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MORNING SICKNESS: A MECHANISM FOR PROTECTING MOTHER AND EMBRYO

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ABSTRACT

Approximately two-thirds of women experience nausea or vomiting during the first trimester of pregnancy. These symptoms are commonly known as morning sickness. Hook (1976) and Profet (1988) hypothesized that morning sickness protects the embryo by causing pregnant women to physically expel and subsequently avoid foods that contain teratogenic and abortifacient chemicals, especially toxic chemicals in strong-tasting vegetables, caffeinated beverages and alcohol. We examined this hypothesis by comprehensively reviewing the relevant medical, psychological and anthropological literature. In its support, (i) symptoms peak when embryonic organogenesis is most susceptible to chemical disruption (weeks 6–18), (ii) women who experience morning sickness are significantly less likely to miscarry than women who do not (9 of 9 studies), (iii) women who vomit suffer fewer miscarriages than those who experience nausea alone, and (iv) many pregnant women have aversions to alcoholic and nonalcoholic (mostly caffeinated) beverages and strong-tasting vegetables, especially during the first trimester. Surprisingly, however, the greatest aversions are to meats, fish, poultry, and eggs. A cross-cultural analysis using the Human Relations Area Files revealed 20 traditional societies in which morning sickness has been observed and seven in which it has never been observed. The latter were significantly less likely to have animal products as dietary staples and significantly more likely to have only plants (primarily corn) as staples than the 20 societies in which morning sickness occurred. Animal products may be dangerous to pregnant women and their embryos because they often contain parasites and pathogens, especially when stored at room temperatures in warm climates. Avoiding foodborne microorganisms is

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particularly important to pregnant women because they are immunosuppressed, presumably to reduce the chances of rejecting tissues of their own offspring (Haig 1993). As a result, pregnant women are more vulnerable to serious, often deadly infections. We hypothesize that morning sickness causes women to avoid foods that might be dangerous to themselves or their embryos, especially foods that, prior to widespread refrigeration, were likely to be heavily laden with microorganisms and their toxins. The alternative hypotheses that morning sickness is (i) an epiphenomenon of mother-offspring genetic conflict or hormones associated with viable pregnancies, or (ii) an indicator to potential sexual partners and kin that the woman is pregnant, resulting in reduced sexual behavior and increased nepotistic aid, were not well supported. Available data are most consistent with the hypothesis that morning sickness serves an adaptive, prophylactic function.

INTRODUCTION

MORNING SICKNESS is the common term for the nausea and vomiting that most women experience during pregnancy. These symptoms have been recognized for thousands of years. Indeed, the earliest recorded description of vomiting in pregnancy dates from about 2000 BC (Järnfelt-Samsioe et al. 1983).

"Morning sickness" is actually a complete misnomer, however; symptoms generally occur throughout the day, not just in the morning (Vellacott et al. 1988; DiIorio et al. 1992; Whitehead et al. 1992), and the term "sickness" implies pathology, even though healthy women experience the symptoms and bear healthy babies (Nesse and Williams 1994). For these reasons, other, more accurate terms have been used to describe morning sickness, including:

(i) Emesis gravidarum. Järnfelt-Samsioe (1987:422) defines this as "nausea alone or the combination of nausea, retching, and occasional vomiting in early pregnancy."

(ii) Pregnancy sickness. Profet (1992:327) calls this "a collection of symptoms—food aversions, nausea, and vomiting—one or all of which occur in women during the first trimester of pregnancy."

(iii) Nausea and vomiting in pregnancy (NVP). According to Fairweather (1968: 135, quoting the 1956 American Council on Pharmacy and Chemistry), this is nausea or vomiting that is "commonly observed during the first 14 or 16 weeks [of pregnancy] and characterized by some disturbance in appetite and reaction to food in a fairly large percentage of cases," but that is not associated with disturbed nutrition.

Of these terms, we favor NVP because it is descriptive, objective, and acknowledged within the medical community.

Why does NVP occur? This question can be addressed from multiple perspectives or "levels of analysis" (Mayr 1961; Tinbergen 1963; Sherman 1988; Alcock and Sherman 1994). Answers to questions about the proximate mechanisms that underlie NVP (i.e., how the symptoms are brought about) and the functional significance of NVP (why the symptoms occur) are complementary, not mutually exclusive. Full understanding requires explanations at both proximate and ultimate levels of analysis. Until recently, however, most research on NVP focused on elucidating its proximate causes in order to discover ways to ameliorate the annoying and sometimes debilitating symptoms.

The neuroendocrine mechanisms underlying NVP have been well studied (reviewed by Andrews and Whitehead 1990). Neural control of nausea and vomiting is coordinated by nuclei in the brainstem. Symptoms are triggered by inputs from two major pathways: the area postrema (the so-called "chemoreceptor trigger zone") and the gastrointestinal afferents. Both pathways are involved in the body's response to ingested toxins. The area postrema also functions in the acquisition of conditioned taste aversions and control of food intake. Although hormonal changes in early pregnancy mediate NVP, no consistent differences in levels of estrogens, progestagens, androgens, cortisol or human chorionic gonadotropin have been demonstrated between women who do and do not experience symptoms. This finding indicates that the hormonal changes function indirectly by activating the neural pathways, rather than being the emetic agents themselves (Walsh et al. 1996).

At the functional level, two questions arise. First, why should hormonal changes make pregnant women more likely to experience nausea and vomiting? Second, is NVP adaptive or pathological? These issues were raised 60

years ago, when Irving (1940:719) reported that "only six of our 225 cases [of pernicious vomiting] miscarried—a frequency of only one in 37.5 cases, as contrasted with the usual expectancy in pregnancy of one in every five or six." Although Irving was actually referring to an extreme and debilitating level of nausea and vomiting known as hyperemesis gravidarum, his surprising results suggested an association between NVP symptoms and positive pregnancy outcomes.

Thirty-six years later, Hook (1976:182) proposed that "NVP (and other symptoms affecting diet) in early pregnancy evolved as a spectrum of response to environmental factors which are selectively toxic (or beneficial) to the fetus." Subsequently, Hook (1978, 1980) explored the possible link between NVP and maternal ingestion of alcohol and caffeinated beverages, as well as the use of tobacco. Following Hook's lead, Profet (1992:328) suggested that "[t]he food aversions, nausea, and vomiting of pregnancy sickness evolved during the course of human evolution to protect the embryo against maternal ingestion of the wide array of teratogens (toxins that cause birth defects) and abortifacients (toxins that induce abortions) abundant in natural foods . . . pregnancy sickness represents a lowering of the usual human threshold of tolerance to toxins in order to compensate for the extreme vulnerability of the embryo to toxins during organogenesis."

Hook (1976, 1978, 1980) and Profet (1988, 1992, 1995) emphasized that the benefits of nausea and vomiting were the expulsion of dangerous foodborne chemicals and the subsequent avoidance of these chemicals via learned aversions to the foods that triggered illness. This "embryo protection" hypothesis is based on the following logic. The chemicals that give many plants their distinctive aromas and flavors evolved to counter the plant's biotic enemies, such as herbivorous insects and vertebrates, fungi, pathogens, and parasites (Ehrlich and Raven 1964; Koul 1993). These substances are known as phytochemicals or secondary compounds because they generally are not essential to the plant's basic or primary metabolism. Humans commonly ingest phytochemicals that occur naturally in vegetables, and also selectively use concentrated phytochemicals in food preparation (spices). Many spices have powerful antimicrobial properties (e.g., Walker 1994; Hirasa and Takemasa 1998), and Billing and Sherman (1998) hypothesized that we use these natural pharmaceuticals to reduce foodborne illnesses and food poisoning by inhibiting microbial and fungal growth and toxin production. These beneficial effects may account for the ubiquity of spice use, especially in hot climates where unrefrigerated foods spoil quickly (Sherman and Billing 1999). However, as Gerber et al. (1999) recently pointed out, too much of a good thing can be harmful. Spices are beneficial in the tiny quantities typically used in cooking, but in large doses many phytochemicals can have deleterious effects as allergens, mutagens, carcinogens, teratogens and abortifacients (Schardein 1985:679–699; Ames et al. 1990a,b; Johns 1990; Shepard 1992; Beier and Nigg 1994). For example, small amounts of chili peppers can yield antimicrobial and therapeutic effects, but ingestion of large amounts of capsaicin has been associated with ulceration, necrosis, and carcinogenesis (Surh and Lee 1996). Likewise, large quantities of caffeine have been associated with spontaneous abortions (Klebanoff et al. 1999). The embryo protection hypothesis proposes that NVP functions to shield the differentiating embryo from these potentially toxic chemicals.

Hook (1976, 1978, 1980) focused on the harmful effects of alcohol, caffeine and tobacco—substances that are often used because of the secondary compounds they contain—whereas Profet (1992) presented an extensive list of common foods that contain potentially embryotoxic chemicals. According to Profet:

> If first-trimester pregnant women develop food aversions because of recalibrated thresholds for detecting and tolerating toxicity, then one would predict that the following foods and beverages would elicit aversions: (a) bitter or pungent foods—indicating high concentrations of plant toxins—such as coffee, tea, vegetables, spices and herbs, and the more pungent or bitter of the alcoholic beverages; (b) foods that emit burnt or fried odors—indicating the creation during cooking of mutagens—such as barbecued, roasted, or fried foods (as opposed to

> boiled foods); and (c) foods that emit smells suggestive of spoilage—indicating parasitization by toxin-producing bacteria—such as animal products that are not extremely fresh . . . On the other hand, one would predict that the best-tolerated foods would be those that have rather bland odors and tastes and that do not spoil easily, such as processed breads, cereals, and grains (1992:346).

Although the embryo protection hypothesis had not been tested rigorously, Profet (1995) published a semipopular book based on the subject, which included specific dietary recommendations for pregnant women. The book, and a subsequent *Scientific American* article about it (Holloway 1996), elicited harsh criticism from Brown et al. (1997), who stated that "claims made in the popular press about food and health relationships should be evaluated by the media as fiction unless supported by scientific research" (p 179). In contrast, Brown et al. recorded the consumption of vegetables among 549 Minnesota women during their first eight weeks of pregnancy: they found that women with and without NVP consumed the same numbers of servings per week of Profet's (1995:150–151) proscribed vegetables, and no relationship between the number of servings consumed per week and "adverse pregnancy outcomes" (miscarriages, fetal deaths or congenital anomalies). However, Brown et al. did not report whether the women who experienced NVP vomited or were nauseated after consuming the proscribed vegetables, whether they avoided those vegetables during the rest of their pregnancies, or whether their pregnancy outcomes differed depending on the occurrence of NVP or food aversions. In addition, many of the vegetables that Brown et al. inquired about were consumed rarely, so there may have been little opportunity for them to affect embryos, or for maternal aversion learning to occur. These omissions are surprising because Brown (1983:59) herself had previously reported that strongly-flavored vegetables and coffee frequently "bring on the feeling of nausea" in pregnancy, and that taste aversions cause pregnant women to eat less of the offending foods (Brown and Toma 1986).

