

Effect of hyperemesis gravidarum on child neurodevelopment

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REVIEW

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ABSTRACT

Background

Pregnancy outcome following hyperemesis gravidarum (HG) has been sparsely reported. This review article aims at critically reviewing the first prospective study of foetal long-term neurodevelopment after maternal HG.

Aims

This review aimed at critically appraising the first prospective human study that aimed at investigating long term child neurodevelopment after exposure to maternal HG.

Methods

In this study, women with nausea and vomiting of pregnancy treated with doxylamine–pyridoxine (Diclectin) or with no pharmacotherapy were prospectively recruited. Their children (ages 3 6/12 to 6 11/12 years) were assessed for development using standardized psychological tests. The study cohort was divided into 2 groups: 1) severe NVP necessitating hospitalization of the woman for rehydration and electrolyte corrections (n=22) and 2) all other cases of nausea and vomiting of pregnancy (n=197).

Results

Children of hospitalized mothers achieved significantly lower IQ scores than the rest of the children on verbal, performance and full scale IQ. In multivariable linear regression duration of hospitalization, maternal depression and maternal IQ were significant predictors for these outcomes.

Conclusion

This first prospective human study documented that HG is associated with an increased risk for lower cognitive outcome among HG- exposed offspring. More research is needed to examine whether early use of anti-emetics may prevent hospitalization, leading to favourable child neurodevelopment.

Key Words

Nausea and vomiting of pregnancy, hyperemesis gravidarum, child development, nutritional deficits

What this study adds:

1. What is known about this subject?

HG affects women's health and their quality of life.

2. What new information is offered in this study?

This critical review suggests that HG increases risk of adverse effect on foetal brain function.

3. What are the implications for research, policy, or practice?

Prevention of HG and its nutritional deficits must be approached much more aggressively.

Background

Nausea and vomiting of pregnancy (NVP) affects up to 85 per cent of pregnant women^{1,2} and its severe end, hyperemesis gravidarum (HG), affecting up to 2 per cent of pregnant women² is typically associated with weight loss greater than 5 per cent of pre-pregnancy weight, dehydration, electrolyte imbalances, need for

hospitalization and nutritional deficiencies.¹⁻⁶

Studies in children born in areas of famine in Netherland and China reveal long term adverse effects on foetal brain neurodevelopment,^{7,8} raising concerns that children exposed in utero to HG may also be adversely impacted due to prolonged deficiencies of nutrients essential for brain development.

Method

We critically reviewed the report by Nulman et al. for methodological advantages, challenges and biological plausibility.⁹

Study setting

The study was conducted by the Motherisk Program in Toronto, an information and consultation service for women, their families and health professionals regarding exposure to drugs, chemicals, radiation, and infectious agents during pregnancy and lactation. Women with NVP were counselled through a special line dedicated to morning sickness, where they were advised on management of their symptoms. In addition, they were invited after 3 years of age to formally assess child development by a team of psychologists.

Selection of patients

For the purpose of the present study, two groups of mother-child pairs were analysed:

1) Mother- child pairs where the mothers needed to be hospitalized for severe symptoms of NVP. 2) All other women counselled for NVP. The investigators excluded from the study women in whom known teratogens were used during the pregnancy, and those who were unwilling to participate in the follow-up program. All patients were assembled prospectively, before pregnancy outcome was known. This obviates the bias that may be created by retrospective cases, where pregnancy outcome is already known. Retrospective studies are often represented by more cases of adverse events.¹⁰

Assessments

Antenatal assessment

At the diagnosis of pregnancy or soon after, the team obtained medical and obstetric history, data on alcohol consumption, use of medicinal and recreational drugs, smoking, medical history and sexually transmitted diseases.

Postnatal assessment

Six to nine months after delivery the mother was questioned about the course of her pregnancy and the

duration of NVP, the drugs used for treatment, the dose of the drugs, and perinatal complications. Details about the type of delivery and attainment of the child reaching developmental milestones were recorded.

Neurobehavioral testing

To assess neurocognitive development, children (ages 3 6/12 to 6 11/12 years) were assessed using the standardized Wechsler Intelligence Scale for Children (WISC-R) test. The WISC generates a Full Scale IQ, representing a child's general intellectual ability. It also provides five primary index scores: Verbal Comprehension Index, Visual Spatial Index, Fluid Reasoning Index, Working Memory Index, and Processing Speed Index. These indices represent a child's abilities in discrete cognitive domains.¹¹ Maternal IQ was assessed with the Wechsler Adult Intelligence Scale-Revised.¹² The mother's level of depression at the time of HG was evaluated with the Edinburgh scale.¹³

The worst severity of symptoms of NVP was measured by the validated Pregnancy Unique Quantification of Emesis (PUQE) score,¹⁴ which combines the scoring of nausea, vomiting and retching. Antiemetic dose of Diclectin (doxylamine 10mg- pyridoxine 10mg delayed release combination), severity of NVP symptoms, hospitalization for NVP, concomitant medications, severity of maternal depression, and maternal intelligence quotient (IQ) were all recorded.

Data analysis

The two groups (hospitalized women with NVP vs. all other NVP cases) were compared on continuous variables by Mann Whitney U test, and with Chi square for dichotomous variables. Subsequently multivariable linear regression was used to adjust for potential confounders.

