FETAL ALCOHOL SPECTRUM DISORDER AND THE NEUROBEHAVIOURAL SCREENING TOOL: EVALUATING THE EFFECT OF MATERNAL DEPRESSION

Kevin Haynes[1,2]; Irena Nulman[1,2,3]; Gideon Koren[1,2,3]
[1]The Hospital for Sick Children, Motherisk Program, Toronto, Canada
[2]The Hospital for Sick Children, Child Health Evaluative Sciences, Toronto, Canada
[3]The University of Toronto, Department of Pediatrics, Toronto, Canada

ABSTRACT

Background
The behaviour of children diagnosed with a Fetal Alcohol Spectrum Disorder (FASD) is characterized by very complex and pervasive neurobehavioural effects. In contrast to children exhibiting the full facial dysmorphology who are relatively easy to assess and diagnose, those children presenting with Alcohol Related Neurodevelopmental Disorder (ARND) are much more challenging to diagnose due to poor specificity of the brain dysfunction; hence identifying the neurodevelopmental phenotype of FASD is extremely challenging. In 2006 the Neurobehavioural Screening Tool (NST) was developed, which derived from a selection of 10 questions from the Child Behaviour Checklist (CBCL) developed by Achenbach. The NST is an official screening tool in the FASD toolkit of the Public Health Agency of Canada, and has been shown to identify a phenotypical neurobehavioural pattern in children affected by FASD with high sensitivity and specificity. A challenge in the interpretation of screening results has been ascertaining the potential influence of maternal psychiatric morbidity. The most common psychiatric morbidity among mothers who consume alcohol in excess during pregnancy is depression.

Objective
The purpose of this study was to examine the influence of maternal depression, evidenced by clinical diagnosis, and use of antidepressant drugs, on the typical behavioural presentation displayed by children diagnosed with an FASD.

Methods
Endorsement rates of NST items among children diagnosed with an FASD reported in three previous studies (n=134) and the typically developing healthy control children from these studies (n=112) were compared with the prospectively collected results of children born to and reared by mothers suffering from clinical depression (n=49) and additional typyically developing healthy control children (n=22).

Results
In this study, none of the children born to the mothers suffering from clinical depression screened positive on the NST, however a significant number of these caregivers reported that their child was hyperactive. The mother's level of depression as indicated by her CES-D score was also shown to correlate with the child's conduct, namely, lying/cheating and disobedience at home.

Conclusion
These results indicate that the sensitivity and specificity of the NST are not significantly affected by maternal depression, however endorsement rates of items measuring impulse control, oppositional behaviours and conduct may be influenced. Further studies are needed to examine the potential effects of other maternal psychopathologies on endorsement rates.

Key Words: *Neurobehavioural Screening Tool, Fetal Alcohol Spectrum Disorder, prenatal alcohol exposure, behavioural phenotype, maternal depression, screening*

The various clinical presentations arising from prenatal alcohol exposure are defined collectively as Fetal Alcohol Spectrum Disorder (FASD). FASD is characterized by a wide range of deficiencies, including cognitive impairment,[1,2] learning disabilities and severe behavioural concerns.[3,4] Difficulties with attention are common among 70% of children diagnosed with an FASD, and meeting criteria for a clinical diagnosis of Attention-Deficit Hyperactivity Disorder (ADHD) is three to nine times more prevalent in children with FASD than in the general population.[5–8] Of importance, comorbidities with Oppositional Defiant Disorder (ODD) and Conduct Disorders (CD) are the next most common among this population, behind ADHD,[8–10] and involve deficits in social/moral development, and difficulty learning from past experiences.[5] Presently, a vast number of children who meet the diagnostic criteria for FASD remain unidentified because skilled professionals trained in assessment techniques are few and far between. As a result of this discrepency, children with FASD are often diagnosed with, and treated for, a comorbid disorder, leaving the effects of the alcohol-related disorder unaddressed, and perpetuating an enourmous public health issue.