In view of these conflicting claims, and their importance for understanding women's health, we decided to evaluate the causes and reproductive consequences of NVP (see Sherman and Reeve 1997). We have comprehensively reviewed the relevant medical, psychological and anthropological literature, and gathered information to test five critical predictions of the embryo protection hypothesis:

1. NVP should be associated with positive pregnancy outcomes.
2. Foods that trigger NVP should contain teratogens, mutagens and abortifacients.
3. NVP should be more common when the embryo is most sensitive to toxic chemicals.
4. Foods containing toxins should be most aversive to women when embryonic organogenesis is most sensitive to disruption by exogenous chemicals.
5. The frequency of NVP should depend on the diet of a population: symptoms should be uncommon in populations where staple foods rarely contain substances that could damage embryos.

Our results confirmed that NVP is associated with beneficial effects, but not just on the embryo. The data suggest a more comprehensive and specific hypothesis, namely, that NVP protects the embryo from teratogenic phytochemicals and shields both the mother and her developing embryo from foodborne pathogens and their associated toxins. This "maternal and embryo protection hypothesis" is consistent with observed variations in food aversions and cravings, and variations in the occurrence of NVP among individuals and cultures.

METHODS

DEFINITIONS

To avoid ambiguity, we briefly explain our use of some key terminology. "NVP" is nausea alone, or in combination with vomiting, that begins before the 20th week of gestation and is not associated with diseases, infections or allergies. NVP encompasses a continuum of symptoms, from heartburn and mild nausea to frequent vomiting. An extreme level of nausea and vomiting known as "hyperemesis gravidarum" occurs in less than 1% of pregnancies (Tsang et al. 1996); vomiting is so severe that patients are unable to perform daily activities, and even have difficulty sleeping. According to Fairweather (1968:136), hyperemesis gravidarum involves vomiting "of such severity as to require the patient's admission to the hospi-

tal," and, if untreated, it can result in disrupted nutrition, liver damage and ketosis (Erick 1995). To focus on "normal" NVP, we excluded all known or likely studies of hyperemesis gravidarum, based on diagnoses of the original authors and whether or not the subjects required hospitalization.

The age of an embryo can be expressed as either its "postconception age" (i.e., its age relative to the date of conception) or its "postmenstrual age" (its age relative to the mother's last menstrual period). We use the latter, unless otherwise indicated. Assuming that fertilization occurs in the middle of a woman's menstrual cycle, an embryo's postmenstrual age is about two weeks greater than its postconception age (Moore and Persaud 1998). A developing human is an "embryo" from conception to eight weeks of age, and a "fetus" from the ninth week after conception until birth (Moore and Persaud 1998). Our analyses focused on the first trimester (13 weeks) of pregnancy, which straddles the definitional embryo-fetus transition. To avoid confusion, we simply use "embryo" throughout.

"Miscarriage" is embryonic mortality during the first 20 postmenstrual weeks, and "stillbirth" is mortality from postmenstrual week 20 to parturition (Anderson et al. 1994). "Fetal death" is the total mortality attributed to both miscarriages and stillbirths. "Preterm birth" is parturition before the 37th postmenstrual week, and "low birth weight" refers to an infant that weighs < 2.5 kg (5.5 lb) at birth. "Neonatal mortality" is death of an infant within one month after birth.

SEARCH TECHNIQUES

First, we gathered information on NVP and pregnancy-related food aversions and cravings using online databases (e.g., AGRICOLA, BIOSIS, CAB Abstracts and MEDLINE). To locate even earlier sources we also searched *Biological Abstracts* from the first volume (1926) forward. We retrieved original sources, and used their reference lists to locate additional sources. We also searched the *Science Citation Index* for recent references to key sources. When numerical data were extracted for analysis, our only criterion for inclusion was that sample sizes (e.g., number of women in a study, number of women exhibiting NVP) were stated in the original source or could be calculated unambiguously.

We sought information on morning sickness-like symptoms in nonhuman mammals by searching textbooks of veterinary physiology and all 38 volumes (1959–98) of *The International Zoo Yearbook*. We also contacted veterinarians (i.e., at the New York State College of Veterinary Medicine) and other animal researchers who had published information about appetite during pregnancy in primates, swine, sheep, cats, dogs, rats, rabbits, horses and goats.

Lastly, we used the Human Relations Area Files (HRAF) to investigate the distribution of NVP in traditional societies (Murdock 1981). Previously, Minturn and Weiher (1984) reported that information on morning sickness was available for 30 societies listed in the HRAF. We reviewed the printed HRAF on these cultures, as well as the new files available on CD-ROM (Installments 43–45). For each culture, we recorded all relevant information about pregnancy symptoms ("Pregnancy," category 843) and dietary habits ("Diet," category 262).

QUANTIFICATION OF AVERSIONS AND CRAVINGS

To quantify women's food cravings and aversions during pregnancy, we follow Dickens and Trethowan (1971) in defining a "pregnancy-related food aversion" as a strongly negative response to a particular food or beverage that was not disliked prior to pregnancy, and a "pregnancy-related food craving" as a strong urge to consume a food or beverage for which there had not been an intense desire prior to pregnancy.

There is a large literature on pregnancy-related food aversions and cravings. To be included in our analyses, studies had to present data specifically on foods that pregnant women craved or found aversive (i.e., "endogenous" responses to foods: Hook 1976), rather than foods simply listed as "preferences" or "taboos." This was done to exclude dietary habits that were based on the advice of others, or what women thought they should say they ate while pregnant. Studies that were excluded under this criterion include Bartholomew and Poston (1970), Darwish and Amine (1982),

and Spielmann (1989). Wijewardene et al. (1994) was excluded because the sample sizes were unclear.

There are no standardized categories used by researchers to classify dietary aversions and cravings. Some authors (e.g., Tierson et al. 1985) have presented data on women's responses to specific food items, such as "olives," "potatoes," and "liver," whereas others (e.g., Dickens and Trethowan 1971) have tabulated responses to broader food categories like "meat, fish, eggs," "vegetables," and "fruit." These differences obviously could have affected the way in which individual responses were scored, making it difficult to synthesize data from different studies. For example, a woman who had aversions to "liver" and "chicken" could be counted as having two different aversions, or only one aversion to "meats." To take this problem into account, we generated a list of food categories that was broad enough to accommodate the variation found in original references, but narrow enough to be useful for analysis. Nine categories emerged: (1) meats, fish, poultry, and eggs, (2) vegetables, (3) grains and starches, (4) dairy and ice cream, (5) fruits and fruit juices, (6) alcoholic beverages, (7) nonalcoholic (caffeinated) beverages (which included only coffee, tea and soda), (8) sweets, desserts, and chocolate, and (9) ethnic, strong and spicy foods. Categories 1–7 are self-explanatory. Regarding category (8), although we would have liked to consider chocolate separately because it contains many phytochemicals (Matissek 1997), most authors did not distinguish sweets or desserts that did and did not contain chocolate. Category (9) is obviously ambiguous, but we retained it because of its frequent occurrence in numerous studies and its potential importance to testing Profet's (1992) hypothesis, since strong and spicy flavors are often derived from phytochemicals (Billing and Sherman 1998). Tobacco and smoke are clearly important to Hook's (1976) hypothesis, but since they are not foods or beverages, they were considered separately. We excluded eight categories of aversions and cravings because the ingredients of these foods were either uncertain, or so heterogeneous that it was impossible to infer exactly what was being craved or avoided. These categories are "soups," "casseroles," "chicken pot pie," "fatty, greasy, and fried," "salty," "savory," "dressings and condiments," and "other." We also excluded "nuts and peanut butter" and "water and ice" because only a few studies listed foods in these categories and the number of aversions or cravings was minuscule (inclusion of these categories would not have altered our conclusions).

For each of the nine food categories that we studied, the total numbers of aversions or cravings from all studies were summed. These totals are not necessarily the same as the total number of women with aversions to or cravings for each category because a woman could express more than one aversion or craving in the same category. To minimize pseudoreplication, we calculated the average number of aversions and cravings per woman to each food category by dividing the total number of aversions or cravings to that category by the total number of women sampled. As an example, suppose one study of 20 women reported that two had aversions to "broccoli" and five had aversions to "spinach," and a second study of 20 women reported that five had aversions to "vegetables." In our analyses, these hypothetical studies would account for 12 aversions to "vegetables" and 0.3 aversions per woman (12/40).

There are several weaknesses in the available information about cravings and aversions. First, data were based on questionnaires instead of on observations of women's responses to foods during pregnancy; it is possible that some women may have responded according to what they thought they were "supposed" to crave or find aversive, rather than what they actually experienced (see Sherman and Reeve 1997). Second, the timing of questionnaire administration was not standardized. Some authors (e.g., Fairburn et al. 1992) interviewed women once or more during gestation, and others (e.g., Hook 1978) conducted only retrospective (postpartum) interviews; women in the latter group may not have recalled their reactions to various kinds of foods as clearly as women in the former group. Third, most studies reported information on aversions and cravings that occurred at any time during pregnancy; only MacIntyre (1983) and Rodin and Radke-Sharpe (1991) separated their data by trimester (we analyzed data from these two studies separately). Finally, some authors (e.g.,

Fairburn and Welch 1990) only reported aversions or cravings that were "frequently" mentioned by interviewees, so representation of some rarely-mentioned food categories might be artificially low. Although all these factors may affect the quality of the original data, they do not systematically bias our analyses for or against any particular hypothesis about the adaptive significance of NVP, especially since few original investigators indicated awareness of any adaptive hypotheses.

STATISTICAL ANALYSES

In general, we report results of statistical tests applied by original authors. We also use G-tests incorporating Williams' correction (Sokal and Rohlf 1995:698) to examine differences in (i) pregnancy outcomes between women who did and did not experience NVP and (ii) diet between cultures with and without NVP, and binomial proportion tests to evaluate differences in (iii) cravings and aversions and (iv) the incidence of NVP by geographic region.

