daarom graag kinders evalueer waar die mammas ten tye van hul geboorte besorgd genoeg was oor die welvaart van hul baba's om aan die dokter te erken dat daar 'tik' gebruik tydens swangerskap was. Indien ons kan bewys dat daar wel sekere ontwikkelings, gedrag of leerprobleme teenwoordig is by kinders etlike jare na hul blootstelling aan 'tik' tydens swangerskap, kan dit dokters and gesondheidsorg personeel in staat stel om meer pro-aktief en oplettend te wees by sulke kinders, meer gereelde neuro-ontwikkelings opvolg te reël en so vroeë onderwys ondersteuning kan bied om te help verseker dat sulke kinders hul vol potensiaal bereik en aktiewe, gelukkige lewens kan lei. Om enige afleidings te kan maak van so 'n studie, moet ons egter ook 'n groep kinders toets wat definitief nie blootgestel is aan metamfetamien tydens swangerskap nie, en hulle toetsuitslae vergelyk met die groep waar daar blootstelling bekend is.

Wat sal deelname aan ons studie behels?

Met u toestemming sal ons u kind uitnoui om deel te neem aan 'n reeks ontwikkelings, gedrag en psigometriese toetse. Hierdie toetse sal ons in staat stel om te identifiseer indien enige ontwikkelingsprobleme teenwoordig is (indien u kind byvoorbeeld nie 'n bepaalde verwagte mylpaal behaal het nie), moontlike leerprobleme (byvoorbeeld 'n probleem met taal en kommunikasie, of ander areas wat toekomstige skoolvordering kan beïnvloed) of gedragsprobleme (byvoorbeeld Hiperaktiwiteit en Aandagafleibaarheid). Ons sal ook 'n volledige fisiese ondersoek uitvoer om seker te maak daar is geen ander mediese toestande teenwoordig nie, asook gehoor en visie toetse. Terwyl u kind saam met ons speel, sal ons u versoek om ook 'n vraelys te voltooi, wat ook sal handel oor aspekte van u kind se gedrag en ontwikkeling. Al hierdie toetse sal waarskynlik min of meer 'n oggend neem om te voltooi en sal uitgevoer word by die Rooikruis Kinderhospitaal deur Dr Jessie van Dyk, 'n algemene kinderarts, met die ondersteuning van Dr Kirsty Donald, van die Departement Neurologie.

U kind se deelname aan ons studie is ten volle vrywillig en indien u besluit om nie deel te neem nie, sal dit geen effek hê op toekomstige behandeling ontvang by ons hospitaal nie.

Watter voordele is daar aan deelname aan ons studie?

Ouers en voogde sal volle toegang hê tot die resultate van die toetse uitgevoer, en indien enige probleme geïdentifiseer word sal ons tot die beste van ons vermoë poog om

toepaslike ondersteuning en advies te bied, asook help met spesiale onderwys ondersteuning and verdere multidissiplinêre verwysing (byvoorbeeld na arbeidsterapie, fisioterapie en ander mediese spesialiste).

Wie sal toegang hê tot die studie inligting en u kind se rekords?

Alle inligting ingesamel tydens die verloop van die studie, hetsy deur toetse of van die vraelyste deur u voltooi, sal as uiters vertroulik beskou en hanteer word. Ons verstaan die sensitiewe aard van inligting aan ons verskaf en die hoeveelheid vertrouwe wat betrokke is tydens die deel van sulke inligting. Indien die resultate van ons studie vir publikasie doeleindes gebruik sou word of vir die voltooiing vir 'n tesis of dissertasie, sal alle deelnemers aan die studie se identiteite anoniem gehou word. Die enigste persone wat toegang sal hê tot all studie-inligting versamel, is Drs van Dyk en Donald. Ons sal ook ons beywer om te sorg dat geen diskriminasie deur u of u kind of familie ondervind word vir inligting aan ons oorgedra nie.

Om te verseker dat ons studie aan al die nodige vereistes voldoen, mag ons rekords moontlik deur ouditeure van die Navorsingsetiek Komitee nagegaan moet word.

Sal ek vergoed word of sal ek moet betaal om deel te neem?

U sal nie betaal word om deel te neem aan ons studie nie, maar ons sal u wel vergoed vir vervoerkostes vir uself en kind, vir besoeke gedurende die verloop van die studie. Omdat die toetsdae ook moontlik lank en uitputtend kan wees, sal ons ook 'n ligte maaltyd vir veral u kind verskaf.

Is daar enigiets meer wat ek behoort te weet?

Indien u enige verdere vrae het, of bekommernisse ten opsigte van die studie, op enige stadium tydens die verloop daarvan het, moet u asseblief nie huiwer om Dr Jessie van Dyk te kontak by 0823329586 of 0124607900.

U kan ook die Komitee vir Menslike Navorsing skakel by 021-4066338 (Fakulteit Gesondheidswetenskappe, Navorsingsetiek Komitee, Kamer E52-24 Groote Schuur Hospitaal, Old Main Building, Observatory, 7925) indien u enige bekommernisse of klagtes het wat nie bevredigend deur u dokter beantwoord is nie.

TOESTEMMING

Ek, gee hiermee
toestemming dat my kind, mag
deelneem aan die navorsingstudie getiteld : Moederlike metamfetamien
gebruik tydens swangerskap en die langtermyn neuro-ontwikkelings en
sielkundige nagevolge vir die kind: 'n Kaapstad ervaring

Ek verklaar dat:

1. ek die inligtingsbrosjyre en toestemmingsvorm gelees het, of dat dit aan my voorgelees is
2. albei geskryf is in 'n taal waarin ek vlot is en gemaklik kommunikeer
3. ek 'n kans gegun is om vrae te vra en voldoende antwoorde op hierdie vrae ontvang het
4. deelname aan hierdie studie ten volle vrywillig is en ek onder geen druk geplaas word om deel te neem nie
5. ek bewus is dat ek op enige stadium tydens die studie my kind en myself daarvan mag onttrek, sonder dat verdere behandeling van my kind by hierdie hospitaal daardeur beïnvloed sal word
6. ek 'n kopie van hierdie vorm sal ontvang vir my eie rekords

Geteken te (plek)

Op (datum)

Handtekeninge:

Pasiënt:

Naam in drukletters

Handtekening (waar oud genoeg)

Datum

Moeder:

Naam in drukletters

Handtekening

Datum

Vader:

Naam in drukletters

Handtekening

Datum

Wettige voog:

Naam in drukletters

Handtekening

Datum

Verwantskap aan pasiënt

APPENDIX D

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Waarom doen ons hierdie studie?