A major challenge in the development of a screening method which accurately identifies the behavioral characteristics of FASD has been the wide and non-specific range of deficits exhibited by the children diagnosed. In an effort to distinguish the neurobehavioural phenotype of FASD, Nash and collegues[12] developed and validated a 10-item screening tool derived from specific items of the standardized Child Behavior Checklist (CBCL) developed by Achenbach.[11] The entire CBCL tool includes 113 items which are endorsed by a child's caregiver, reporting their observations regarding the child's behavioural presentation. Factor analysis of these items revealed a combination of 10 items which accurately separated children with FASD from the two comparison groups.[12] In this original study, children diagnosed with FASD (n=30) were compared with children diagnosed with ADHD (n=30) and with typically developing children (n=30).[12] This neurobehavioural test showed an 86% sensitivity and 82% specificity for identifying behaviours suggestive of FASD. Given the prevalence of the disorder's comorbidity with ADHD, a behavioural phenotype which could accurately identify children who did not present with symptoms of hyperactivity or attention-deficits was also defined. Table 1 presents the Neurobehavioural Screening Tool (NST) in detail, with scoring instructions and two exemplary cases to allow readers to better understand how the tool is applied. The NST, validated for children 6-13 years of age, can be applied by social workers and other healthcare professionals interviewing the primary caregiver(s) of the child of concern. The NST has been endorsed by the Public Health Agency of Canada as a screening tool for FASD and is included in the agency-sponsored FASD Screening Toolkit.[13]

In 2011, Nash and colleagues[14] published a second study which replicated the original, using a new and larger sample of children (n=216) which included children with FASD (n=56), ADHD (n=50), ODD/CD (n=60) and typically developing controls (n=50).[14] This study corroborated the results of the previous study's findings, and found that children with FASD exhibited poor attention and impulse control (behaviours suggestive of ADHD), but unlike ADHD, a significant number of children with FASD displayed a greater lack of remorse after misbehaving, cruel behaviours, tendencies of lying and cheating, and an increased tendency to act younger that their chronological age.

The latter finding supports previous and current research indicating poor social and moral development in children with FASD.[10,15–19] Children with FASD were also found to be significantly more likely to act younger than their chronological age than children diagnosed with ODD/CD, while the children diagnosed with ODD/CD presented as more cruel and disobedient at home. This finding suggested that children with FASD may have a distinct profile of behavioural concerns which can be differentiated from those behaviours typically presented by children with ODD/CD. The increased prevalence of immaturity in children diagnosed with FASD in comparison to children with ODD/CD (as well as ADHD) is

consistent with reports of arrested social development within this population.[20]

The two studies mentioned above were recently replicated in Western Canada,[21] in which relatively high screening capabilities were shown, despite attempting to control for prenatal alcohol exposure not resulting in a diagnosis of FASD. It is critical to highlight that the Neurobehavioural Screening Tool is intended for *screening* purposes, and *is not a diagnostic tool*. A number of challenges have been identified regarding the NST and its ability to screen as in previous studies, the influence of maternal depression and other psychiatric morbidities common among alcohol-dependent women could not be adequately measured or controlled for. As depression is the most prevalent psychiatric morbidity among women with difficulties inhibiting their consumption of alcohol,[22] the objective of the present study was to evaluate the performance of the NST as a screening tool, using a population of children born and raised by mothers suffering from clinical depression, and to compare and contrast these results with children diagnosed with FASD, as well as typically developing healthy control children.

METHODS

The Neurobehavioural Screening Tool

The NST is presented in Table 1, with scoring instructions, and 2 exemplary cases. As part of the Motherisk Program at The Hospital for Sick Children, we conduct long term follow-up of children born to women diagnosed with clinical depression and treated with Selective Serotonin Reuptake Inhibitors (SSRIs) during gestation. One of the evaluation methods included in the battery of tests and evaluations used with this population is the Child Behavior Checklist (CBCL).[11]

Participants and Analysis

For the purpose of the present study we randomly selected the CBCL data of children aged 6-12 years (n=49) born to women suffering from clinical depression being followed by us, and a group of typically developing healthy control children (n=22). Independent Sample T-Tests and chi-square tests were used to compare groups on demographic variables and endorsement rates of NST items. Pearson's correlation was used to correlate variables. The characteristics of this group are presented in Table 2**.** The children's NST scores were then compared to the combined group of children diagnosed with FASD (n=134) in the 3 studies which used the NST mentioned above,[12,14,21] as well as with the combined group of normally developing children (n=112) from these 3 studies. In addition to evaluating the overall NST screening result of positive or negative, we also compared the three groups on the endorsement of each NST item independently.