RESULTS

CHARACTERIZING NAUSEA AND VOMITING IN PREGNANCY

Frequency of Occurrence

There were 56 studies that reported the frequency of NVP in 75 groups of women from 16 countries worldwide, with a total of 79,146 pregnancies of 64,876 individuals. The number of groups exceeds the number of studies because some studies included more than one group of women. Groups ranged in size from 9 to 11,481, with a median of 151 and a mean of 865 ± 2,089 (SD). Among all the groups, the mean proportion of women who experienced NVP was 66% ± 16, the median proportion was 68%, and the range was 11–100% (Figure 1).

Frequencies of NVP differed among countries. The highest mean frequency for a single country was 84% in Japan (1 group, 132 pregnancies: Mori et al. 1988), and the lowest was 35% in India (1 group, 2,500 pregnancies: Ananth and Rao 1993). In the United Kingdom, 75% ± 12 of women experienced symptoms (range: 53–94%, N = 20 groups, 5,746 pregnancies), as compared to 64% ± 14 of women in the United States (range: 27–89%, N = 22 groups, 35,387 pregnancies), and 62% ± 10 in all other countries in our sample combined (range: 11–100%, N = 33 groups, 38,283 pregnancies; references in the legend to Figure 1). Binomial proportion tests indicated significant differences in the incidence of NVP between the USA, UK, and all other countries combined (all pairwise $P < 0.01$). In view of the differences among countries, we reanalyzed the frequency data, this time eliminating pseudoreplication by using only the mean frequency for each country. For the 16 countries in our sample, the mean proportion of women experiencing NVP was 62% ± 13, the median proportion was 64%, and the range was 35–84%.

Timing of NVP

Circadian

During weeks 6 to 13 of gestation, NVP symptoms occur with equal probability throughout normal waking hours: 40–45% of women experienced nausea at least once during each 4-hr period from 0700 to 2300 (Figure 2). The probability of experiencing nausea dropped to less than 10% during the two 4-hr periods from 2300 to 0700. Differences in the occurrence of symptoms between waking and sleeping hours were highly significant ($P < 0.001$), but there were no significant differences among the four time periods during normal waking hours.

Weekly

Tierson et al. (1986) and Vellacott et al. (1988) documented the weekly occurrence of NVP symptoms, based respectively on interviews of 414 women in Albany, New York (89% of whom experienced NVP) and 500 women in London (76% of whom experienced NVP). Both studies reported that NVP occurs primarily in the first half of pregnancy (Figure 3a,b). Tierson et al.'s study is especially reliable because it excluded episodes of nausea or vomiting that might have resulted from illnesses, infections, or "flu-like" symptoms. Beginning in the fourth postmenstrual week (i.e., when the embryo was about two weeks old), the fraction of pregnant women experiencing nausea or vomiting rose rapidly. By the sixth week, more than half the women experienced symptoms. The frequency of NVP peaked dur-

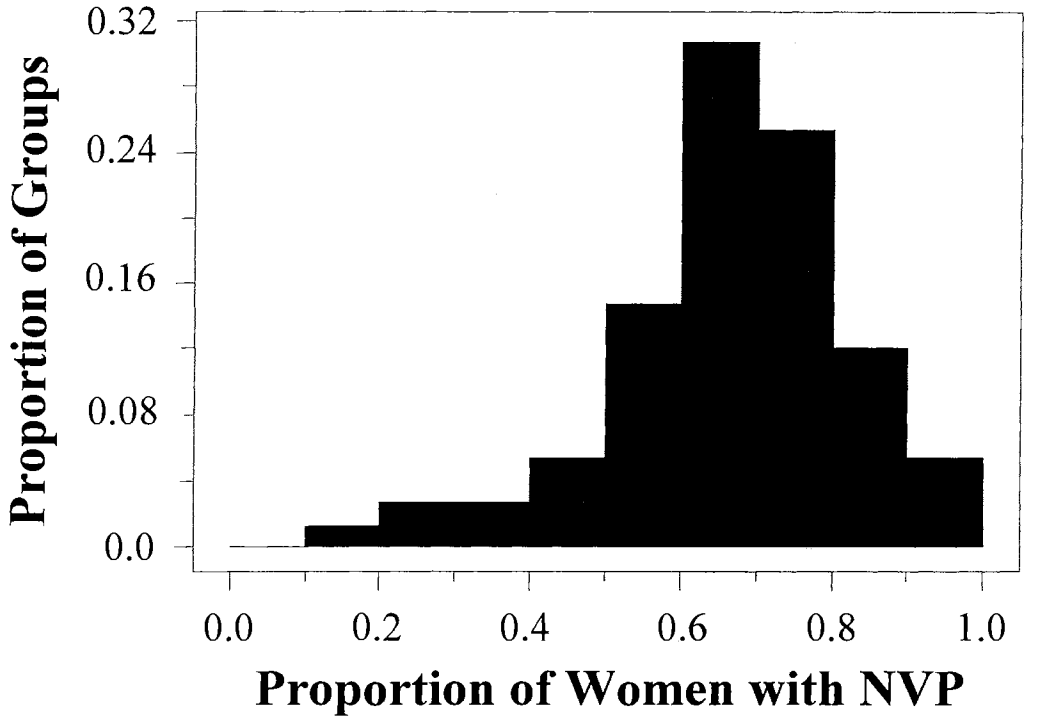


FIGURE 1. FREQUENCY OF NVP AMONG 75 GROUPS OF WOMEN REPORTED IN 56 STUDIES.

The mean frequency of NVP was 0.66, and the average group size was 865 women (N = 79,146 pregnancies from 64,876 women). The studies were done in **Australia** (N = 116 pregnant women: Biggs 1975; N = 429: Kricker et al. 1986; N = 100: Abraham et al. 1994), **Amsterdam** (N = 396: Paarlberg et al. 1996), **Canada** (N = 20: Drake et al. 1988; N = 732: McBride et al. 1991), **Greece** (N = 102: Iatrakis et al. 1988), **Hong Kong** (N = 1,453: Chin 1989), **India** (N = 2,500: Ananth and Rao 1993), **Israel** (N = 100: Medalie 1957), **Japan** (N = 132: Mori et al. 1988), **Kenya** (N = 68: Pike 1997), **Nigeria** (N = 400: Jinadu and Daramola 1990), **Norway** (N = 22,241 pregnancies from 8,675 women: Corey et al. 1992), **South Africa** (N = 1,771: Walker et al. 1985), **Sri Lanka** (N = 1,000: Wijewardene et al. 1994), **Sweden** (N = 152: Uddenberg et al. 1971; N = 5,377: Kullander and Källén 1976; N = 948 pregnancies from 244 women: Järnfelt-Samsioe et al. 1983; N = 102: Järnfelt-Samsioe et al. 1985), the **United Kingdom** (N = 100: Diggory and Tomkinson 1962; N = 105: Wolkind and Zajicek 1978; N = 42: Baylis et al. 1983; N = 50: MacIntyre 1983; N = 86: Fitzgerald 1984; N = 116: Masson et al. 1985; N = 212: Davies et al. 1986; N = 342: Evans et al. 1986; N = 86: Fairburn 1986; N = 242: Stewart et al. 1988; N = 500: Vellacott et al. 1988; N = 50: Fairburn and Welch 1990; N = 100: Fairburn et al. 1992; N = 1,000: Whitehead et al. 1992; N = 363: Gadsby 1994; N = 1513: Meyer et al. 1994; N = 569: Robinson et al. 1996), and the **United States** (N = 256: Speert and Guttmacher 1954; N = 3,853: Yerushalmy and Milkovich 1965; N = 7,027: Brandes 1967; N = 11,481: Milkovich and van den Berg 1976; N = 210: Little and Hook 1979; N = 78: DiIorio 1985; N = 180: Schuster et al. 1985; N = 70: Fawcett and York 1986; N = 7,767: Pettiti 1986; N = 414: Tierson et al. 1986; N = 55: Jenkins and Shelton 1989; N = 903: Weigel and Weigel 1989a; N = 270: Werler et al. 1989; N = 1,908: Fenster et al. 1991; N = 80: Rodin and Radke-Sharpe 1991; N = 126: O'Brien and Zhou 1995; N = 160: Snell 1996; N = 549: Brown et al. 1997). One additional study was unpublished (Abney 1986, cited in DiIorio 1988, location not stated, N = 144).

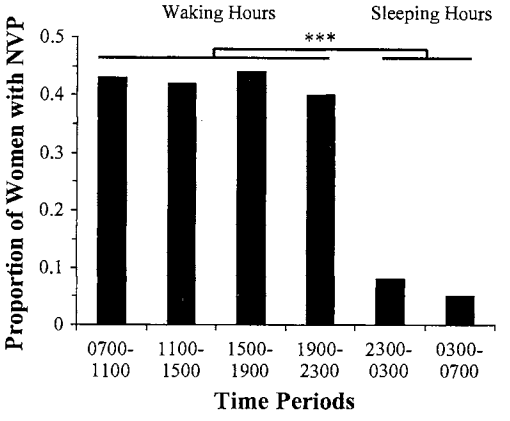


FIGURE 2. TIMES DURING THE DAY WHEN HEALTHY, PREGNANT WOMEN EXPERIENCE NVP.

The bars represent the proportion of women in a study who experienced nausea or vomiting at least once during each 4-hour time period. Data (replotted) and statistical analyses are from DiIorio et al. (1992), based on diaries of symptoms kept by 19 women for at least one week during weeks 6-13 of gestation. *** indicates $P < 0.001$.

ing weeks 9 to 14, when 60–70% of the women experienced nausea and 30–40% vomited. Thereafter, the frequency declined gradually, and by the 20th week only 20–30% of the women experienced nausea and 10–20% continued to vomit. Some women (less than 10%) experienced symptoms of NVP right up to the time of birth.

Relative to Embryonic Organogenesis

Embryonic tissues are most susceptible to damage from teratogens during certain, well-defined "critical periods" when cell division, cell differentiation and morphogenesis of a number of organ systems peak simultaneously (Figure 3c). Teratogens rarely cause congenital anomalies during the first four postmenstrual weeks (Carlson 1994). Periods of vulnerability for various organ systems begin at about week five, when the developing central nervous system and heart become critically sensitive. The peak of organogenesis and embryonic susceptibility to teratogens occurs during weeks 6 to 12. The embryo's central nervous system continues to be sensitive through week 18. There is an obvious—indeed striking—correspondence between the sensitive periods in embryonic organogenesis (Figure 3c) and the peak occurrence of NVP (Figures 3a,b).

