Long-term Neurodevelopment of Children Exposed to Maternal Nausea and Vomiting of Pregnancy and Diclectin

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Objective To determine the effects of nausea and vomiting of pregnancy (NVP) and its treatment with diclectin on child neurodevelopment.

Study design An observational cohort study of mother-child pairs ascertained via a pregnancy call-in center was conducted. Three groups of children were studied: 45 with NVP and diclectin, 47 with NVP no diclectin, and 29 with no NVP. Phone calls to mothers during pregnancy and 6 to 9 months after childbirth yielded information on pregnancy, birth, and early child development. Children aged 3 to 7 years received a comprehensive set of psychological tests. Mothers were assessed for IQ and socioeconomic status.

Results All children scored in the normal range for IQ, with the NVP-exposed group scoring higher than the non-exposed group on Performance IQ ($P < .02$), NEPSY Verbal Fluency ($P < .003$) and Phonological Processing ($P < .004$), and McCarthy Numerical Memory ($P < .004$). Predictors of enhanced results were NVP severity and maternal IQ.

Conclusions NVP has an enhancing effect on later child outcome. Diclectin does not appear to adversely affect fetal brain development and can be used to control NVP when clinically indicated. *(J Pediatr 2009;155:45-50)*.

See related article, p 39

Nausea and vomiting of pregnancy (NVP) is a poorly understood phenomenon seen in as much as 80% of pregnancies, with symptoms peaking between 5 and 12 weeks gestation.[1] Although self-limited, NVP may have an unfavorable impact on women's health. Approximately one-half to two percent of pregnant women experience the most severe form of NVP, hyperemesis gravidarum (HG),[2] which is defined as persistent vomiting not related to other causes that may interfere with nutrition and fluid intake. HG is associated with ketonuria, electrolyte imbalance, dehydration, and weight loss.[3-5] It is additionally associated with childhood behavioral difficulties in offspring.[6]

HG, the most common reason for hospitalization in the first trimester of pregnancy, may be prevented with timely treatment with anti-emetic drugs.[7] In Canada, the only approved anti-emetic drug for use in pregnancy is diclectin, which contains 10 mg each of doxylamine and vitamin B6 in a delayed-release formulary. Separately, these components are used worldwide to control NVP.

It has been postulated that NVP, which is a byproduct of altered secretion of hormones (namely human chorionic gonadotropin and thyroxine) to ensure adequate placental growth, is a marker for fetal protection deemed the "Maternal and Embryo Protection Hypothesis."[7-10] NVP is associated with favorable fetal outcomes, including reduced rates of miscarriage, stillbirth, preterm birth, intrauterine growth retardation, and congenital malformations.[4,11-16]

Although these findings suggest an early protective benefit of NVP, the effects of NVP on long-term child neurodevelopment, particularly intelligence and specific cognitive skills, have not been directly investigated. Shapiro et al (1977) examined the effect of treatment for NVP with doxylamine succinate and reported neither an increased rate of congenital malformations nor reduced IQ scores in 4-year-old children.[17] This study was not designed to directly assess neurocognitive development or subtle cognitive functions and only addressed the effect of treatment, not the effect of NVP. In contrast, NVP in late pregnancy has been found to be associated with effects on child's emotions, increased motor activity, and attention and learning problems in school-age children.[6]

CBCL	Child Behavior Checklist
CES-D	Center for Epidemiologic Studies Depressed Mood Scale
FSIQ	Full-scale IQ
HG	Hyperemesis gravidarum
HSC	Hospital for Sick Children
NVP	Nausea and vomiting of pregnancy
PIQ	Performance IQ
PUQE	Pregnancy-unique quantification of emesis and nausea
SES	Socioeconomic status
VIQ	Verbal IQ
WASI	Wechsler Abbreviated Scale of Intelligence
WPPSI	Wechsler Preschool and Primary Scale of Intelligence
WRAVMA	Wide Range Assessment of Visual Motor Abilities

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A study designed to assess the neurodevelopment of children exposed to maternal NVP independent of pharmacotherapy with formal standardized tests has not been preformed. Therefore, the primary objective of this study was to determine the effect of maternal NVP on child's long-term neurodevelopment.

Methods

We conducted an observational cohort of children ascertained through a prospectively collected database.