CES-D Scores

Using the results rendered from the administration of the Centre for Epidemiological Studies Depression Scale (CES-D), sub-analysis of the correlation between the mothers' CES-D scores on individual items of the NST (at the time of the CBCL's administration) was also completed. The CES-D is included within the battery of tests administered for long term follow-up of the participants referenced above.

TABLE 1 The Neurobehavioural Screening Tool, Scoring, and Exemplary Cases

1. Has your child been seen, or accused of, or thought to have acted too young for his or her age?	**YES**	**NO**	**SCORING** **STEP 1:** ***Identifying behaviour suggestive of FASD*** If the parent/caregiver answers 'yes' to **at least 6 out of 7 items** from questions 1-7, this is suggestive of FASD with 86% sensitivity and 82% specificity. ***OR*** If the child does not exhibit behavior consistent with ADHD (i.e., answer is negative for questions 5-7), then if the parent/caregiver answers 'yes' to **at least 3 out of 4 items** from questions 1-4, this is also suggestive of FASD. **STEP 2:** ***Differentiating FASD from ADHD*** The parent/caregiver needs to endorse **at least 2 out of 3** of the following items: Question 1, Question 4, Question 8 ***OR*** The parent/caregiver needs to endorse **at least 3 out of 6** of the following items. Question 1, Question 3, Question 4, Question 8, Question 9, Question 10
2. Has your child been seen, or accused of, or thought to be disobedient at home?	**YES**	**NO**	
3. Has your child been seen, or accused of, or thought to lie or cheat?	**YES**	**NO**	
4. Has your child been seen, or accused of, or thought to lack guilt after misbehaving?	**YES**	**NO**	
5. Has your child been seen, or accused of, or thought to have difficulty concentrating or pay attention for long?	**YES**	**NO**	
6. Has your child been seen, or accused of, or thought to act impulsively and without thinking?	**YES**	**NO**	
7. Has your child been seen, or accused of, or thought to have difficulty sitting still, to be restless or hyperactive?	**YES**	**NO**	
8. Has your child been seen, or accused of, or thought to display acts of cruelty, bullying or meanness to others?	**YES**	**NO**	
9. Has your child been seen, or accused of, or thought to steal items from home?	**YES**	**NO**	
10. Has your child been seen, or accused of, or thought to steal items outside of the home?	**YES**	**NO**	

Adapted from: K. Nash, G Koren & J Rovet (2009), The Hospital for Sick Children, Toronto, ON, Canada

Exemplary Cases

Vignette 1

A 7 year old boy has severe learning and behavioral issues. His parents indicate that he behaves like his 4 year old sister, does not follow instructions, and has been caught several times stealing items from their bedroom. The child often argues with his 4 year old sister, which often results in bullying and displays of physical aggression. After hitting his younger sister, he does not seem to express remorse. The child's teacher reports that he is very impulsive, cannot sit still, nor can he concentrate on any task for more than 5 minutes. The child's teacher also reports that he frequently takes items from her desk, as well as items out of other students' bags.

Scoring: After interviewing the caregivers, items 1-2 and 4-10 would be endorsed, therefore this child WOULD screen positive on the NST.

Vignette 2

A 9 year old girl is having academic challenges, and does not follow her parents' instructions. She is known to cheat on tests at school. When confronted by her teacher, she is always remorseful, and explains that her schoolwork is too hard for her. The child has great difficulty concentrating on her homework after school, and her parents note that she will not sit still and work on it, and she acts very impulsively.

Scoring: After interviewing the caregivers, items 2-3 and 5-7 would be endorsed, therefore this child WOULD NOT screen positive on the NST.

RESULTS

This study reviews the NST scores from a total of 482 children. The sensitivity of the NST as compared to healthy controls ranged between 62.5% and 98% among the 3 previous studies included. In contrast, similar to the normally developing children, none of the children born to mothers suffering from clinical depression scored positive. The performance of the NST across the studies is outline in Table 3 below. Table 4 presents the endorsement rates of individual NST items from the 3 previous studies, as compared to the children born to the mothers suffering from depression in the present study and the healthy controls. Although none of the children born to the mothers suffering from depression scored positive on the NST, the endorsement rate for the NST item "sit still, restless, or hyperactive" was shown to be significantly ($0.01< p \leq 0.05$) elevated in the group of children born to mothers suffering from depression ($p = 0.044$).