Dit is welbekend dat die gebruik van enige middels, en selfs sommige medikasies, tydens swangerskap potensieel skadelik kan wees vir die groeiende fetus (ontwikkelende baba). In die geval van metamfetamien, hier by ons bekend as 'tik', is daar maar min navorsing tot

dusver op kinders, net 'n beperkte hoeveelheid op diere en volwassenes wat self die middel gebruik. Ons weet dat dit skadelike gevolge inhou vir volwasse gebruikers en diere daaraan blootgestel, en omdat ons bewyse het van die potensiele gevare vir die swanger ma, plasenta en die groeiende fetus, is dit ons kommer dat daar moontlik ontwikkelings en leerprobleme mag wees by kinders wie se ma's 'tik' gebruik het tydens hul swangerskappe. Hierdie probleme mag moontlik nie eers sigbaar wees wanneer die baba klein is nie, maar later soos hy of sy ontwikkel en gereed maak om skool toe te gaan na vore kom.

Ons wil daarom graag kinders evalueer waar die mammas ten tye van hul geboorte besorgd genoeg was oor die welvaart van hul baba's om aan die dokter te erken dat daar 'tik' gebruik tydens swangerskap was. Indien ons kan bewys dat daar wel sekere ontwikkelings, gedrag of leerprobleme teenwoordig is by kinders etlike jare na hul blootstelling aan 'tik' tydens swangerskap, kan dit dokters and gesondheidsorg personeel in staat stel om meer pro-aktief en oplettend te wees by sulke kinders, meer gereelde neuro-ontwikkelings opvolg te reël en so vroeë onderwys ondersteuning kan bied om te help verseker dat sulke kinders hul vol potensiaal bereik en aktiewe, gelukkige lewens kan lei. Om enige afleidings te kan maak van so 'n studie, moet ons egter ook 'n groep kinders toets wat definitief nie blootgestel is aan metamfetamien tydens swangerskap nie, en hulle toetsuitslae vergelyk met die groep waar daar blootstelling bekend is.

Wat sal deelname aan ons studie behels?

Met u toestemming sal ons u kind uitnoui om deel te neem aan 'n reeks ontwikkelings, gedrag en psigometriese toetse. Hierdie toetse sal ons in staat stel om te identifiseer indien enige ontwikkelingsprobleme teenwoordig is (indien u kind byvoorbeeld nie 'n bepaalde verwagte mylpaal behaal het nie), moontlike leerprobleme (byvoorbeeld 'n probleem met taal en kommunikasie, of ander areas wat toekomstige skoolvordering kan beïnvloed) of gedragsprobleme (byvoorbeeld Hiperaktiwiteit en Aandagafleibaarheid). Ons sal ook 'n volledige fisiese ondersoek uitvoer om seker te maak daar is geen ander mediese toestande teenwoordig nie, asook gehoor en visie toetse. Terwyl u kind saam met ons speel, sal ons u versoek om ook 'n vraelys te voltooi, wat ook sal handel oor aspekte van u kind se gedrag en ontwikkeling. Al hierdie toetse sal waarskynlik min of meer 'n oggend neem om te voltooi en sal uitgevoer word by die Rooikruis Kinderhospitaal deur Dr Jessie van Dyk, 'n algemene kinderarts, met die ondersteuning van Dr Kirsty Donald, van die Departement Neurologie.

U kind se deelname aan ons studie is ten volle vrywillig en indien u besluit om nie deel te neem nie, sal dit geen effek hê op toekomstige behandeling ontvang by ons hospitaal nie.

Watter voordele is daar aan deelname aan ons studie?

Ouers en voogde sal volle toegang hê tot die resultate van die toetse uitgevoer, en indien enige probleme geïdentifiseer word sal ons tot die beste van ons vermoë poog om

toepaslike ondersteuning en advies te bied, asook help met spesiale onderwys ondersteuning and verdere multidissiplinêre verwysing (byvoorbeeld na arbeidsterapie, fisioterapie en ander mediese spesialiste).

Wie sal toegang hê tot die studie inligting en u kind se rekords?

Alle inligting ingesamel tydens die verloop van die studie, hetsy deur toetse of van die vraelyste deur u voltooi, sal as uiters vertroulik beskou en hanteer word. Ons verstaan die sensitiewe aard van inligting aan ons verskaf en die hoeveelheid vertrouwe wat betrokke is tydens die deel van sulke inligting. Indien die resultate van ons studie vir publikasie doeleindes gebruik sou word of vir die voltooiing vir 'n tesis of dissertasie, sal alle deelnemers aan die studie se identiteite anoniem gehou word. Die enigste persone wat toegang sal hê tot all studie-inligting versamel, is Drs van Dyk en Donald. Ons sal ook ons beywer om te sorg dat geen diskriminasie deur u of u kind of familie ondervind word vir inligting aan ons oorgedra nie.

Om te verseker dat ons studie aan al die nodige vereistes voldoen, mag ons rekords moontlik deur ouditeure van die Navorsingsetiek Komitee nagegaan moet word.

Sal ek vergoed word of sal ek moet betaal om deel te neem?

U sal nie betaal word om deel te neem aan ons studie nie, maar ons sal u wel vergoed vir vervoerkostes vir uself en kind, vir besoeke gedurende die verloop van die studie. Omdat die toetsdae ook moontlik lank en uitputtend kan wees, sal ons ook 'n ligte maaltyd vir veral u kind verskaf.

Is daar enigiets meer wat ek behoort te weet?

Indien u enige verdere vrae het, of bekommernisse ten opsigte van die studie, op enige stadium tydens die verloop daarvan het, moet u asseblief nie huiwer om Dr Jessie van Dyk te kontak by 0823329586 of 0124607900.

U kan ook die Komitee vir Menslike Navorsing skakel by 021-4066338 (Fakulteit Gesondheidswetenskappe, Navorsingsetiek Komitee, Kamer E52-24 Groote Schuur Hospitaal, Old Main Building, Observatory, 7925) indien u enige bekommernisse of klagtes het wat nie bevredigend deur u dokter beantwoord is nie.

TOESTEMMING

Ek, gee hiermee
toestemming dat my kind, mag
deelneem aan die navorsingstudie getiteld : Moederlike metamfetamien
gebruik tydens swangerskap en die langtermyn neuro-ontwikkelings en
sielkundige nagevolge vir die kind: 'n Kaapstad ervaring

Ek verklaar dat:

1. ek die inligtingsbrosjyre en toestemmingsvorm gelees het, of dat dit aan my voorgelees is
2. albei geskryf is in 'n taal waarin ek vlot is en gemaklik kommunikeer
3. ek 'n kans gegun is om vrae te vra en voldoende antwoorde op hierdie vrae ontvang het
4. deelname aan hierdie studie ten volle vrywillig is en ek onder geen druk geplaas word om deel te neem nie
5. ek bewus is dat ek op enige stadium tydens die studie my kind en myself daarvan mag onttrek, sonder dat verdere behandeling van my kind by hierdie hospitaal daardeur beïnvloed sal word
6. ek 'n kopie van hierdie vorm sal ontvang vir my eie rekords

Geteken te (plek)

Op (datum)

Handtekeninge:

Pasiënt:

Naam in drukletters

Handtekening (waar oud genoeg)