Heritability of NVP

Women were significantly more likely to experience NVP if their mother (Whitehead et al. 1992; Gadsby et al. 1997) or sisters (Vellacott et al. 1988; Corey et al. 1992) had also experienced the symptoms. These studies did not include formal heritability estimates, and we were unable to calculate heritability from the data presented. Corey et al. (1992) did report highly significant ($P < 0.001$) tetrachoric correlations in the likelihood of experiencing NVP between monozygotic twin sisters who were raised together (54% ± 5 [SE], N = 830 pairs) and dizygotic twin sisters who were raised together (24% ± 5, N = 902 pairs). These results imply a genetic component to experiencing NVP.

NVP AND PREGNANCY OUTCOMES

Miscarriages

Information on the relationship between NVP and spontaneous abortions during the first 20 weeks was summarized by Weigel and Weigel (1989b). Their meta-analysis included seven studies based on 18,464 pregnancies of 17,760 women. In every study, women who experienced NVP were significantly less likely to miscarry than women who did not experience NVP (Figure 4).

The validity of any meta-analysis may be challenged on the grounds that only positive results are published. Weigel and Weigel's (1989b) study is unlikely to suffer from this problem, however, because there is no reason to suppose that contrary results would be suppressed. We located two additional relevant studies (Petitti 1986; Fenster et al. 1991), and both of them reported that women who experienced NVP were significantly less likely to miscarry than women who did not experience NVP, in agreement with Weigel and Weigel (1989b).

There is one way the relationship between NVP and lower miscarriage rates could be misleading. In most of the studies analyzed by Weigel and Weigel (1989b), women were enrolled soon after conception. If those who miscarried usually did so in the first few weeks,

they may have lost their embryo before NVP occurred (see Figures 3a,b). Thus early miscarriage would have avoided NVP. This possibility can only be ruled out for one study (Brandes 1967: #4 in Figure 4), in which most women were enrolled after their 8th postmenstrual week (i.e., near the peak of symptoms). We located two additional studies that controlled for the timing of miscarriages. Klebanoff et al. (1985) and Tierson et al. (1986) only considered pregnancies that lasted ≥ 14 weeks and ≥ 12 weeks, respectively. In both cases, fetal death rates (i.e., miscarriages plus stillbirths) were significantly lower among women who experienced NVP than among women who did not (Figure 5). These results imply that NVP reduces miscarriages, rather than vice versa.

Cohen (1997) claimed that an unpublished study in Bangladesh by K O'Connor et al. indicated that the association between NVP and reduced miscarriage rate disappeared when the effect of maternal age was controlled. According to Cohen, maternal age was positively correlated with miscarriages and negatively correlated with NVP symptoms. Neither Medalie (1957: #2 in Figure 4) nor Järnfelt-Samsioe et al. (1983: #6 in Figure 4) found any association between NVP and maternal age, however, although both reported highly significant associations between NVP and reduced chances of miscarriage. Klebanoff et al. (1985) and Jinadu and Daramola (1990) did find a higher incidence of NVP among younger women, but Vellacott et al. (1988), Chin (1989), Paarlberg et al. (1996), and Gadsby et al. (1997) found no relationship between maternal age and NVP.

Relationships between levels of NVP symptoms and the likelihood of miscarriages and fetal deaths were investigated by Weigel and Weigel (1989a) and Tierson et al. (1986), respectively. In each case, the lowest frequencies of both outcomes were among women who vomited during pregnancy, the next lowest frequencies were among women who experienced only nausea, and the highest frequencies were among women that did not experience any symptoms (Figure 6).

Other Pregnancy Outcomes

NVP does not affect the frequency of stillbirths (Yerushalmy and Milkovich 1965; Brandes 1967; Chin 1989). This implies that the negative relationships between NVP and fetal deaths (Figures 5 and 6b) are due primarily to the association between NVP and reduced frequencies of miscarriages.

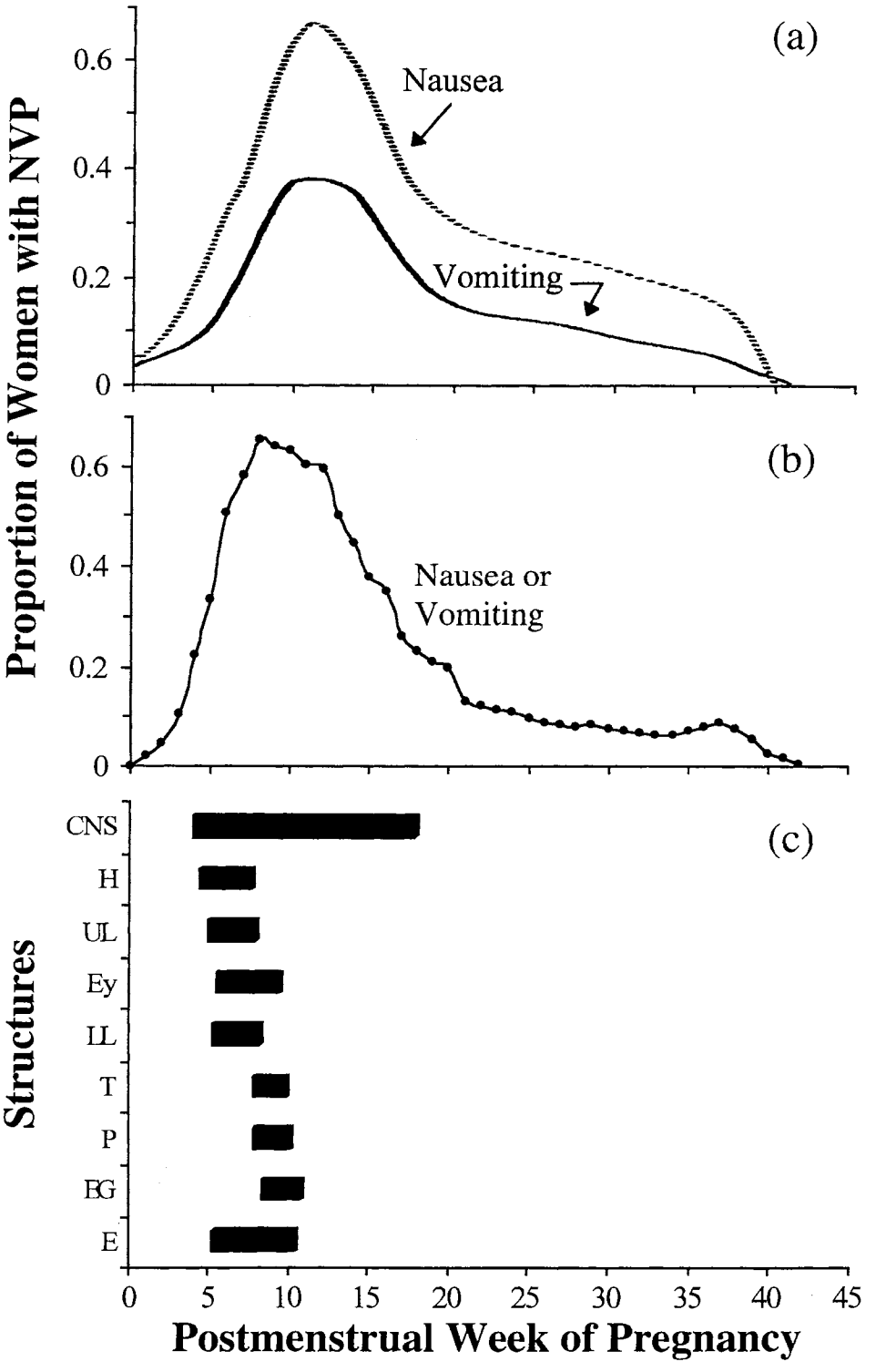
There were no consistent associations between NVP and four other pregnancy outcomes:

1. Preterm birth. Brandes (1967), Klebanoff et al. (1985), and Ananth and Rao (1993) reported that women who experienced NVP were less likely to give birth prematurely than women who did not experience NVP, but Chin (1989), Järnfelt-Samsioe et al. (1983, 1985), Tierson et al. (1986), and Weigel and Weigel (1989a) found no significant differences in frequencies of preterm births between women who did and did not experience NVP.

2. Low birth weight. Brandes (1967), Little (1980), and Tierson et al. (1986) found that women who did not experience NVP were more likely to give birth to offspring weighing < 2.5 kg (5.5 lb) than women who experienced NVP, but no significant association between NVP and low birth weight was observed by Järnfelt-Samsioe et al. (1985), Klebanoff et al. (1985), Weigel and Weigel (1989a), Ananth and Rao (1993), and Gadsby et al. (1997).

FIGURE 3. TIME COURSE OF NVP AND ITS RELATIONSHIP TO CRITICAL PERIODS IN EMBRYONIC ORGANOGENESIS.

(a) Time course of nausea and vomiting (dashed line: nausea with or without vomiting; solid line: vomiting); reprinted (scanned) from Tierson et al. (1986), with permission from Mosby, Inc. (b) Time course of nausea, with or without vomiting, modified from Vellacott et al. (1988), with permission from Elsevier Science. (c) Critical time periods when various developing structures are most susceptible to disruption by teratogens, based on information in Moore and Persaud (1998:156). CNS = central nervous system, H = heart, UL = upper limbs, Ey = eyes, LL = lower limbs, T = teeth, P = palate, EG = external genitalia, E = ears.



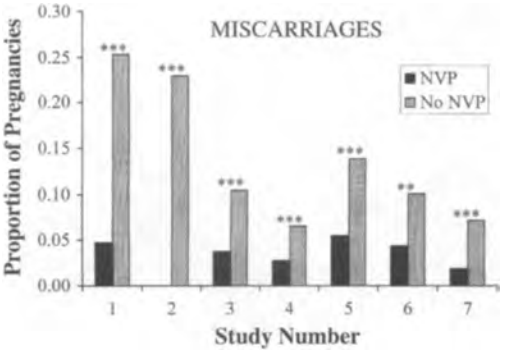


FIGURE 4. ASSOCIATION OF NVP WITH REDUCED MISCARRIAGE RATES (FETAL DEATH AT < 20 WEEKS).