TABLE 2 Demographic Information (Current Study)

	DEPR (N=49)	**Controls (n=22)**	**Sig.**
Age	7.55 (SD 1.42)	8.00 (SD 1.64)	.641 (ns)*
Sex (% Male)	44.9%	50.0%	.637(ns)*
Gestational Age	40.0 (SD 1.29)	40.1 (SD 1.30)	.801(ns)*
Age at Childbirth (Mother)	31.8 (SD 4.24)	32.5(SD 4.87)	.342 (ns)*
CES-D Score (Mother)	15.5	--	--
(Range)	(0-45)		
SES (%)[1]			.780 (ns)*
High[2]	81.6%	68.2%	
Medium[3]	12.2%	4.5%	
Low[4]	6.1%	4.5%	
Current Living Arrangement:			--
Foster	0%	0%	
Adopted	0%	0%	
Biological Parent(s)	100%	100%	

*Analysed by an Independent Sample T-Test; SES: Socioeconomic status; ns: non significant ;[1]SES data not available for all children; [2]SES = 1 or 2; [3]SES = 3; [4]SES = 4 or 5 Hollingshead's Four-Factor Index of Social Status

TABLE 3 NST Performance from Included Studies

	Nash et. al. 2006	**Nash et. al. 2011**	**LeFrance et. al. 2014**	**Current Study**
FASD	30	56	48	0
Controls	60a	163b	54c	71d
Sensitivity	86%	98%	62.5%	N/A
Specificity	82%	42%	100%	100%

[a]Controls included children diagnosed with ADHD (n=30), and typically developing controls (n=30)
[b]Controls included children diagnosed with ADHD (n=50), ODD/CD (n=60), and typically developing controls (n=50)
[c]Controls included children prenatally exposed to alcohol (n=22) and typically developing controls (n=32)
[d]Controls included children born to/raised by mothers diagnosed with clinical depression (n=49) and typically developing controls (n=22)

TABLE 4 Endorsement Rates for Individual Items of the Neurobehavioural Screening Tool from Various Studies

	Neurobehavioural Screening Tool Item	Nash et. al. 2006			Nash et. al. 2011			LaFrance et. al. 2014			Current Study		
		FASD (n=30)	HC (n=30)	p-value	FASD (n=56)	HC (n=50)	p-value	FASD (n=48)	HC (n=32)	p-value	DEPR (n=49)	HC (n=22)	p-value
1	Has your child been seen, or thought to have acted too young for his/her age?	90%	23%	.001	80.4%	24.5%	<.001	72.9%	3.1%	<.001	26.5%	13.6%	.229
2	Is your child disobedient at home?	93%	27%	.001	87.5%	24.5%	<.001	81.3%	6.3%	<.001	44.9%	22.7%	.075
3	Has your child been seen, or accused, or thought to lie or cheat?	90%	18%	.001	82.1%	17.0%	<.001	72.9%	18.8%	<.001	14.3%	13.6%	.942
4	Has your child been seen, or accused, or thought to lack guilt after misbehaving?	97%	17%	.001	83.9%	11.3%	<.001	70.8%	0.0%	<.001	16.3%	18.2%	.847
5	Has your child been seen, or thought to have difficulty concentrating or paying attention for long?	97%	23%	.001	92.9%	24.5%	<.001	91.7%	12.5%	<.001	38.8%	18.2%	.086
6	Has your child been seen, or thought to act impulsively and without thinking?	97%	35%	.001	94.6%	30.2%	<.001	91.7%	18.8%	<.001	40.8%	18.2%	.062
7	Has your child been seen, or thought to have difficulty sitting still, to be restless or hyperactive?	93%	31%	.001	83.9%	24.5%	<.001	85.4%	6.3%	<.001	42.9%	18.2%	.044
8	Has your child been seen, or accused, or thought to display acts of cruelty, bullying or meanness to others?	48%	3%	.001	66.1%	5.7%	<.001	47.9%	12.5%	.001	10.4%*	0%	.116
9	Has your child been seen, or accused, or thought to steal items from home?	59%	0%	.001	66.1%	1.9%	<.001	41.7%	3.1%	<.001	6.1%	4.5%	.790
10	Has your child been seen, or accused, or thought to steal items outside of the home?	45%	0%	.001	46.4%	1.9%	<.001	39.6%	0.0%	<.001	0.0%	4.5%	.133

*Data not available for all children in DEPR group (n=48); HC: Healthy controls; DEPR: Depression group.

