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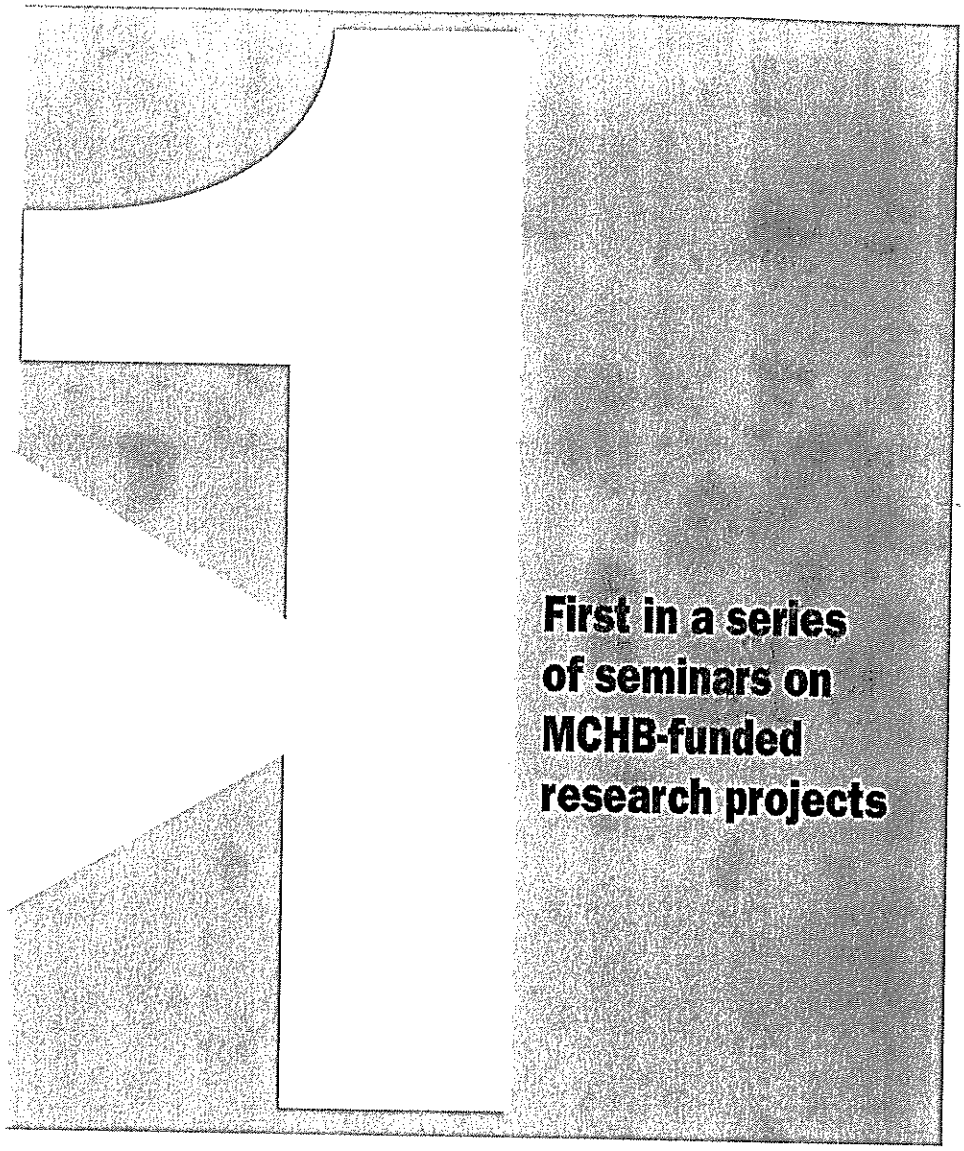
Research Roundtable



December 9, 1992 ☞ 1:00 to 2:30 pm
Parklawn Building, Conference Room L

Periconceptional Vitamin Use and Neural Tube Defects

Speaker: **Allen A. Mitchell, M.D.** ▫ **Research Professor of Epidemiology**
Slone Epidemiology Unit, Boston University School of Medicine
Reactor: **To be announced**

RSVP to Shelley Spisak at the National Center for Education in Maternal and Child Health (703) 524-7802.
Bring your lunch and enjoy the coffee and dessert provided.

Preconceptional Vitamin Use and Neural Tube Defects

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Research
MCJ-250567
03/01/88–02/28/92
Project Director(s):
Allen A. Mitchell, M.D.