Data are from seven studies (N = 18,464 pregnancies from 17,760 women). Statistical results are from Weigel and Weigel's (1989b) meta-analysis, with ** $P < 0.01$ and *** $P < 0.001$. Study numbers correspond to the following (with odds ratios and 95% confidence intervals calculated by Weigel and Weigel [1989b]): 1. Speert and Guttmacher 1954, N = 256 women, OR: 0.16, CI: 0.07–0.36; 2. Medalie 1957, N = 100, OR: 0.03, CI: 0.00–0.54; 3. Yerushalmy and Milkovich 1965, N = 3,853, OR: 0.34, CI: 0.26–0.45; 4. Brandes 1967, N = 7,027, OR: 0.41, CI: 0.32–0.53; 5. Kullander and Källén 1976, N = 5,377, OR: 0.36, CI: 0.30–0.44; 6. Järnfelt-Samsioe et al. 1983, N = 948 pregnancies from 244 women (analysis of outcomes based on 911 pregnancies), OR: 0.41, CI: 0.24–0.70; 7. Weigel and Weigel 1989a, N = 903, OR: 0.25, CI: 0.12–0.52. All studies compared pregnancy outcomes for women who did and did not experience NVP except Medalie (1957), who distinguished between "none/mild" NVP versus "moderate/severe" NVP.

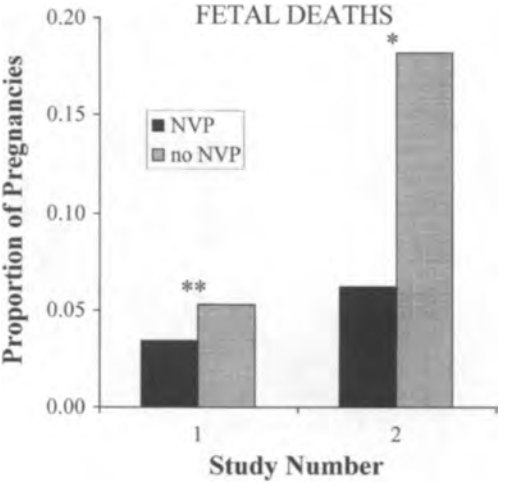


FIGURE 5. ASSOCIATION BETWEEN NVP AND REDUCED FETAL DEATH (MISCARRIAGE PLUS STILLBIRTH) RATES.

Study 1 (Klebanoff et al. 1985) included 9,098 women whose pregnancies lasted ≥ 14 weeks; ** indicates $P < 0.005$. Study 2 (Tierson et al. 1986, incorporating corrections of Tierson et al. 1989) included 414 women whose pregnancies lasted ≥ 12 weeks; * indicates $P < 0.05$. Klebanoff et al. distinguished only between women who vomited during pregnancy and those who did not (regardless of nausea).

3. Neonatal survival. Yerushalmy and Milkovich (1965) reported that babies born to women who had experienced NVP were significantly more likely to survive ≥ 1 month than babies born to women who had not experienced NVP, but Brandes (1967) and Chin (1989) found no association between NVP and neonatal mortality.

4. Congenital anomalies. Yerushalmy and Milkovich (1965) reported that women with NVP were less likely to bear children with "severe" anomalies (e.g., disruptions of major organ systems) than women who did not experience NVP. However, Milkovich and van den Berg (1976), Petitti (1986), and Weigel and Weigel (1989a) found no significant differences in frequencies of severe anomalies between women who did and did not experience NVP, Saxén (1975) and Golding et al. (1983) found no relationships between NVP and cleft lip or cleft palate, and Klebanoff and Mills (1986) found no relationship between NVP and any birth defects. Kullander and Källén (1976) reported that women who experienced NVP were significantly more likely to bear children with severe anomalies than women who did not experience NVP, and Kricker et al. (1986) found that women who vomited during pregnancy were significantly more likely to bear children with limb defects than women who did not vomit.

FOOD AVERSIONS AND CRAVINGS

Frequency

We summarized the results of 20 studies of food aversions during pregnancy that included information from 5,432 women, and

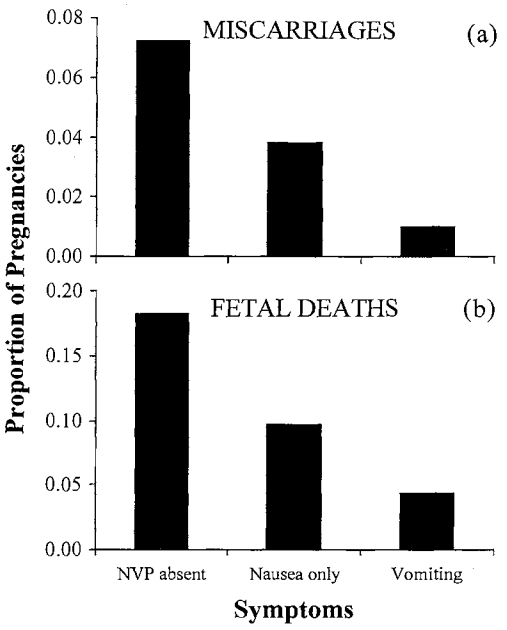


FIGURE 6. ASSOCIATION OF NVP SYMPTOMS WITH MISCARRIAGES AND FETAL DEATHS.

Increased severity of NVP symptoms are significantly associated with decreased chances of (a) miscarriages ($P < 0.001$: Weigel and Weigel 1989a), and (b) fetal deaths ($P < 0.001$: Tierson et al. 1986). Data were extracted from the original papers and replotted.

21 studies of food cravings of 6,239 women (see Table 1). The majority of women (65% ± 15) experienced at least one aversion during pregnancy; similarly, 67% ± 15 experienced at least one craving. Corresponding median proportions were 66% for aversions and 68% for cravings. Cravings were thus slightly more common than aversions ($P < 0.05$).

Ontogeny

Food aversions expressed during pregnancy were apparently novel developments in women's attitudes toward particular foods, rather than exaggerations of preexisting dislikes. For example, Fairburn et al. (1992) found that 80 of 100 women they interviewed experienced gestational food aversions, and all 80 reported that their aversions began during pregnancy. In an earlier study, Dickens and Trethowan (1971) considered as gestational aversions only those that began during pregnancy. Among 100 women, 62 experienced such aversions. Schwab and Axelson (1984) followed Dickens and Trethowan's protocol and definitions, and obtained similar results: of 60 women they interviewed, 37 (62%) experienced gestational aversions. A number of additional studies have reported connections between gastrointestinal distress during pregnancy and avoidance of the offending foods (e.g., Nobmann and Adams 1970; Hook 1976, 1978; Ojofeitimi et al. 1982; Finley et al. 1985; Brown and Toma 1986; Al-Kanhal and Bani 1995).

Foods avoided or craved throughout pregnancy

Pregnant women most often reported aversions to "meat, fish, poultry, and eggs" (Figure 7). Per capita aversions to these animal products (0.28/woman) were nearly double those of the second most aversive food category, "nonalcoholic beverages" (0.16 aversions/woman), and more than triple the aversions to "vegetables" (0.08/woman). Per capita aversions to "alcoholic beverages" and "ethnic, strong and spicy foods" were only 0.04/woman, and aversions to "dairy and ice cream," and "sweets, desserts, and chocolate" were even less frequent. Aversions to "grains and starches" and "fruit and fruit juice" were very rare (< 0.02/woman).

In contrast, pregnant women most often reported cravings for "fruit and fruit juice" (0.20 cravings/woman) and "sweets, desserts, and chocolate" (0.17/woman). Per capita cravings were slightly less common for "dairy and ice cream" (0.12/woman), "meat, fish, poultry, and eggs" (0.12/woman), and "grains and starches" (0.08/woman). Pregnant women seldom craved "vegetables" (0.06/woman), "ethnic, strong and spicy foods" (0.04/woman), and "nonalcoholic beverages" (0.03/woman). Very few pregnant women craved alcoholic beverages (< 0.01/woman).

Interestingly, patterns of gestational cravings and aversions were virtually mirror images (Figure 7). Per capita aversions were significantly greater than cravings for "meat, fish, poultry, and eggs," "nonalcoholic beverages," "vegetables," and "alcoholic beverages" ($P < 0.001$ for all), whereas per capita cravings were significantly greater than aversions for "fruit and fruit juice," "grains and starches," "sweets, desserts, and chocolate," and "dairy and ice cream" ($P < 0.001$ for all). Only for "ethnic, strong and spicy foods" were cravings and aversions equally common (Figure 7, middle).

TABLE 1

Studies used in the summaries of aversions and cravings

Authors	Year	Location	Sample size (number of women)	Quantitative data given on
Abraham et al.	1994	Sydney, Australia	100	Cravings
Alberti-Fidanza et al.	1996	Assisi, Italy	53	Cravings
Alberti-Fidanza and Fidanza	1986	Umbria, Italy	86	Cravings and Aversions
Al-Kanhal and Bani	1995	Riyadh, Saudi Arabia	321	Aversions
Baylis et al.	1983	United Kingdom	42	Aversions
Coronios-Vargas et al.	1992	Long Beach, California	160	Cravings and Aversions
Dickens and Trethowan	1971	Nuneaton, United Kingdom	100	Cravings and Aversions
Edwards et al.	1954	Tuskegee Institute, Alabama	55	Cravings
Fairburn et al.	1992	Oxford, United Kingdom	100	Cravings and Aversions
Fairburn and Welch	1990	Oxford, United Kingdom	50	Aversions
Finley et al.	1985	Northern California	60	Cravings and Aversions
Harries and Hughes	1958	United Kingdom	509 women, 820 pregnancies	Cravings and Aversions
Hook	1978	Albany, New York	250	Cravings and Aversions
Knox	1993	West Belfast, Northern Ireland	100	Cravings and Aversions
Landman and Hall	1983	Kingston, Jamaica	125	Cravings and Aversions
Marcus	1965	Manchester, United Kingdom	80 women, 225 pregnancies	Cravings and Aversions
Osman	1985	Sudan	308	Cravings and Aversions
Payton et al.	1960	Nashville, Tennessee	571	Aversions
Pope et al.	1992	Tennessee	97	Cravings and Aversions
Posner et al.	1957	New York, New York	600	Cravings
Schwab and Axelson	1984	Maryland	60	Cravings and Aversions
Stewart et al.	1988	Scotland, England	242	Cravings and Aversions
Tierson et al.	1985	Albany, New York	400	Cravings and Aversions
Walker et al.	1985	South Africa	1771	Cravings and Aversions
Whitehead et al.	1992	London, United Kingdom	983	Cravings
			Totals: 5432 women for aversions 6239 women for cravings	