Based on the results reported in these studies, statistics indicate that the NST was able to correctly separate children with FASD from controls with a combined sensitivity of 82% across the studies. Of the combined total of controls, which included children diagnosed with ADHD (n=80), ODD/CD (n=60), children prenatally exposed to alcohol (n=22), children borned and reared by mothers suffering from depression (n=49), and healthy controls (n=134), specificity varied across comparison groups. In the present study, the NST did not render any false-positive results. It is important to note that in addition to the correlation between NST item "sit still, restless, or hyperactive" and the clinical group, analysis using Pearson's correlation revealed that the mother's level of depression as indicated by her CES-D score showed significant ($0.01< p \leq 0.05$) correlations with endorcement rates for NST items "disobedient at home" (p=0.012) and "lying and cheating" (p= 0.012). The CES-D scores' correlation with other NST items were not significant.

DISCUSSION

The consumption of alcohol in significant amounts by a child's biological mother (a prerequisite for FASD) is often associated with comorbid depression.[22] It is therefore theoretically possible that depression in pregnancy, its therapies, as well as maternal depression during the early years of a child's life may adversely affect a child's behaviours. Previous research from the Motherisk Program has shown that maternal depression during the early years is associated with lower cognitive achievements.[23] Also of note, because a child's mother is typically within the child's immediate environment, maternal depression may lead the mother to respond differently, initiate less, and thus, adversely affect the child's emotional development.[24]

The present study was designed to examine whether maternal depression, evidenced by clinical diagnosis and use of antidepressant drugs, may be associated with the combination of behaviours typically displayed by children diagnosed with FASD. As not a single child born to and raised by a mother suffering from depression tested positive on the screen, this finding strongly suggests that maternal depression does not significantly affect the NST's validity as a screening tool, and further corroborates is specificity. Many women suffering from depression also suffer from various degrees of anxiety[23]. Although our analysis concentrated on the depressive symptomatology, these results may also indicate that maternal anxiety too does not contribute substantially to the NST score. Further studies are needed to examine the potential effects of other maternal psychopathologies on the screening results rendered by the NST.

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Conflict of Interest Statement

The authors declare no conflict of interest related to this article.

Corresponding Author: gkoren@sickkids.ca

REFERENCES

1. Streissguth AP, Bookstein FL, Barr HM, Sampson PD, O'Malley K, Young JK. Risk factors for adverse life outcomes in fetal alcohol syndrome and fetal alcohol effects. J Dev Behav Pediatr 2004;25:228–238.
2. Jacobson SW, Jacobson JL, Sokol RJ, Chiodo LM, Corobana R. Maternal age, alcohol abuse history, and quality of parenting as moderators of the effects of prenatal alcohol exposure on 7.5-year intellectual function. Alcohol Clin Exp Res 2004;28(11):1732–1745.
3. Rasmussen C. Executive functioning and working memory in fetal alcohol spectrum disorder. Alcohol Clin Exp Res 2005;29(8):1359–1367.
4. Mattson SN, Riley EP. Parent Ratings of Behavior in Children with Heavy Prenatal Alcohol Exposure and IQ-Matched Controls. Alcohol Clin Exp Res 2000;24(2):226–231.
5. Niccols A. Fetal alcohol syndrome and the developing socio-emotional brain. Brain Cogn 2007;65(1):135–142.