Datum

Moeder:

Naam in drukletters

Handtekening

Datum

Vader:

Naam in drukletters

Handtekening

Datum

Wettige voog:

Naam in drukletters

Handtekening

Datum

Verwantskap aan pasiënt

APPENDIX E

PARENTAL BACKGROUND QUESTIONNAIRE (English)

Mother

Date: _____

Name	
Date of birth	
Occupation	
Highest level of schooling obtained	
Home language	
Marital status	
Monthly income	
Criminal offences	
Own health status	

Father

Name	
Date of birth	
Occupation	
Highest level of schooling obtained	
Home language	
Marital status	
Monthly income	
Criminal offences	
Own health status	

Legal guardian (if other than parents)

Name	
Date of birth	
Occupation	
Highest level of schooling obtained	
Home language	
Marital status	
Monthly income	
Criminal offences	
Own health status	

Housing (type, suburb, amenities)

Details of siblings:

Care situation of child (ie foster care, adopted, protective care orders etc)

APPENDIX F

OUERLIKE AGTERGROND VRAELYS (Afrikaans)

Moeder

Datum: _____

Naam	
Geboortedatum	
Beroep	
Hoogste graad op skool behaal	
Huistaal	
Huwelikstatus	
Maandelikse inkomste	
Kriminele oortredings	
Eie gesondheidstatus	

Vader

Naam	
Geboortedatum	
Beroep	
Hoogste graad op skool behaal	
Huistaal	
Huwelikstatus	
Maandelikse inkomste	
Kriminele oortredings	
Eie gesondheidstatus	

Wettige voog (indien anders as ouers)

Naam	
Geboortedatum	
Beroep	
Hoogste graad op skool behaal	
Huistaal	
Huwelikstatus	
Maandelikse inkomste	
Kriminele oortredings	
Eie gesondheidstatus	

Behuising (tipe, voorstad of area, fasiliteite)

Besonderhede van sibbe

Voogdyskap/ sorg van kind (byvoorbeeld in pleegsorg of aangeneem, beskermende sorg)

APPENDIX G

DESCRIPTION OF NEURODEVELOPMENTAL SCREENS USED IN THIS STUDY:

1. **Griffiths Mental Development Scales.** The scale to be used has been proven appropriate for an age group of 3-7years, and is a sophisticated assessment tool to evaluate the different aspects of normal infant and child development. It has been validated for use in children of different language groups in South Africa. The GMDS measures areas, or sub-scales of development according to the following categories: locomotor, personal-social, hearing and language, eye-hand co-ordination, fine motor performance and reasoning. Raw scores are calculated for each sub-scale by adding the total number of items passed on a particular sub-scale. Raw scores from all the sub-scales are then added to obtain a total raw score that can be converted and evaluated as either age equivalents, sub-quotients and general quotients, or percentile equivalents. (57,58,59,60,61)

4. **Achenbach Parent Questionnaire.** The Child Behaviour Checklist (Achenbach, 2001) is completed by parents or guardians and is designed to assess behavioural problems and social competencies in children. There are two versions of the checklist: one for ages 18 months to 5 years and a second for ages 6 to 18 years. It consists of 113 questions each scored by way of three possible responses: 0= not true, 1= somewhat true and 2= very true, and is able to generate an 8 syndrome report, as well as three more general scores: a total score, internalising behaviour score (fearful, shy, anxious and inhibited) and externalising behaviour score (aggressive, anti-social and under-controlled). The questionnaire rates behaviour according to Diagnostic Statistic Manual-IV related categories. (67)

APPENDIX H: Academic Pediatrics author guidelines

http://www.elsevier.com/wps/find/journaldescription.cws_home/717484/authorinstructions

Academic Pediatrics

Official Journal of the Academic Pediatric Association

Guide for Authors

Overview

Academic Pediatrics strives to improve the health and wellbeing of children, their families, and their communities through:

Providing a forum for the publication of general pediatric studies, commentaries and reviews that are of interest to learners and professionals who care for children and adolescents;

Helping to advance the field of academic pediatrics;

Strengthening the research and educational base of academic pediatrics; and

Providing the evidence base for optimal child health care, pediatric education, and child health policy.

The content areas of the Journal reflect the general interests of Academic Pediatric Association members and other health professionals who care for children. Areas of particular interest include child health services research, quality of clinical care, pediatric education, child health policy, and research methodology. Content areas for the Journal include such diverse topics as adolescent medicine, child maltreatment and protection, chronic illness, community pediatrics, developmental and behavioral pediatrics, emergency medicine, environmental medicine, financing, global pediatrics, health disparities, holistic medicine, hospital medicine, informatics, injury, medical education across the continuum, pediatric advocacy, prevention, pediatric primary care problems, and public health.

Please address editorial questions to:

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Article Types

Research articles - Quantitative and Qualitative Research

Most research articles published in the Journal use quantitative methods, and the maximum length for these manuscripts is 3500 words. The word limit for manuscripts reporting qualitative research is 4000 words. Mixed methods research will also be accepted. Manuscripts reporting original research should have clear organization with:

A structured abstract less than 250 words (see below);

A brief description, no more than 40 words, of key findings for the What's New section

An introduction that describes the importance of the problem addressed

A methods section that briefly explains the study design and procedures. For randomized clinical trials (RCTs), please include the CONSORT flow diagram in the methods section, and submit the CONSORT Checklist with the manuscript. Academic Pediatrics will take into consideration the registration of RCTs in a public trials registry, as described by the International Committee of Medical Journal Editors (ICMJE).¹

A results section that describes the key characteristics of the sample and then describes the findings for the dependent (outcome) variables and key independent variables.

A discussion section that begins with a brief statement of the important findings of the study and then places these results in the context of previous related research. Please make specific recommendations rather than a general plea for more research.

Articles describing educational research and interventions should measure and report outcomes beyond participants' reactions and change in knowledge. Demonstration of the impact of educational interventions should include changes in observed behaviors of learners as a result of the intervention. Ultimately, new learned behaviors should have measurable impact through improved patient outcomes and/or enhanced child health.

Brief Reports

The Journal also publishes brief reports that describe interesting new ideas or innovations in pediatric medicine, health services, and medical education. Brief reports typically raise new questions of interest to the Journal readership. Brief reports should have no more than 2,000 words (excluding abstract, tables, and references) and a maximum of three tables or figures and 25 references. Other elements (abstracts and references) meet usual Journal requirements for length and formatting.

Perspectives

Perspectives presents important pediatric topics, with an emphasis on research findings in the previous five years and identifying areas for future study. The Perspectives Editors solicit most articles with input about topics and potential authors from the Journal's senior editorial group. Authors will generally be respected authorities in the area and may include a fellow or junior faculty member as a co-author. The manuscript should be about 4500-5000 words. It should include an overview of key questions and important research in a field, indicating the recent advances in the underlying science, and ending with a vision of the research and/or policy issues that should be addressed in the near future. Where appropriate, Perspectives should also discuss implications for pediatric education and practice. The editors will work with authors as needed and may request an annotated outline of the manuscript. All Perspectives manuscripts are peer-reviewed. For questions or suggestions about a Perspectives topic, please contact Elena Fuentes-Afflick at efuentes@sfghpeds.ucsf.edu or John Pascoe at john.pascoe@wright.edu.