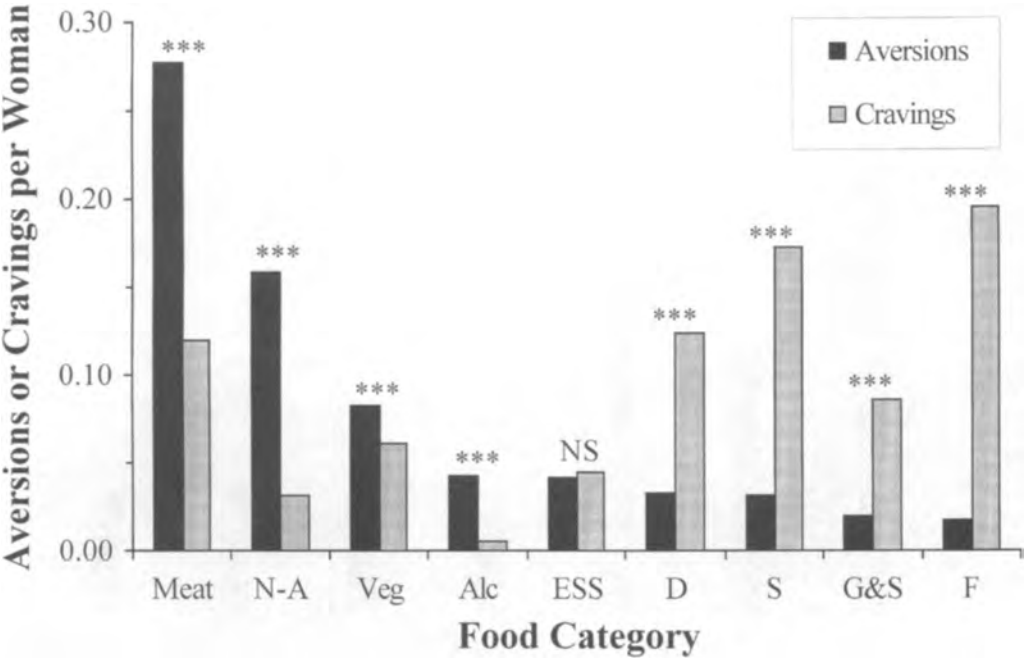


FIGURE 7. FOOD AVERSIONS AND CRAVINGS OF PREGNANT WOMEN (ALL TRIMESTERS). Numbers on the vertical axis represent the average number of aversions or cravings each woman in the sample had to each food category. These numbers were calculated by dividing the total number of aversions or cravings to each category by the total number of women in the sample. Aversions were based on 20 studies that included 5,432 women, and cravings were based on 21 studies that included 6,239 women (see Table 1). Here *** indicates $P < 0.001$, and NS indicates no significant differences. Food category abbreviations: "Meat" is meats, fish, poultry, and eggs, "N-A" is nonalcoholic beverages, "Veg" is vegetables, "Alc" is alcoholic beverages, "ESS" is ethnic, strong and spicy foods, "D" is dairy and ice cream, "S" is sweets, desserts, and chocolate, "G&S" is grains and starches, and "F" is fruits and fruit juices.

Foods avoided in each trimester

Per capita aversions to all food categories were highest early in pregnancy, and declined dramatically thereafter (Figure 8). Aversions were significantly more frequent in the first trimester than in the second trimester for six of seven food categories (all $P < 0.05$); aversions to the odd category ("vegetables") also were lower in the second trimester, but the decline was only marginally significant ($P = 0.06$). Aversions were significantly more frequent in the first trimester than in the third trimester for six of seven food categories (all $P < 0.05$); aversions to the odd category ("grains and starches") also were lower, but the decline was only marginally significant ($P = 0.07$). Aversions were significantly greater in the second trimester than in the third trimester for three of seven food categories, namely "meat, fish, poultry, and eggs," "vegetables," and "nonalcoholic beverages." Declines in per capita aversions between the successive trimesters thus were most consistent for these three food categories. Interestingly, cravings for animal products and vegetables also declined significantly between the first and third trimesters (data not shown).

Rodin and Radke-Sharpe (1991) monitored dietary preferences of women in the first trimester and, simultaneously, nonpregnant "control" women. The pregnant women exhibited more aversions per capita than controls to all seven food categories (Figure 9). Six of these seven comparisons were highly significant ($P < 0.01$), and the seventh ("grains") was marginally significant ($P = 0.07$). In general, food aver-

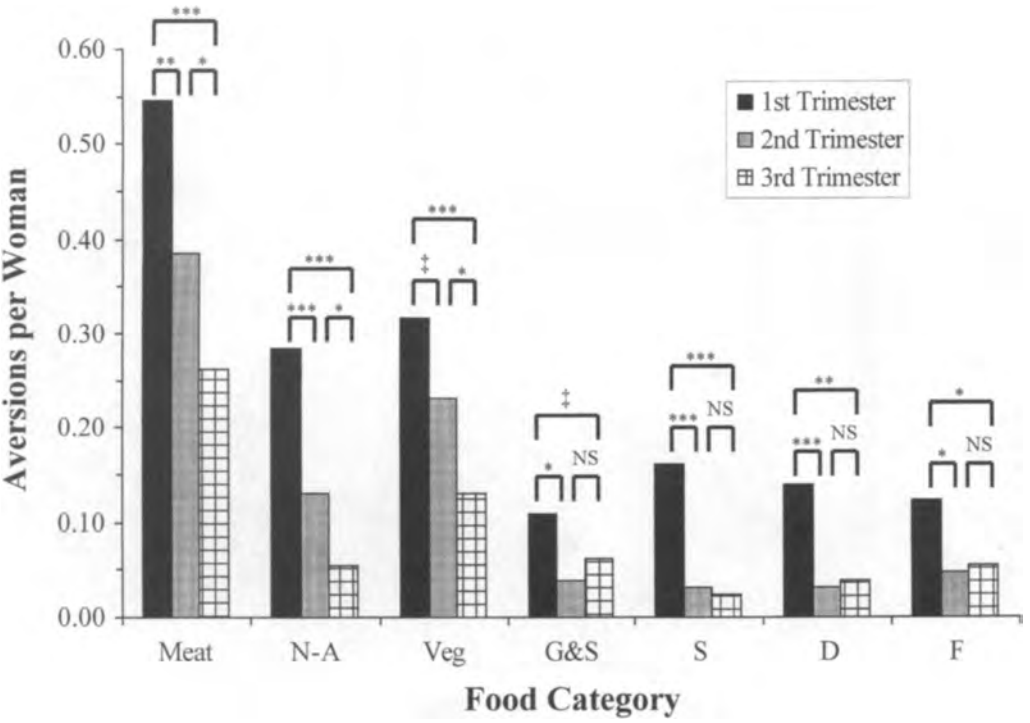


FIGURE 8. CHANGES IN FOOD AVERSIONS DURING THE THREE TRIMESTERS OF PREGNANCY. Based on interviews by MacIntyre (1983, N = 50 women) and Rodin and Radke-Sharpe (1991, N = 80 women). Food category abbreviations and calculations of per capita numbers of aversions are as in Figure 7. Significant differences are indicated as follows: ‡ $0.05 < P < 0.1$, * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, NS = not significant.

sions were rare (< 0.10/woman) among controls. "Meat, fish, poultry, and eggs" were the most common targets of aversions in nonpregnant women, in agreement with previous reports (e.g., Midkiff and Bernstein 1985; De Silva and Rachman 1987; Mattes 1991). However, aversions to these animal products were more than twice as frequent among pregnant women (0.78/woman) as among controls (0.30/woman).

NVP IN TRADITIONAL SOCIETIES

Minturn and Weiher (1984) claimed that information on the occurrence of "morning sickness" was available in the Human Relations Area Files for 30 traditional societies. We carefully checked the HRAF for data on these 30 societies, but were able to locate relevant information for only 26. We also located data on one society that was not cited by Minturn and Weiher. Among these 27 societies (Table 2), morning sickness was observed in 20 (74%). For the other seven, original investigators made specific statements to the effect that they did not observe any symptoms of morning sickness. These seven cultures are not clustered geographically: they are located on five continents (Table 2). Of course, we cannot rule out the possibility that morning sickness actually occurred in these societies but was undetected. However, HRAF sources gave us no reason to suppose that observations of these seven societies were any less complete or accurate than observations of the 20 societies in which morning sickness was recorded. Therefore, we accepted the HRAF data at face value.

For the 27 societies in our sample, we tabulated (Table 2) all foods listed as "staples" (i.e., foods eaten every day). Meat was a staple in 14 societies (52%), milk in two (7%), corn in 10

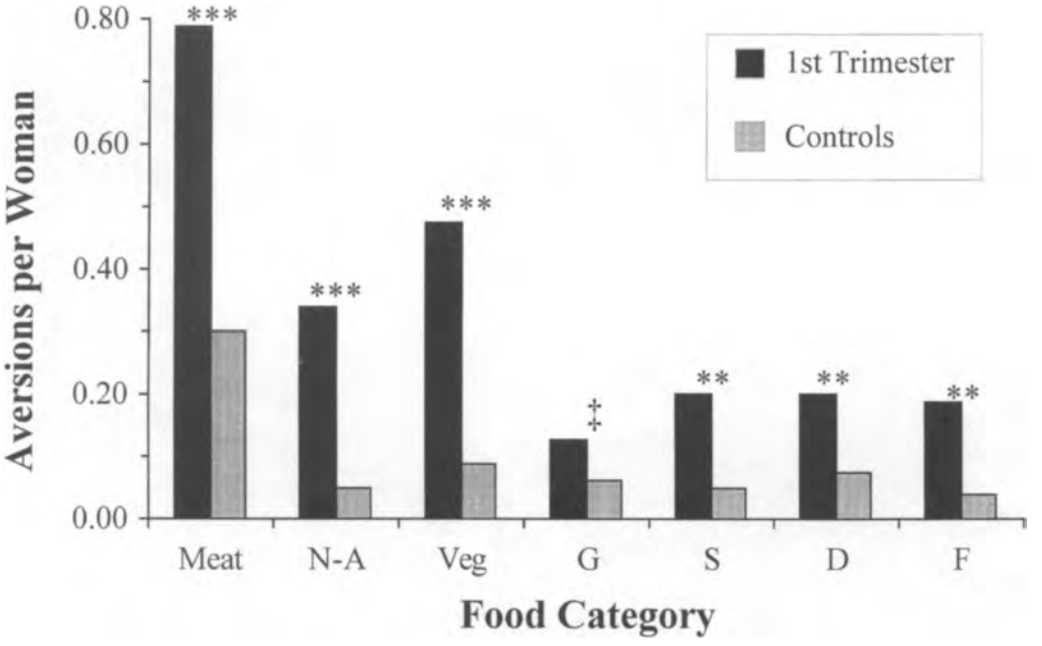


FIGURE 9. FOOD AVERSIONS OF FIRST TRIMESTER PREGNANT WOMEN COMPARED TO AVERSIONS OF NONPREGNANT WOMEN.