6. O'Malley KD, Nanson J. Clinical implications of a link between fetal alcohol spectrum disorder and attention-deficit hyperactivity disorder. Can J Psychiatry Rev Can Psychiatr 2002;47(4):349–354.
7. Oesterheld JR, Kofoed L, Tervo R, Fogas B, Wilson A, Fiechtner H. Effectiveness of methylphenidate in Native American children with fetal alcohol syndrome and attention deficit/hyperactivity disorder: a controlled pilot study. J Child Adolesc Psychopharmacol 1998;8(1):39–48.
8. Steinhausen HC, Willms J, Spohr HL. Long-term psychopathological and cognitive outcome of children with fetal alcohol syndrome. J Am Acad Child Adolesc Psychiatry 1993;32:990–994.
9. O'Connor MJ, Shah B, Whaley S, Cronin P, Gunderson B, Graham J. Psychiatric illness in a clinical sample of children with prenatal alcohol exposure. Am J Drug Alcohol Abuse 2002;28:743–754.
10. Famy C, Streissguth AP, Unis AS. Mental illness in adults with fetal alcohol syndrome or fetal alcohol effects. Am J Psychiatry 1998;155:552–554.
11. Achenbach T, Rescolora A. Child Behavior Checklist for 6-18 Years. 2001. Available at: http://www.aseba.org/forms/schoolagecbcl.pdf.
12. Nash K, Rovet J, Greenbaum R, Fantus E, Nulman I, Koren G. Identifying the behavioural phenotype in fetal alcohol spectrum disorder: sensitivity, specificity and screening potential. Arch Womens Ment Health 2006;9(4):181–186.
13. Goh YI, Chudley AE, Clarren SK, et al. Development of Canadian screening tools for fetal alcohol spectrum disorder. Can J Clin Pharmacol J Can Pharmacol Clin 2008;15 (2):e344–e366.
14. Nash K, Koren G, Rovet J. A differential approach for examining the behavioural phenotype of fetal alcohol spectrum disorders. J Popul Ther Clin Pharmacol 2012;18(3):e440–453.
15. Fryer SL, McGee CL, Matt GE, Riley EP, Mattson SN. Evaluation of psychopathological conditions in children with heavy prenatal alcohol exposure. Pediatrics 2007;119:e733–e741.
16. Greenbaum RL, Stevens SA, Nash K, Koren G, Rovet J. Social cognitive and emotion processing abilities of children with fetal alcohol spectrum disorders: a comparison with attention deficit hyperactivity disorder. Alcohol Clin Exp Res 2009;33(10):1656–1670.
17. Rasmussen C, Talwar V, Loomes C, Andrew G. Brief report: lie-telling in children with fetal alcohol spectrum disorder. J Pediatr Psychol 2008;33(2):220–225.
18. Nash K, Stevens S, Rovet J, Fantus E, Nulman I, Sorbara D, Koren G. Towards identifying a characteristic neuropsychological profile for fetal alcohol spectrum disorders. Analysis of the Motherisk FASD clinic. J Popul Ther Clin Pharmacol 2013;20(1):e44-52.
19. Stevens SA, Nash K, Fantus E, Nulman I, Rovet J, Koren G. Towards identifying a characteristic neuropsychological profile for fetal alcohol spectrum disorders. 2. Specific caregiver-and teacher-rating. J Popul Ther Clin Pharmacol 2013;20(1):e53-62.
20. Thomas SE, Kelly SJ, Mattson SN, Riley EP. Comparison of social abilities of children with fetal alcohol syndrome to those of children with similar IQ scores and normal controls. Alcohol Clin Exp Res 1998;22(2):528–533.
21. LaFrance MA, McLachlan K, Nash K, Andrew G, Loock C, Oberlander TF, Koren G, Rasmussen C. Evaluation of the neurobehavioural screening tool in children with fetal alcohol spectrum disorders (FASD). J Popul Ther Clin Pharmacol 2014;21(2):e197-210. Epub 2014 May.
22. Procopio DO, Saba L, Walter H, Lesch O, Skala K, Schlaff G, et al. Genetic markers of co-morbid depression and alcoholism in women. Alcohol Clin Exp Res 2013;37:894-904.
23. Nulman I, Rovet J, Stewart DE, Wolpin J, Pace-Asciak P, Shuhaiber S, Koren G. Child development following exposure to tricyclic antidepressants or fluoxetine throughout fetal life: a prospective, controlled study. Am J Psychiatry 2002 Nov;159(11):1889-95.
24. Beeber LS, Schwartz TA, Martinez MI, Holditch-Davis D, Bledsoe SE, Canuso R, Lewis VS. Depressive symptoms and compromised parenting in low-income mothers of infants and toddlers: distal and proximal risks. Res Nurs Health 2014;37(4):276-91.