Systematic Reviews

Systematic, critical assessments of literature and data sources pertaining to one of four areas: 1) pediatric research methods, 2) pediatric education and pediatric professional development, 3) pediatric health policy, and 4) pediatric health care delivery. All articles or data sources should be selected systematically for inclusion in the review and critically evaluated, and the selection process should be described in the article. Typical length: 2000 to 3500 words (not including tables, figures, and references). Evidence tables that list specific studies would generally be published in an online-only appendix, while the print version would include the critical summary tables. Any manuscript over 4000 words will not be considered unless this has been previously discussed with the editor.

Submissions should meet at a minimum the standards published by an international group led by David Moher, Ph.D. of the Ottawa Hospital Research Institute (OHRI) and the University of Ottawa entitled Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Authors should access the PRISMA Statement (www.prisma-statement.org), which consists of the 27-item PRISMA Checklist, the PRISMA Flow Diagram, and the PRISMA Explanation and Elaboration Document.² The PRISMA Explanation and Elaboration Document also includes additional considerations for systematic reviews of non-randomized intervention studies or for other types of systematic reviews. We would encourage authors also to consider the recommendations of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) Group.³

The submitted report should include all 27 PRISMA items listed on the PRISMA Checklist including the PRISMA Flow Diagram (Item 17 on the checklist). The flow diagram depicts the flow of information through the different phases of a systematic review. It maps out the number of records identified, included and excluded, and the reasons for exclusions. We will publish the flow diagram as a figure as part of the print version as well as the online version. As stated above, we will publish

evidence tables to address Item 18 on the checklist in the online version only, which, nevertheless, is the article of record for the journal.

The submitted manuscript should include a Title Page. On a separate page, list MeSH Key Words for the purpose of indexing the report. Include on a separate page an Abstract. Structure the abstract as a summary of the report and include the following headings, as applicable, as prescribed in the PRISMA checklist: Background; Objectives; Data Sources; Study Eligibility Criteria, Participants, and Interventions; Study Appraisal and Synthesis Methods; Results; Limitations; Conclusions and Implications of Key Findings; and Systematic Review Registration Number. For the body of the paper, use the major headings of Introduction, Methods, Results, and Discussion. Also, on a separate page, list Acknowledgments. Acknowledgments should specify the sources of funding for the systematic review and other support and note the role of the funders for the systematic review. Refer to the PRISMA Flow Diagram as a figure in the Results section. Include each figure and table as separate pages in the manuscript to follow the References. Use this journal's Instructions for Authors for details regarding citations. Along with the figures and tables, include on a separate page a box containing no more than 40 words to be entitled, "What this Systematic Review Adds" describing perhaps in three bullet points this systematic review's contribution to the literature. Also, include on a separate page a box containing no more than 40 words to be entitled "How to Use this Systematic Review" and discuss, perhaps in 3 bullets, how academic pediatricians should apply these findings to their work.

In the Moment - Personal Narratives

We invite submissions to "In the Moment", the personal narratives section of Academic Pediatrics. "In the Moment" is a forum for authors to relate their personal experience of pediatrics. We are seeking narrative pieces about research, contact with patients, the influence of mentors, the impact of policy and current events, and the relationship of the author's work to their lives and the lives of others. Essays should describe these experiences and make connections to larger themes in pediatrics education, research, policy, and clinical care. The section is a vibrant forum for all of us to relate the stories and perspectives that are such an important part of our work and ongoing medical education.

Submissions should be no more than 2500 words in length and do not need abstracts or "What's New" descriptions. Data and the work of others must be appropriately referenced. Papers should be submitted through the editorial website. Please direct questions to Anjali Jain, MD (anjali.jain@lewin.com).

Commentaries

The editors occasionally solicit brief (about 1000 word) commentaries regarding papers published in the Journal or recent reports of activities of interest to readers. Commentaries differ from Perspectives by being briefer and more focused on specific topics, questions, or manuscripts. If you wish to submit a commentary, please contact the editor-in-chief.

Supplements

The Journal publishes supplements on topics of interest to its readers. Authors interested in supplements to the Journal should contact the Editor-in-Chief to discuss interest and procedures. Supplements should have a guest editor, who helps with the initial review of manuscripts and organization of the supplement, as well as suggesting reviewers for the manuscripts. All manuscripts proposed for a supplement have external review (as with other submissions to the Journal), and final decisions on publication remain with the Journal's editors, in consultation with the guest editor for the supplement.

Preparing a Manuscript

Formatting

All manuscripts should be prepared with standard word processing software. Text should be double spaced in 12 point font, and pages numbered. Tables should be placed together at the end of the manuscript. Black and white figures will be printed without charge. Authors bear the costs for printing colored tables or figures. Do not mail original artwork or printed forms. Figures should be saved separately as ppt, tif, eps, or jpg files. The online submission system is unable to process multi-worksheet or multi-slide files. To submit such documents, save each worksheet table or slide in a separate file. Symbols and special characters should not be created graphically; instead, use the character set provided in your word processor. Use a legend as part of the figure when symbols are used. Do not use any automated word-processing features, such as track changes or citation links.

Submission Letter

All manuscripts begin with a submission letter. This letter should be included with the online submission but the original copy signed by all authors should be sent to the editorial office at the above address. The authors should affirm that:

They are responsible for the reported research.

They have participated in the concept and design, analysis and interpretation of data, and drafting or revising of the manuscript; and that they have approved the manuscript as submitted.

They are disclosing any affiliation, financial agreement, or other involvement of any author with any company or other organization with a financial interest in the subject matter in the submitted manuscript. The Journal generally prints information on potential conflict of interest.

The manuscript is being submitted only to Academic Pediatrics, that it will not be submitted elsewhere while under consideration, that it has not been published elsewhere, and, should it be published in Academic Pediatrics, that it will not be published elsewhere—either in similar form or verbatim—without permission of the editors. These restrictions do not apply to abstracts or to press reports of presentations at scientific meetings.

If the submitted paper contains data that have been previously published, are in press or currently under review by another publication in any format, the authors are required to submit a reprint or a copy of the manuscript to the Editor-in-Chief with a clarification of the overlap and justification for consideration of the current submitted manuscript. This requirement includes manuscripts with the same or similar authors and using the same data source. Final decisions on the appropriateness of additional publication remain with the Editor-in-Chief.

An institutional review board reviewed and approved the research.