STATEMENT OF THE PROBLEM: Birth defects resulting from abnormal development of the embryonic brain and spinal cord are among the most traumatic birth defects, to both families and society. Collectively known as neural tube defects (NTDs), they include anencephaly (absent brain and skull) and spina bifida (various degrees of involvement of the spinal cord [myelomeningocele] and/or the surrounding tissues [meningocele]).

NTDs are relatively common birth defects, affecting approximately 1.5 per thousand births. Perhaps more important than the absolute numbers of affected infants is the burden they create for society in general and for the health care delivery system in particular. While NTDs include some defects that are of relatively minor consequence, and some that are incompatible with life, the large proportion of NTDs present serious and persistent medical and functional disabilities.

The etiology for the large majority of NTDs is unknown, though it is widely believed that they are of multifactorial origin. Based on experiments in animals and observations in women who previously had an NTD-affected pregnancy, it has been suggested that women who supplemented their diets with multivitamins before conception would reduce by at least 50% their risk of having another NTD-affected pregnancy. In addition, although the evidence regarding preconceptional vitamin supplementation concerns only recurrent NTDs, it is generally assumed that occurrent NTDs might also be reduced by such supplementation. However, the potential risks of a massive preconceptional vitamin supplementation effort among women of childbearing potential must be considered. Specifically, the risk of actually increasing birth defects cannot be ruled out.

This situation requires resolution as rapidly as possible. We believe the most rapid, efficient, and feasible approach is a case-control study specifically designed to examine the potential benefit of preconceptional vitamin supplementation with respect to NTDs and, secondarily, to examine some of the potential hazards of excessive supplementation.

RESEARCH QUESTIONS OR HYPOTHESES:
Primary hypotheses:
(a) Multivitamin supplementation in the month immediately preceding the last menstrual period (LMP) is associated with a 50% reduction in NTDs.
(b) Folate supplementation in the month immediately preceding the LMP is associated with a 50% reduction in NTDs.

Secondary hypothesis: Excessive supplementation with vitamins or minerals in the month preceding or including conception, or in the months following conception, increases the risk of selected birth defects.

This hypothesis is deliberately stated in broad terms. We will examine the collected data to test the existing hypothesis that excessive vitamin A supplementation is associated with increased risks of craniofacial malformations, heart defects, and brain defects. Also, we will systematically review categories of specific defects to identify new hypotheses regarding excessive supplementation and birth defects.

STUDY DESIGN AND METHODS: The present study follows the case-control approach to: (1) Evaluate the relationship between NTDs and preconceptional multivitamin and/or folate supplementation; and (2) identify possible risks of specific birth defects in relation to excessive vitamin/mineral supplementation before and during pregnancy. A common data set will be used for both objectives.

Study subjects (cases and controls) are recruited through an active surveillance network of hospitals and clinics in the metropolitan areas of Boston, Philadelphia, and Toronto. Cases and controls consist of malformed infants and fetuses, and include liveborn infants under six months of age, stillborn infants, and therapeutic abortions (TAbs).

For the first hypothesis, cases are subjects with NTDs and controls are subjects with other malformations. The distribution of defects in the control series will approximate that found in the general population. Since pregnancies complicated by fetal malformation may be terminated by therapeutic abortion, it is important that the case series include NTDs which are electively aborted (and therefore, that the control series include other malformations from the same setting). Vitamin supplementation may be related to socioeconomic status and health behaviors, which are likely to be associated with both the opportunity for prenatal diagnosis and the decision to undergo a TAb. For these reasons, NTDs which have been electively aborted are included in the study sample, along with their respective controls.

For the secondary hypothesis, there are various case groups. To test the hypothesis that excess vitamin A intake is teratogenic, case series include subjects with specific craniofacial, heart, and brain defects. To consider possible effects of excessive supplementation with other vitamins and minerals, additional case series include craniosynostosis and aortic stenosis. In these comparisons, controls will consist of malformed subjects (with appropriate exclusions) not included in the respective case series.

A malformed control series is used in an effort to reduce the likelihood of recall bias, assuming that the accuracy of exposure reporting by mothers of malformed infants is different than that by mothers of normal infants.

Because it is important that bias not be introduced in our selection of cases and controls, we identify and enroll all study subjects in an identical fashion. In addition, controls are ascertained from the same institutions as cases.