Participants were recruited through the database of women who called the Toronto Motherisk NVP hot-line, an information and counseling service for women and healthcare professionals on NVP and treatment safety. During initial calls, counselors asked expectant mothers about their medical (co-morbidities and use of medications, alcohol, and tobacco) and obstetric histories, including information on the severity and duration of NVP, defined as the presence of nausea, vomiting, and/or retching before 20 weeks gestation without underlying pathology. Weekly follow-ups documented the treatment (number of diclectin tablets) and clinical presentation of NVP. Additional information on NVP treatment, severity, and duration was received from the physicians who treated the mothers. Also as part of the Motherisk protocol, women were interviewed 6 to 9 months after childbirth to document delivery outcomes and child developmental milestones.

The NVP Motherisk database from 1998 to 2003 was searched to identify mother-child pairs who met study inclusion criteria. Help-line callers who inquired about non-teratogens (eg, acetaminophen) and reported no NVP served as control subjects. All 3 groups were matched for maternal age at conception (± 3 years); pregnancy duration (± 2 weeks), child sex, and child age at testing (± 6 months).

The study cohorts were 3 groups of mother-child pairs: group 1, NVP treated with diclectin; group 2, NVP, no diclectin; and group 3, no NVP. Women exposed to teratogens (eg,isotretinoin, anti-epileptics, alcohol), treated for NVP with poly-pharmacotherapy, with co-morbidities (eg, thyroid disease, epilepsy), or multiple gestations were excluded. Mothers and children were excluded for inadequate English proficiency. Children were excluded after head injury, central nervous system infections, or metabolic disorders.

Women were contacted by letter and a follow-up phone call to discuss participation and to schedule an appointment for a medical and psychological assessment at the Hospital for Sick Children (HSC) in Toronto. After approval from the research ethics board and receipt of informed consents/assents, mother and child were assessed by a psychometrist under the supervision of a licensed psychologist, both of whom were masked to the study group.

Tests and Measures

Children aged 3 to 7 years were assessed with a comprehensive battery of standardized age-appropriate psychological tests, including measures of intelligence, selective neurocognitive abilities, and behavior that were previously shown to detect effectively subtle neurocognitive deficits and behavior problems in the presence of intact intellectual functioning.[18-20] Maternal IQ and socioeconomic status (SES) were assessed as potential confounders to the child outcome measures.

Children's intelligence was evaluated with the Wechsler Preschool and Primary Scale of Intelligence–Revised (WPPSI-R)[21] or the Wechsler Preschool and Primary Scale of Intelligence, Third Edition (WPPSI-III),[22] which provided an index of Verbal IQ (VIQ), Performance IQ (PIQ), and Full-Scale IQ (FSIQ). Children also underwent: 6 NEPSY subtests (Visual Attention, Verbal Fluency, Comprehension of Instructions, Visuomotor Precision, Sentence Repetition, Narrative Memory); the Preschool Language Scale (PLS-III or PLS-IV); the Beery Developmental Test of Visual-Motor Integration (VMI); Wide Range Assessment of Visual Motor Abilities (WRAVMA) Pegboard and Matching subtests, and 3 memory subtests of McCarthy Scales of Children's Abilities (Pictorial Memory and Forward and Backward Numerical Memory).[23-28] All tests administered were applicable to the range of ages in the study cohort. In addition, mothers completed the Child Behavior Checklist (CBCL) and Conner's Parent Rating Scale questionnaires to assess child behavior and attention problems for children aged 3 to 17 years. The physician also assessed children's general health, weight, height, and head circumference.[29,30]

Maternal FSIQ was determined with the Vocabulary and Matrix Reasoning subtests of Wechsler Abbreviated Scale of Intelligence (WASI).[31] SES was measured with the Hollingshead Four Factor Index, which provides a 5-point social class ranking (1 = high, 5 = low) on the basis of parents' education and employment. [32]

NVP was also rated by the mothers with the Pregnancy-Unique Quantification of Emesis and Nausea (PUQE) scoring system, which uses a 5-point scale to categorize degrees of nausea, vomiting, or retching. These scores are summed to determine the women's total PUQE score, which is then categorized as mild (0-6), moderate (7-12), or severe (13+).[33]

Statistical Analysis

The 3 groups were compared with an analysis of variance model to detect any differences on the main outcomes. Similarly, *t* tests were used for 2 group comparisons. Baseline comparisons of the 3 groups were also conducted for all variables of interest with analysis of variance, followed by a post-hoc Bonferroni analysis with SPSS software version 16 (SPSS, Chicago, Illinois). Imputation of missing data and sensitivity analysis (with best case–worst case) were performed when >5% of data were missing for any variable. Regression models were built to compare the 3 groups on each outcome of interest, while adjusting for age and sex.

Results

Of the 178 women identified and who consented for follow-up, 25 could not be located, 18 were excluded for use of anti-

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