Title Page

The title page is the first page of all manuscripts. It includes:

The manuscript's title;

Names, degrees, department, affiliation, city and state of all authors;

Name, mailing address, email address, phone and fax number of the corresponding author;

3-5 keywords;

Running title or header of no more than 60 characters including spaces;

Separate word counts for the abstract and the main text;

Acknowledgement of research or project support with the relevant agency, grant or project number, and the principal investigator;

Description of potential conflicts of interest and corporate sponsors.

Abstracts

The abstract is the second page of all manuscripts with the exception of "In the Moment - Personal Narratives" for which an abstract is not required. Abstracts should be prepared with a structured format with a maximum of 250 words. Four elements should be addressed: objective, methods, results, and conclusions. Please label each section clearly with the appropriate subheading.

What's New

What's New provides authors an opportunity to summarize in 40 words or less how this research contributes to the knowledge base of the field.

Manuscript Text

The manuscript's text varies with the type of article submitted. Please consult the "Article Types" section for guidelines, and direct specific questions to the Editorial Office or section editor.

All manuscripts, including title page, tables, figures, and references, should be prepared according to "Uniform requirements for manuscripts submitted to biomedical journals."⁴ Grammar, punctuation, scientific writing style and abbreviations should follow the American Medical Association Manual of Style, 9th edition.⁵ Please use conventional system measurements followed in parentheses by equivalent Systeme International (SI) values.^{6,7} Any uncommon abbreviations should be listed at the beginning of the article. Confidence intervals usually provide more helpful information than P values.

References

All authors should have read all cited references. Please number references in the order they appear in the text. Unpublished references or meeting abstracts should not be included although articles accepted for publication or in press are permissible. Include the names of all authors for six and fewer; for references with more than six authors, provide the names of the first three and then et al. References should be double-spaced and generally not exceed 35. Spell out journal titles or use standard AMA abbreviations. References should follow AMA style.

Submitting a Manuscript

Authors should submit all manuscripts through the Journal's editorial website, <http://ees.elsevier.com/academicped/>. The manuscript submission process is broken into a series of screens that gather detailed information about the manuscript, including title, article type, author listings, abstract, keywords, topical classifications, and that allow authors to upload all pertinent files including the submission letter, manuscript, figures, and tables. A detailed tutorial with a step-by-step walk-through is available for download on the EES homepage

Before beginning the submission process, please gather the following information and files:

- For each author
 - o First name, middle name/initial, last name, credentials
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- Cover letter with all authors' names and signatures
- Manuscript title (you may copy and paste this from your manuscript)
- Abstract (you may copy and paste this from your manuscript)
- Key words
- Manuscript in common word processing format. Do not submit the manuscript in PDF format. The manuscript file must include
 - o Title page
 - o Abstract (not required for In the Moment - Personal Narratives)
 - o "What's New" description (also not required for In the Moment) and
 - o Manuscript text with references.
- Tables, figures or images in PDF, XLS, or PPT format or embedded at end of the manuscript file.

One author must be specified as the correspondent with the Journal. He or she will receive all communications from the Editor. Provide full mailing address, phone and fax numbers, and e-mail address for the corresponding author on the title page. The Journal limits authors to a maximum of eight. Exceptions to this rule will require justification and approval by the Editor-in-Chief.

After submitting the manuscript files, authors select the order in which the files will appear in a merged PDF file that the system creates. When the system finishes generating the PDF file, authors are directed to a page that allows review of the pdf-formatted manuscript. If the conversion is not correct, authors can replace or delete manuscript files as necessary. The final screen includes an "Ethics in Publishing" statement that authors should read and accept if in agreement. After reviewing the converted files, authors need to click on "Approve Submission." This completes the manuscript submission process.

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Three outside peer reviewers review most manuscripts. The Journal makes every effort to expedite this process. The average time from submission to initial decision is 39 days. As part of the submission process, you will be able to suggest possible peer reviewers. Suggested individuals should have no conflicts of interest, and should not have any knowledge of the submitted manuscript. Please indicate names of reviewers who may have a conflict of interest.

Manuscript Status

You can check the status of your manuscript at any time by:

1. Logging into the system with your password
2. Clicking on the link "Submissions Being Processed."

This procedure will display the status of your manuscript during the submission/peer-review process.

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Relevance to readers (esp., educators, scientists, policymakers, and clinicians) is of major importance in manuscript selection. Reports of original research will be judged on the importance and originality of the research; the scientific strength; the relevance to clinical care, programs, education, or policy; the clarity with which it is presented, and the novelty of the new knowledge it adds.

The Journal will generally accept manuscripts in the following categories: reports of original research, particularly clinical, health services, and health policy research; systematic reviews of primary care and general pediatric topics; studies and descriptions of educational interventions; educational symposia; and papers regarding methodology. In general, commentaries and topic reviews will be limited to careful systematic reviews of the literature or to research agenda setting papers indicating important next steps in a field. The Journal does not publish clinical case reports

Education interventions must include an evaluation component, preferably one that goes beyond increasing knowledge to assessing and demonstrating whether the intervention changes learners' behavior, skills, or potentially health care quality or outcomes. Multi-site education innovations are generally reviewed more favorably than single site experiments.

Journal Editorial Policies

Conflict of Interest

Conflicts of interest can arise for authors, reviewers and editors. Conflicts of interest can arise for authors, reviewers and editors. The Journal makes every effort to avoid such conflicts within its control by blinding editors for whom conflicts may exist and by selecting reviewers without obvious conflicts. We rely on authors to make similar efforts and to reveal potential conflicts of interest in areas of financial relationships, sources of research support, and writing or other assistance. For more information about conflicts of interest, please refer to the International Committee of Medical Journal Editors' Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication at <http://www.icmje.org/#conflicts>. Please direct specific questions regarding potential conflicts of interest to the Journal office at: journal@academicpediatrics.org.

Academic Pediatrics requires that authors completely disclose all relevant financial or personal arrangements or interests at the time of submission of a manuscript. Disclosures should appear on the acknowledgement section of the manuscript, and should describe specifically all sources of funding for the study as well as the nature of the financial arrangements. If the manuscript is accepted for publication, the disclosure will be published.

Authors should indicate the role of the study sponsor in terms of study design, fieldwork, writing of the manuscript, and decision to submit for publication.

Authors should also specifically indicate in the acknowledgements if no conflicts of interest exist.

Authorship Criteria

In order to meet authorship criteria, each author must have participated sufficiently in the work of the study and manuscript to acknowledge publicly responsibility for the manuscript. At least one author must be able to take public responsibility for the entire work, from idea to complete manuscript. Academic Pediatrics follows published uniform recommendations for criteria for authorship (see references). All three of the following criteria must be met for authorship:

1. Substantial involvement and contribution to the idea or the study question, or to the study design, or to the fieldwork component, or to the analysis, or to the interpretation of study findings; and

2. Writing drafts of the manuscript, or reviewing drafts or revisions critically with substantial input; and
3. Approval of the final version of the manuscript.

Group Authorship

The Journal limits authors to a maximum of eight. Exceptions to this rule will require justification and approval by the Editor-in-Chief. One person should be designated as the lead author. If authorship is attributed to a group of individuals, each individual must achieve the criteria for authorship described above.