Results

In this prospective study,⁹ twenty-two women were hospitalized for severe NVP and 219 women with NVP were not hospitalized. The two groups of women had similar rates of smoking and alcohol consumption, of sexually transmitted diseases and perinatal complications. As expected, the hospitalized women initiated recommended antiemetic drugs significantly later [median 6.8 compared with 5.7 weeks of gestation, $P=0.02$], experienced more severe nausea and vomiting of pregnancy [median PUQE score 11.1 out of 15 compared with 7.5 out of 15, $P<0.001$], and more severe depression [median Edinburgh score 10.1 compared with 5.1, $P=0.03$]. They also needed significantly higher median daily doses of Diclectin (1.0 compared with 0.4mg/kg per day, $P<0.001$) (Table 1).

Children of hospitalized mothers achieved significantly lower median IQ scores (verbal 107.2 compared with 112.7, $P=0.04$; performance 105.6 compared with 112.3, $P=0.03$; full scale 108.7 compared with 114.2, $P=0.05$ (Table 1)). In multivariable linear regression, the duration of hospitalization, maternal depression, and maternal IQ were significant predictors for these outcomes. Daily intake of Diclectin was not associated with any adverse outcomes.

Discussion

The study by Nulman et al.⁹ is to date the only prospective published study on child development after exposure to HG during pregnancy. It suggests that in women with insufficiently- managed HG, there is an apparent increased foetal risk for adverse neurodevelopment. The study concurs with a retrospective observational study from California, which reported neurodevelopmental outcome of 312 children born to 203 mothers with HG as compared to 169 children conceived by 89 women with no HG.¹⁵ Children exposed to HG had an odds ratio of 3.8 (95 per cent CI 1.56–11.55) for attention deficit hyperactivity disorder, OR of 4.02 (95 per cent CI 1.36–17.24) for learning difficulties, and 2.5 (95 per cent CI 1.43–31.83) for speech or language impairment. Only early onset of HG symptoms (prior to five weeks gestation) was associated with neurodevelopmental delay. These data, based on parental response to a questionnaire, concurred that common antiemetic treatments have not been associated with developmental delay, whereas early symptoms of HG may play such a role. In an additional study, Mulin and colleagues have shown in a retrospective design that neuropsychological deficits associated with HG can be documented in the offspring during adulthood.¹⁶

Potential strengths of the Nulman's study include a prospective study design, which obviated the potential bias encountered in retrospective recruitment,¹⁰ where typically there may be over representation of adverse cases. Importantly, Nulman's study did not base its observations on maternal questionnaires, but rather executed direct measures of child and maternal IQ, as well as validated measure of severity of morning sickness. The mothers of both groups were otherwise healthy women, with normal expected ranges of IQ. Hence the lower IQ achievements of the children are very likely caused by HG and not by any maternal confounder. Both Nulman's⁹ and Fezjo's study¹⁵ did not confirm an adverse effect on cognition by the medications used.

A potential challenge of Nulman's study is the relatively small numbers of hospitalized women with severe NVP. Yet,

this relatively small sample size was sufficiently powered to show significant differences in child IQ when compared to women with NVP who did not need hospitalization.

HG causes prolonged periods of maternal malnutrition and starvation characterized by severe shortage of numerous nutritional elements needed for optimal foetal brain development.¹⁶ These include caloric restriction, lack of optimal protein intake, shortage in vitamin B12, vitamin B1 deficiency, restricted maternal choline intake, vitamin C shortage, iodine and folate deficiency, lack of copper, restricted maternal iron intake, and shortage in dietary zinc.

Because NVP occurs in up to 85 per cent of women, and up to 2 per cent of them experience HG, at least 1 per cent of unborn babies are expected to be exposed to HG. Hence, a cognitive decrease of 5–7 points IQ would translate into large economic loss, as a result of the effects on child intellectual performance.¹⁷

Conclusion

This dramatic observation transforms HG from a condition that was largely reviewed as impacting women's quality of life to an event that inflicts serious adverse effects on foetal brain development. More research is needed to confirm these findings and address the long term outcome of HG-exposed offspring. However, presently there is no centre worldwide conducting prospective cognitive developmental follow up studies in NVP or HG, and it is likely that Nulman's study will remain a major compass in informing clinicians and regulators. As NVP affects 85 per cent of pregnant women, research in this field must gain higher priority among professional societies, regulators and the pharmaceutical industry to minimize these long term effects.

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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PEER REVIEW

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Table 1: Comparison of maternal characteristics and median child IQ between pregnancies exposed to hospitalization and control non hospitalized NVP cases

	Hospitalized NVP women	No hospitalization	P
	(n=22)	(n=219)	
Time antiemetics started (median wks)	6.8	5.7	0.02
PUQE score (median)	11.1	7.5	<0.001
Edinburgh score (median)	10.1	5.1	0.03
Dose of Diclectin (mg/kg/d)	1	0.4	<0.001
Child verbal IQ	107.2	112.7	0.04
Child performance IQ	105.6	112.3	0.03
Child Full scale IQ	108.7	114.2	0.05