Information on exposure to vitamins and minerals is obtained by interview of the mother. The nurse-interviewer in each study center sends an introductory letter to the mothers of designated subjects, followed by a telephone call. Informed consent is obtained prior to the interview, which is conducted in the woman's home at a time convenient to her. Interviews are done at home because we believe this setting is more relaxed and less threatening; it also affords the nurse the opportunity to examine available medication bottles. Interviews are conducted between three to six months after delivery.

The questionnaire, which takes approximately 45 minutes to administer, includes data on vitamin and mineral supplementation, as well as other factors which may be related to supplementation or to the risk of NTDs or other birth defects.

POPULATION DESCRIPTION AND SAMPLING PLAN: All mothers of infants (or fetuses) with major birth defects identified within six months of age and residing within the catchment area are eligible for inclusion in the study with the following exceptions: non-English-speaking women without a translator are excluded because our interviewers are English-speaking only; women who have given up the study child for adoption are excluded for social reasons; and women who have previously been interviewed for our Birth Defects Study are excluded to reduce the potential for information bias.

The mothers of approximately 350 subjects with NTDs and 1900 subjects with other major birth defects will be interviewed. Ten percent of these mothers are estimated to be 20 years old

or younger and 10 percent are estimated to be over 35 years of age. Approximately 15 percent of mothers will have less than a high school education and approximately 30 percent will have a college degree. The estimated racial distribution of the mothers is 90 percent white, 5 percent black, and 5 percent other races.

ANALYSIS PLAN: Frequency distributions and cross-tabulations by outcome of all variables will be generated. Odds ratios and test-based 95% confidence intervals (alpha=.05, two-tailed) will be calculated to test and estimate associations for the relevant exposure variables. Potential confounding effects of other factors will be assessed in a univariate manner by the Mantel-Haenszel procedure; each adjusted odds ratio will be compared to the crude estimate. Logistic regression, using the method of maximum likelihood, will allow estimation of odds ratios and confidence intervals while adjusting for the joint effects of potential confounders. The multivariate regression model will include terms for known risk factors for the outcome, as well as those factors which alter the crude odds ratio when controlled in a univariate manner.

For all relationships observed, effect modification among subgroups of women will be examined, using two approaches. First, separate logistic regression procedures will be carried out for subpopulations of interest. Second, indicator terms will be created which represent all combinations of independent variables for which interaction is of interest.

Trends in associations will be examined by the Mantel extension test and by logistic regression modeling.

Primary Hypothesis: Vitamin supplementation and NTDs.
The outcome variable will be created from each infant's diagnostic codes (up to four diagnoses are recorded). The case group will include infants with NTDs and the control group will include infants with malformations other than NTDs. Infants with malformations possibly associated with vitamin use, or found to be associated with vitamin use in the data, will be excluded from the control group.

Information regarding the exposure period (in relation to the LMP and pregnancy) and frequency of vitamin use will be used to create the primary exposure groups. Preconceptional multivitamin users will be compared to non-users of multivitamins to assess an overall multivitamin effect. The group of multivitamin users will then be divided into two groups: users of multivitamins with folate, and users of multivitamins without folate; each will be compared to non-users of multivitamins. Separate effects, if any, of multivitamins and the folate component of multivitamins will be identified by these two comparisons.

The potential confounding effects of many maternal characteristics and demographic factors will be evaluated. Particular concern will be focused on confounding by socioeconomic status, ethnicity, family history of NTDs, and a variety of health behaviors. Logistic regression will be used to estimate the relative risk for preconceptional vitamin use while simultaneously adjusting for these effects. Other measures of vitamin use, such as dose and duration, are also of interest and will be compared among cases and controls.

Secondary Hypothesis: Excess vitamin supplementation and specific birth defects.
We will examine the data for possible associations between excess vitamin/mineral supplementation and birth defects. One specific hypothesis concerns excess vitamin A intake during the first trimester in relation to certain cardiac, craniofacial (including oral clefts), and brain malformations. Other suggested associations between excess supplementation and certain malformations will also be explored, such as high calcium and/or vitamin D supplementation in relation to craniosynostosis or aortic stenosis, and excess folate, iron, and/or calcium supplementation in relation to NTDs or other malformations. For each vitamin and mineral component, the dose, frequency, and duration of use will be taken into account in the creation of exposure categories.