Duplicate Publication or Previous Publication

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Appropriate approval by all institutional or other human subjects review boards must be designated in the methods section. Authors should indicate formal review and approval, or formal review and waiver.

Funding

All sources of funding for the study should be identified in the Acknowledgements section. In addition, if not apparent from the type of study, the specific role of the funder should be delineated as described in the Conflicts of Interest section above.

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Updated November 2010

APPENDIX J

Methamphetamine use in pregnancy / developmental outcome Literature search

SEARCH STRATEGIES

We ran searches using the OVID search platform in the following databases: MEDLINE, EMBASE, PsycINFO, and CCTR. We retrieved a total of **617** references from all 4 databases. All references were saved in an EndNote library used to identify the **116** duplicates. The author reviewed the remaining **501** unique references against our inclusion criteria.

The following tables and text record the search strategies and terms used.

MEDLINE:

The search strategy for MEDLINE (1948 to **June 21, 2011**) retrieved **120** references of which **111** were unique and not duplicated in our other searches. The following combination of MeSH and free text terms for

Set	History	Results	Comments
1	methamphetamine/ or benzphetamine/	6186	Methamphetamine Terms
2	exp "congenital, hereditary, and neonatal diseases and abnormalities"/ or Prenatal Exposure Delayed Effects/ or exp "Embryonic and Fetal Development"/ or exp Embryonic Structures/ or exp Teratogens/ or exp PREGNANCY/	1683411	Pregnancy Filter terms
3	exp mental disorders/ or exp "behavior and behavior mechanisms"/ or exp "psychological phenomena and processes"/ or exp neurologic manifestations/ or exp human development/ or exp fetal alcohol syndrome/ or exp Nervous System/ or exp Nervous System Diseases/ [***GENERAL NEURODEVELOPMENT***]	4765373	GENERAL NEURODEVELOPMENT Filter terms
4	exp central nervous system/ or exp central nervous system diseases/ or child development/ or exp Delirium, Dementia, Amnestic, Cognitive Disorders/ or exp psychophysiology/ or exp diagnostic techniques, neurological/ or exp neuropsychological tests/ or cerebral arteries/ or cerebrovascular circulation/ or brain chemistry/ or exp nerve growth factors/ or exp nervous system physiology/ or nervous system diseases/ or exp cranial nerve diseases/ or exp nervous system malformations/ or exp neurodegenerative diseases/ or exp neurotoxicity syndromes/ or exp nervous system/ or exp neurotransmitters/ or exp receptors,	3525472	PHYSICAL BRAIN AND NERVOUS SYSTEM Filter terms

	neurotransmitter/ or microcephaly/ or circadian rhythm/		
5	exp mental disorders/ or mental health/ or exp personality/ or exp personality tests/ or psychological tests/ or exp social behavior disorders/ or exp behavior/ or exp adaptation, psychological/ or exp emotions/ or mental competency/ or attention/ or child psychiatry/ or child development/ or adolescent development/ or exp psychophysiology/ or exp neuropsychological tests/ or hallucinations/ or illusions/ or fetal alcohol syndrome/ or exp psychology/ or exp motivation/ or exp defense mechanisms/	2233572 9	MENTAL HEALTH, BEHAVIOR, SOCIAL Filter terms
6	communication/ or language/ or exp verbal behavior/ or exp nonverbal communication/ or exp communication disorders/ or language tests/ or exp psycholinguistics/ or exp language development/ or autistic disorder/	172353	COMMUNICATION AND LANGUAGE Filter terms
7	intelligence/ or exp learning disorders/ or exp mental processes/ or exp aptitude tests/ or developmental disabilities/ or exp mental retardation/ or exp memory disorders/ or cognition disorders/ or exp child development/ or autistic disorder/ or fetal alcohol syndrome/ or cerebral palsy/	820654	INTELLIGENCE AND LEARNING Filter terms
8	exp psychomotor performance/ or exp psychomotor disorders/ or exp movement disorders/ or exp gait disorders, neurologic/ or motor skills disorders/ or exp orientation/ or exp perception/ or exp movement/ or exp sensation disorders/ or exp nervous system physiology/ or exp perceptual disorders/ or exp ocular motility disorders/ or exp sensation/ or exp vision tests/ or cerebral palsy/	1349021	PSYCHOMOTOR AND SENSORY Filter terms
9	Or/3-8	5619235	ALL NEURODEVELOPMENT Filter terms
10	1 and 2 and 9	258	Base clinical set
11	limit 11 to humans	120	Human limit Final Results

Disregard the short paragraph sections

MEDLINE:

The search strategy for MEDLINE (1948 to **June 21, 2011**) retrieved **120** references of which **111** were unique and not duplicated in our other searches. We used a combination of MeSH and free text terms for

methamphetamine/ or benzphetamine/ **AND** Pregnancy terms **AND** Neurocognitive and developmental terms **AND** limited to human studies

EMBASE

The search strategy for EMBASE (1980 to **2011 Week 24**) retrieved **417** references of which **353** were unique and not duplicated in our other searches. We used a combination of EMBASE and free text terms for

Set	History	Results	Comments
1	methamphetamine/ or amphetamine derivative/ or benzphetamine	14346	Methamphetamine Terms
2	exp pregnancy/ or exp teratogenesis/ or exp teratogenic agent/ or prenatal development/ or prenatal drug exposure/ or exp prenatal exposure/ or exp embryonic structures/ or exp congenital disorder/	1223242	Pregnancy Filter terms
3	exp mental disease/ or exp behavior/ or exp "psychological and psychiatric phenomena"/ or exp neurologic disease/ or exp human development/ or fetal alcohol syndrome/ or exp nervous system/	5547911	GENERAL NEURODEVELOPMENT Filter terms
4	exp central nervous system/ or exp central nervous system disease/ or child development/ or postnatal development/ or cognitive defect/ or "disorders of higher cerebral function"/ or exp psychophysiology/ or exp neurologic examination/ or neuropsychological test/ or brain artery/ or exp brain circulation/ or exp brain level/ or nerve growth factor/ or exp nervous system function/ or exp neurologic disease/ or exp cranial neuropathy/ or exp nervous system malformation/ or exp degenerative disease/ or exp "toxicity and intoxication"/ or exp nervous system/ or exp neurotransmitter/ or neurotransmitter receptor/ or microcephaly/ or circadian rhythm/	4193875	PHYSICAL BRAIN AND NERVOUS SYSTEM Filter terms
5	exp mental disease/ or exp mental health/ or exp personality/ or exp psychologic test/ or exp sociopathy/ or exp behavior/ or exp mental capacity/ or exp attention/ or child psychiatry/ or postnatal development/ or child development/ or adolescent development/ or exp psychophysiology/ or neuropsychological test/ or exp hallucination/ or exp illusion/ or	3022951	MENTAL HEALTH, BEHAVIOR, SOCIAL Filter terms