Data are from Rodin and Radke-Sharpe (1991), based on concurrent surveys of 80 women who were in their first trimester of pregnancy and 80 nonpregnant "control" women. Food category abbreviations and calculation of per capita numbers of aversions are as in Figure 7; statistical results are indicated as in Figure 8.

(37%), rice in 6 (22%), and other plants (mostly tubers) in 19 (70%). Societies in which morning sickness was not observed were equally likely to have plants as dietary staples as societies in which morning sickness was observed (Table 3). Compared to societies in which morning sickness was observed, however, societies in which it was not observed were significantly more likely to have (i) *only* plants as staples, (ii) corn as a staple, and (iii) corn as the *only* staple, and they were (iv) significantly less likely to have meat as a staple, and (v) slightly less likely to have rice as a staple (Table 3).

NVP IN OTHER MAMMALS

We searched widely for information on NVP in nonhuman mammals. We found only suggestive evidence for three species. Female domestic dogs (*Canis familiaris*) typically exhibit a sharp drop in food consumption during weeks 3 to 5 of their 9-week gestation (Lewis et al. 1987; Bebiak 1988; Jackson 1995). In some lab colonies, this change in appetite is a reliable indicator of pregnancy (Lewis et al. 1987; D M Bebiak, personal communication). Captive rhesus macaques (*Macaca mulatta*) also often exhibit a decrease in appetite during weeks 3 to 5 of their 23-week gestation (Czaja 1975). Their appetite loss is accompanied by hormonal changes that parallel those occurring in women during the first trimester of pregnancy. Finally, for captive chimpanzees (*Pan troglodytes*), Keeling and Roberts (1972:145) noted that among the "subtle factors" that might strengthen a questionable diagnosis of pregnancy, "[t]he pregnant female may initially experience morning sickness and irregularities in appetite." The authors provided no further information or references, and we were unable to locate any other mention of morning sickness in wild or captive chimpanzees (e.g., in Bourne 1970–73; Goodall 1986; Wrangham et al. 1994).

TABLE 2

Cultures for which information on NVP was available in Human Relations Area Files

Culture	Location	Staples (eaten every day)					NVP?
		Meat	Milk	Corn	Rice	Other Plant[1]	
Alor	Oceania			X			Yes
Aranda	Australia	X				X	Yes
Bhil	Asia			X		X	No
Burmese	Asia	X			X	X	Yes
Cuna	South America	X				X	Yes
Garo	Asia	X			X	X	Yes
Goajiro	South America	X	X	X			Yes
Gond	Asia				X	X	Yes
Hottentot	Africa	X	X			X	Yes
Ifugao	Oceania	X			X	X	Yes
Kaska	North America	X					Yes
Mbundu	Africa			X			No
Okinawa	Asia	X			X	X	Yes
Omaha[2]	North America			X			No
Papago	North America			X			No
Pukapuka	Oceania	X				X	Yes
Siriono	South America	X		X			No
Tallensi	Africa			X		X	Yes
Tarahumara	North America			X			No
Terena	South America					X	Yes
Tonga	Oceania	X				X	Yes
Toradja	Oceania				X	X	Yes
Trobriand	Oceania					X	Yes
Truk	Oceania	X				X	Yes
Wogeo	Oceania					X	Yes
Woleai	Oceania					X	No
Zulu	Africa	X		X		X	Yes

[1] The more common "other plant" staples were taro, plantains, millet, breadfruit, sweet potatoes, cassava, and other tuberous plants.

[2] In addition to HRAF, Fletcher and La Flesche (1972) was also used for information about the Omaha.

DISCUSSION

Hook (1976, 1978, 1980) and Profet (1988, 1992, 1995) hypothesized that NVP serves a useful function—protecting the embryo—by causing pregnant women to physically expel and subsequently avoid foods that contain teratogenic, mutagenic, and abortifacient chemicals. This hypothesis predicts that NVP should coincide with the greatest susceptibility of the embryo to developmental disruption. Consistent with this hypothesis, NVP symptoms peak during the first trimester, which is a critical period in organogenesis (Figure 3). During gestational weeks 6 to 14, the embryo is especially sensitive to disruption by exogenous chemicals because cell division, cell differentiation, and morphogenesis of multiple organ systems are occurring simultaneously.

The embryo protection hypothesis also predicts that women who experience NVP should have positive pregnancy outcomes more frequently than women who do not experience NVP. In support of this prediction, in all nine of nine studies, women who experienced "normal" NVP (i.e., excluding hyperemesis gravidarum) were significantly less likely to miscarry than women who did not (Figure 4). In two additional studies, fetal deaths (miscarriages plus stillbirths) were significantly less likely to occur in women who experienced NVP (Figure 5), and pregnant women who vomited were less likely to suffer miscarriages and fetal deaths than women who felt nauseated but did not vomit (Figure 6). The latter result may implicate physical expulsion of certain foods in enhancing pregnancy outcomes.

TABLE 3

Characteristics of diets in traditional societies in relation to the presence or absence of NVP

Dietary characteristic	Number of societies with NVP ($N = 20$) [fraction (proportion)]	Number of societies without NVP ($N = 7$) [fraction (proportion)]	G statistic	Significance level
Plants are staples	18/20 (0.90)	7/7 (1.0)	0.928	Not significant
Only plants are staples	7/20 (0.35)	6/7 (0.86)	5.337	$P < 0.05$
Meat is a staple	12/20 (0.60)	1/7 (0.14)	4.388	$P < 0.05$
Corn is a staple	4/20 (0.20)	6/7 (0.86)	9.063	$P < 0.005$
Corn is the only staple	2/20 (0.10)	5/7 (0.71)	8.586	$P < 0.005$
Rice is a staple	6/20 (0.30)	0/7 (0.0)	3.709	$0.05 < P < 0.1$

In contrast to the strong and consistent negative associations between NVP and miscarriage—a typical consequence of developmental disruptions that occur early in embryonic organogenesis—NVP was not reliably associated with pregnancy outcomes in later fetal development or postpartum. Whether women experienced NVP or not, they were equally likely to suffer stillbirths and neonatal mortality. The frequency of NVP (Figure 1), its timing relative to critical periods in embryonic organogenesis (Figure 3), and the positive pregnancy outcomes associated with "normal" NVP (Figures 4–6)—especially when juxtaposed with the absence of negative outcomes—together imply that NVP indeed serves a protective function.

What exactly does NVP protect the embryo from? Hook (1976, 1978) focused on the teratogens in alcohol, caffeinated beverages and tobacco. Profet (1992, 1995) presented a more comprehensive list of potentially dangerous foods, and recommended that pregnant women "protect their baby-to-be" by avoiding vegetables that contain teratogenic phytochemicals. Consistent with Profet's hypothesis, in large quantities phytochemicals in many common vegetables and caffeinated beverages are mutagens, teratogens, abortifacients, and allergens (e.g., Pieters 1982; Nagao et al. 1986; Ames et al. 1990a,b; Friedman et al. 1991; Shepard 1992; Beier and Nigg 1994; Klebanoff et al. 1999). For example, crude juice extracts from plants in the genus *Brassica* (e.g., cabbage, Brussels sprouts) contain isothiocyanates and other breakdown products of glucosinolates that can induce chromosomal aberrations in mammalian cells (Kassie et al. 1996). Extracts from vegetables not containing these chemicals do not have such genotoxic effects.

In contrast, however, Brown et al. (1997: 181) stated that "[s]peculation offered in a recent popular-press book [Profet 1995] that links intake of certain vegetables and other foods to nausea and vomiting of early pregnancy and to adverse pregnancy outcomes is not supported by this study. We conclude that intake of pungent and bitter vegetables and other proscribed foods is not hazardous to pregnant women." Neither Profet (1988, 1992, 1995) nor Brown et al. (1997) quantified what foods triggered NVP or resulted in pregnancy-related aversions. We did so. Among the food categories we recognized (Figures 7–9), "nonalcoholic (caffeinated) beverages," "vegetables," and "ethnic, strong and spicy foods" all include items that contain potentially teratogenic phytochemicals. If we therefore combine them into a single super-category (Figure 10), they indeed account for a large number of per capita aversions (0.29/woman)—as many as to meat products. Also consistent with Profet's version of the embryo protection hypothesis, pregnant women reported (i) significantly more aversions than cravings to "vegetables" and "nonalcoholic beverages" (Figure 7), (ii) significantly more aversions to "vegetables" and "nonalcoholic beverages" in the first trimester of pregnancy than in the second or third trimesters (Figure 8), and (iii) significantly more aversions to "vegetables" and "nonalcoholic beverages" than did nonpregnant women (Figure 9).