	fetal alcohol syndrome/ or exp psychology/ or defense mechanism/		
6	interpersonal communication/ or communication skill/ or exp language ability/ or exp nonverbal communication/ or exp verbal communication/ or exp language/ or verbal behavior/ or exp communication disorder/ or language test/ or exp linguistics/ or language development/ or exp autism/	294952	COMMUNICATION AND LANGUAGE Filter terms
7	exp intelligence/ or exp learning disorder/ or exp mental function/ or cognition/ or conation/ or personality/ or psychophysiology/ or aptitude test/ or developmental disorder/ or exp mental deficiency/ or exp memory disorder/ or cognitive defect/ or postnatal development/ or child development/ or adolescent development/ or exp autism/ or fetal alcohol syndrome/ or cerebral palsy/	1879637	INTELLIGENCE AND LEARNING Filter terms
8	exp psychomotor performance/ or exp psychomotor disorder/ or exp motor dysfunction/ or exp psychomotor disorder/ or exp orientation/ or exp perception/ or exp "movement (physiology)"/ or exp sensory dysfunction/ or exp nervous system function/ or exp perception disorder/ or exp eye movement/ or exp eye movement disorder/ or exp sensation/ or exp vision test/ or cerebral palsy/	1858865	PSYCHOMOTOR AND SENSORY Filter terms
9	Or/3-8	6454100	ALL NEURODEVELOPMENT Filter terms
10	1 and 2 and 3	417	Base clinical set and Final results

EMBASE

The search strategy for EMBASE (1980 to **2011 Week 24**) retrieved **417** references of which **353** were unique and not duplicated in our other searches. The following combination of EMBASE and free text terms for

methamphetamine/ or benzphetamine/ **AND** Pregnancy **AND** Neurocognitive and developmental terms

PsycINFO

The search strategy for PsycINFO (1967 to June Week 3 **2011**) retrieved **89** references of which **37** were unique and not duplicated in our other searches. This database content emphasizes psychological and developmental outcomes. Given the small retrieval, the search was limited to the drug and pregnancy terms. The following combination of PsycINFO descriptors for

Set	History	Results	Comments
1	methamphetamine/ or methylenedioxymethamphetamine/	3377	Methamphetamine Terms
2	exp congenital disorders/ or prenatal exposure/ or prenatal developmental stages/ or embryo/ or fetus/ or teratogens/ or prenatal exposure/ or teratology/ or exp pregnancy/ or exp pregnancy outcomes/	31281	Pregnancy terms
3	1 and 2	89	Base Clinical Set and Final results

The search strategy for EMBASE (1980 to **2011 Week 24**) retrieved **417** references of which **353** were unique and not duplicated in our other searches. We used a combination of EMBASE and free text terms for

methamphetamine/ or benzphetamine/ **AND** pregnancy terms

EBM Reviews - Cochrane Central Register of Controlled Trials

The search strategy for CCTR (2nd **Quarter 2011**) retrieved **1** reference of which **0** were unique and not duplicated in our other searches. The following combination of MeSH and EMBASE descriptor terms for

Set	History	Results	Comments
1	methamphetamine/ or amphetamine derivative/ or benzphetamine	153	Methamphetamine Terms
2	exp "congenital, hereditary, and neonatal diseases and abnormalities"/ or Prenatal Exposure Delayed Effects/ or exp "Embryonic and Fetal Development"/ or exp Embryonic Structures/ or exp Teratogens/ or exp PREGNANCY/ or exp teratogenesis/ or exp teratogenic agent/ or prenatal development/ or prenatal drug exposure/ or exp prenatal exposure/ or exp congenital disorder/	22013	Pregnancy Filter terms
3	exp mental disorders/ or exp "behavior and behavior mechanisms"/ or exp "psychological phenomena and processes"/ or exp neurologic manifestations/ or exp human development/ or exp fetal alcohol syndrome/ or exp Nervous System/ or exp Nervous System Diseases/ or exp mental disease/ or exp behavior/ or exp "psychological and psychiatric phenomena"/ or exp neurologic disease/ or exp human development/	122301	GENERAL NEURODEVELOPMENT Filter terms
4	exp central nervous system/ or exp central nervous system diseases/ or	113874	PHYSICAL BRAIN AND NERVOUS

	<p>child development/ or exp Delirium, Dementia, Amnestic, Cognitive Disorders/ or exp psychophysiology/ or exp diagnostic techniques, neurological/ or exp neuropsychological tests/ or cerebral arteries/ or cerebrovascular circulation/ or brain chemistry/ or exp nerve growth factors/ or exp nervous system physiology/ or nervous system diseases/ or exp cranial nerve diseases/ or exp nervous system malformations/ or exp neurodegenerative diseases/ or exp neurotoxicity syndromes/ or exp nervous system/ or exp neurotransmitters/ or exp receptors, neurotransmitter/ or microcephaly/ or circadian rhythm/ or exp central nervous system disease/ or postnatal development/ or cognitive defect/ or "disorders of higher cerebral function"/ or exp neurologic examination/ or neuropsychological test/ or brain artery/ or exp brain circulation/ or exp brain level/ or nerve growth factor/ or exp nervous system function/ or exp neurologic disease/ or exp cranial neuropathy/ or exp nervous system malformation/ or exp degenerative disease/ or exp "toxicity and intoxication"/ or exp nervous system/ or exp neurotransmitter/ or neurotransmitter receptor/ or microcephaly/ or circadian rhythm/</p>		SYSTEM Filter terms
5	<p>exp mental disorders/ or mental health/ or exp personality/ or exp personality tests/ or psychological tests/ or exp social behavior disorders/ or exp behavior/ or exp adaptation, psychological/ or exp emotions/ or mental competency/ or attention/ or child psychiatry/ or child development/ or adolescent development/ or exp psychophysiology/ or exp neuropsychological tests/ or hallucinations/ or illusions/ or fetal alcohol syndrome/ or exp psychology/ or exp motivation/ or exp defense mechanisms/ exp mental disease/ or exp mental health/ or exp personality/ or exp psychologic test/ or exp sociopathy/ or exp behavior/ or exp mental capacity/</p>	82167	MENTAL HEALTH, BEHAVIOR, SOCIAL Filter terms

	or exp attention/ or child psychiatry/ or postnatal development/ or child development/ or adolescent development/ or exp psychophysiology/ or neuropsychological test/ or exp hallucination/ or exp illusion/ or fetal alcohol syndrome/ or exp psychology/ or defense mechanism/		
6	communication/ or language/ or exp verbal behavior/ or exp nonverbal communication/ or exp communication disorders/ or language tests/ or exp psycholinguistics/ or exp language development/ or autistic disorder/ or interpersonal communication/ or communication skill/ or exp language ability/ or exp nonverbal communication/ or exp verbal communication/ or exp language/ or verbal behavior/ or exp communication disorder/ or language test/ or exp linguistics/ or language development/ or exp autism/	5111	COMMUNICATION AND LANGUAGE Filter terms
7	exp learning disorders/ or exp mental processes/ or exp aptitude tests/ or developmental disabilities/ or exp mental retardation/ or exp memory disorders/ or cognition disorders/ or exp child development/ or autistic disorder/ or exp intelligence/ or exp learning disorder/ or exp mental function/ or cognition/ or conation/ or personality/ or psychophysiology/ or aptitude test/ or developmental disorder/ or exp mental deficiency/ or exp memory disorder/ or cognitive defect/ or postnatal development/ or child development/ or adolescent development/ or exp autism/ or fetal alcohol syndrome/ or cerebral palsy/	28782	INTELLIGENCE AND LEARNING Filter terms
8	exp psychomotor disorders/ or exp movement disorders/ or exp gait disorders, neurologic/ or motor skills disorders/ or exp orientation/ or exp perception/ or exp movement/ or exp sensation disorders/ or exp nervous system physiology/ or exp perceptual disorders/ or exp ocular motility disorders/ or exp sensation/ or exp vision tests/ or exp psychomotor performance/ or exp psychomotor disorder/ or exp motor dysfunction/ or exp psychomotor disorder/ or exp	44352	PSYCHOMOTOR AND SENSORY Filter terms

	orientation/ or exp perception/ or exp "movement (physiology)"/ or exp sensory dysfunction/ or exp nervous system function/ or exp perception disorder/ or exp eye movement/ or exp eye movement disorder/ or exp sensation/ or exp vision test/ or cerebral palsy/		
9	Or/3-8	164794	ALL NEURODEVELOPMENT Filter terms
10	1 and 2 and 9	1	Base clinical set and Final results

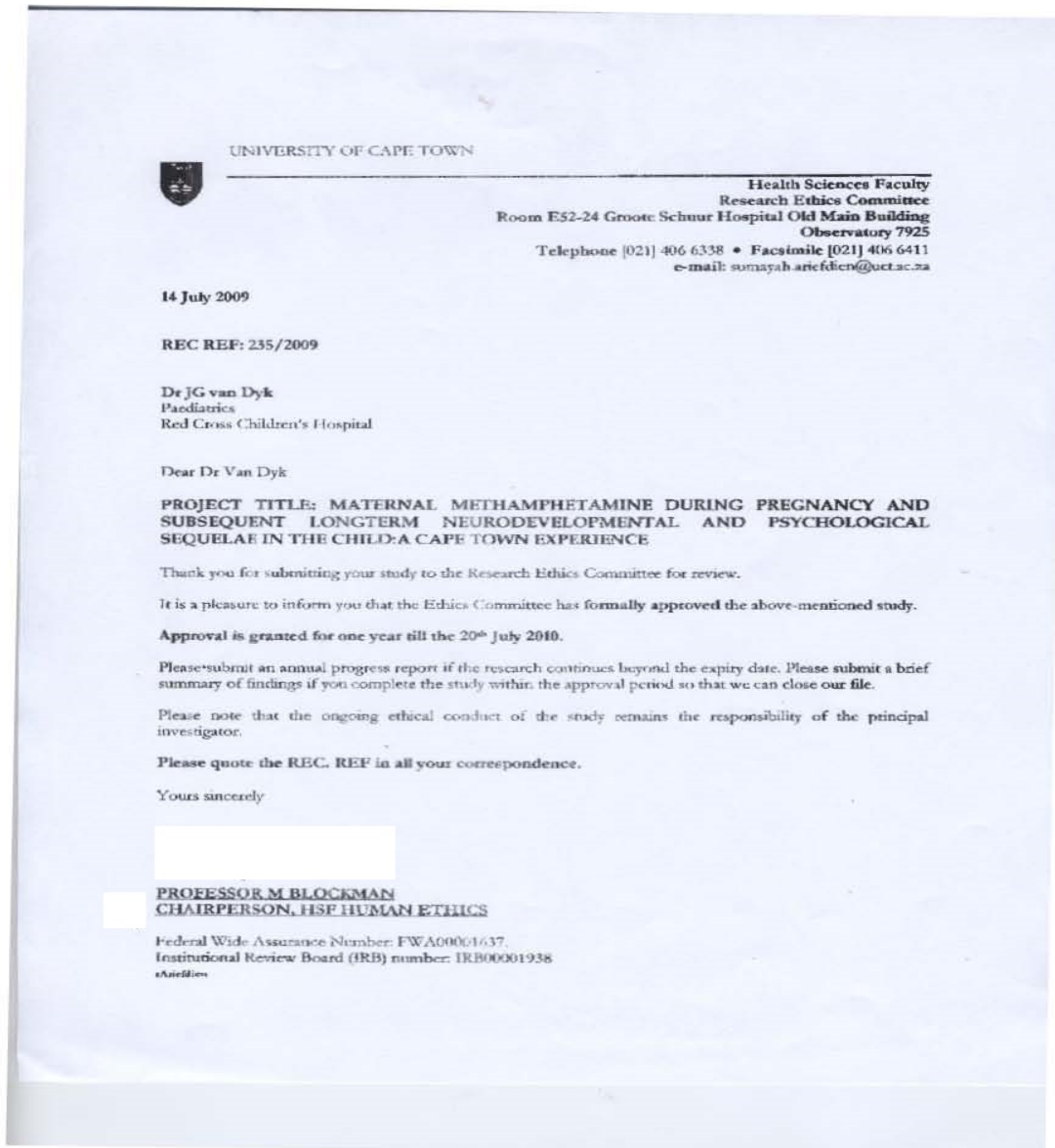
EBM Reviews - Cochrane Central Register of Controlled Trials

The search strategy for CCTR (**2nd Quarter 2011**) retrieved **1** references of which **0** were unique and not duplicated in our other searches. This database consists exclusively of RCTs, no study design terms were used. The following combination of primarily MeSH and free text terms for

methamphetamine/ or benzphetamine/ **AND** pregnancy terms **AND** Neurocognitive and developmental terms

University of Cape Town

APPENDIX K: Research Ethics Board approval letter



Research Ethics Board amendment approval



UNIVERSITY OF CAPE TOWN

Health Sciences Faculty
Faculty of Health Sciences Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
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07 September 2011

HREC REF: 235/2009

Dr K Donald
Room 420, ICH Building
SCAH

Dear Dr Donald

PROJECT TITLE: MATERNAL METHAMPHETAMINE DURING PREGNANCY AND SUBSEQUENT LONGTERM NEURODEVELOPMENTAL AND PSYCHOLOGICAL SEQUELAE IN THE CHILD:A CAPE TOWN EXPERIENCE

Thank you for your letter to the Faculty of Health Sciences Human Ethics Research Committee dated 06 September 2011.

It is a pleasure to inform you that the HREC has **approved** the Amendment dated 06 September 2011 with reference to the above mentioned study.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the REC. REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

Attachment