Hook's (1976) version of the embryo protection hypothesis also correctly predicted a subset of pregnancy-related aversions. "Nonalcoholic (caffeinated) beverages" was consis-

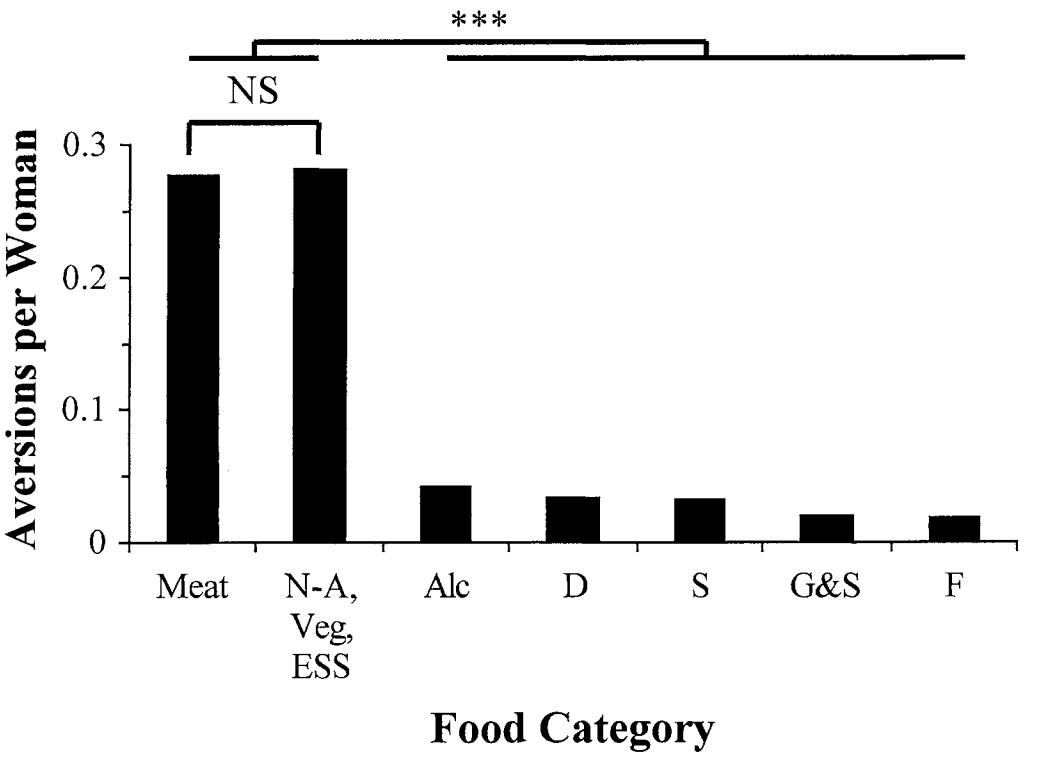


FIGURE 10. FOOD AVERSIONS OF PREGNANT WOMEN (ALL TRIMESTERS).
This figure replots the data in Figure 7, combining the three categories that include foods containing phytochemicals (e.g., "nonalcoholic beverages," "vegetables," and "ethnic, strong and spicy foods"). Per capita frequencies of aversions to meats and these phytochemical-containing foods do not differ significantly, but each of these two categories is a target of aversions significantly more frequently than any other category (*** indicates $P < 0.001$).

tently the second (Figure 7) or third (Figures 8, 9) most aversive food category, and aversions to "nonalcoholic beverages" were significantly higher in the first trimester of pregnancy than in the second or third trimesters (Figure 8). Contrary to Hook, however, aversions to alcoholic beverages were much less common (Figure 7). This is surprising, because alcohol is a well-known teratogen (Kaufman 1997). It is possible that some researchers did not consider alcohol to be a "food," and therefore did not question women about its use. Additionally, some women may have been reluctant to reveal information about alcohol consumption during pregnancy.

Several investigators did include "alcoholic beverages" in their questionnaires, however. Among them, Hook (1978, N = 250 pregnancies) and Stewart et al. (1988, N = 242) reported that per capita aversions to alcohol were almost as common as aversions to "meat, fish, poultry, and eggs" and "nonalcoholic beverages," and significantly more common than aversions to "vegetables." In contrast, Tierson et al. (1985, N = 400) and Finley et al. (1985, N = 60) found that gestational aversions to alcoholic beverages were significantly less common than aversions to "meat, fish, poultry, and eggs" or "nonalcoholic beverages," and about as frequent as aversions to "vegetables." Furthermore, Dickens and Trethowan (1971, N = 100), Schwab and Axelson (1984, N = 60), and Alberti-Fidanza et al. (1996, N = 86) reported that aversions to alcoholic beverages were relatively infrequent (< 0.1 aversions per woman), and Harries and Hughes (1958, N =

509), Baylis et al. (1983, N = 42), and Knox (1993, N = 100) found that aversions to alcoholic beverages were extremely rare (< 0.05 aversions per woman). Most reports thus offer little support for Hook's hypothesis as applied to alcoholic beverages.

Also apparently contrary to Hook (1976), only two studies reported aversions to cigarette smoke (Tierson et al. 1985; Fairburn et al. 1992). However, the relationship between NVP and tobacco use is complicated. Among women who smoked before conceiving, those who experienced NVP were more likely to quit than those who did not experience NVP (Wolkind and Zajicek 1978; Meyer et al. 1994; but see Paarlberg et al. 1996). This suggests that NVP contributed to an aversion to smoking. If so, it provides a novel explanation for the frequently reported, but heretofore paradoxical, association between smoking and the absence of NVP (e.g., Wolkind and Zajicek 1978; Little and Hook 1979; Vellacott et al. 1988; Meyer et al. 1994; Gadsby et al. 1997; but see Palmer 1973; Klebanoff et al. 1985; Paarlberg et al. 1996). Alternatively, it is possible that chemicals in cigarette smoke reduce NVP symptoms by interfering with their underlying neuroendocrine mechanisms (e.g., Bernstein et al. 1989), or by damaging placental cells that may be responsible for triggering NVP (e.g., Langhan's cells: Sastry et al. 1989; Arnholdt et al. 1991). Placental cell damage also could explain why mothers who smoke are less likely than nonsmokers to experience preeclampsia (Klonoff-Cohen et al. 1993; Cnattinguis et al. 1997).

Undoubtedly our most intriguing finding is that pregnant women consistently find "meats, fish, poultry, and eggs" to be more aversive than any other single food category (Figures 7–9). This was not predicted by Hook (1976) or Profet (1988). Interestingly, Hook (1978: 1360) reported results similar to ours, but he termed them "unexpected" in light of his emphasis on alcohol, tobacco and caffeine. Profet (1992:346) mentioned the potential dangers of spoiled or burned meats, but her arguments focused primarily on plant toxins, and no animal products were included in her list of "worst foods to eat during the first trimester" (1995:151).

There are three possible explanations for the association between animal products, food aversions and NVP. First, digestive breakdown of animal products could conceivably create or release teratogenic or abortifacient substances. Categories of compounds associated with meat digestion include dipeptides, tripeptides, triglycerides, phospholipids, sterols, amino acids, uric acid, and the fat-soluble vitamins A, D, E and K (Davenport 1982:205–210; Johnson 1997). Among these compounds, only vitamin A (retinoic acid) is known to cause birth defects (Schardein 1985; Keen et al. 1993), and this occurs only if it is ingested in pharmacological doses daily (that is, > 15,000 IU) over several months of gestation (Hathcock et al. 1990; Rothman et al. 1995). Thus, constituents of meats in a normal diet are unlikely to endanger a developing embryo.

The second possibility is that certain culinary practices (e.g., frying, broiling and smoking) create cooking mutagens (Profet 1992) and introduce phytochemicals, such as those in spices (Billing and Sherman 1998). Before the widespread availability of refrigeration (i.e., before the 20th century), these practices—along with heavy salting—were the primary means of preserving animal products. By avoiding roasted, burned, smoked or heavily spiced meats, pregnant women could minimize the exposure of their embryo to toxic chemicals. But exposure to bacteria or fungi and their toxins is a serious potential cost of eating meats that are not thoroughly cooked, spiced or salted (Sherman and Billing 1999).

This suggests the third and most likely reason why pregnant women benefit from avoiding animal products: to minimize exposure to foodborne illnesses and food poisoning. Raw meats and meat dishes that are prepared in advance and stored at ambient temperatures for more than a few hours, especially in tropical climates, typically show massive increases in bacterial and fungal content (Bryan et al. 1979; Michanie et al. 1988; Hobbs and Roberts 1993). Meats are more dangerous than vegetables because meats spoil faster (an animal's immune system ceases functioning at death), and thus meats are more often associated with foodborne illnesses (Bryan 1988; Roberts 1990; Todd 1994, 1996; Sockett 1995). Vegetables and plant seeds are colonized less rapidly, partly because cellulose and lignin are not eas-

ily broken down by aerobic bacteria, and also because of the antimicrobial and antifungal properties of the phytochemicals that many plants contain, including protease inhibitors, chitinases, glucanases, phenolics, and ribosome-inactivating proteins (Vigers et al. 1991; Darnetty et al. 1993).

There is a special reason why pregnant women may benefit from avoiding meat products: their immune system is suppressed (Formby 1995; Gennaro and Fehder 1996; Matthiesen et al. 1996). Although a woman's humoral immune response is unaltered or possibly strengthened during gestation, her cell-mediated immune response is weakened (Bisset et al. 1990; Formby 1995; Sabahi et al. 1995; Blumberg and Heal 1996; Lim et al. 1996). Numerous investigators have reported that the activities of natural killer cells are depressed during pregnancy (e.g., Barrett et al. 1982; Gonik et al. 1987; Salméron et al. 1991; Haig 1993; Beer et al. 1996; Gennaro and Fehder 1996; Matthiesen et al. 1996; but see Hidaka et al. 1991; Opsahl et al. 1994). This occurs in some nonhuman mammals as well (Chaouat and Menu 1997). Temporary immunosuppression is essential for a successful pregnancy; if the immune system functioned normally, the mother might reject her own offspring, whose cellular phenotypes are foreign because half of their genotype is paternally derived (Haig 1996). Indeed, women who do not exhibit normal decreases in levels of decidual killer cell activity more frequently suffer recurrent spontaneous abortions (Chao et al. 1995; Beer et al. 1996; Christiansen 1996).

Impairment of killer cell activity reduces a pregnant woman's innate immunity to bacteria, viruses, and tumor cells (i.e., her "first response"; Blumberg and Heal 1996), as well as her antibody-dependent, cell-mediated cytotoxicity response (i.e., killing of cells that are labeled with antibodies; Janeway and Travers 1994). As a result, immunosuppression during gestation can have important negative consequences (Formby 1995). First, pregnant women are at greater risk of serious illnesses and death from foodborne and waterborne enteric microorganisms than nonpregnant women (Gerba et al. 1996). Pregnant women have higher fatality rates than nonpregnant women from certain hepatitis strains, amoebic colitis, typhoid fever, smallpox, coccidioidomycosis, malaria (*P. falciparum*), and influenza (Brabin 1985). Second, viral, fungal and protozoan infections are generally more severe during pregnancy than similar infections experienced by nonpregnant women (Gennaro and Fehder 1996), including influenza, cholera, measles, varicella, diphtheria, scarlet fever, gonorrhea, giardiasis, and babesiosis (Brabin 1985). As one example, *Toxoplasma gondii*—a common, foodborne protozoan parasite, often acquired by handling or eating raw or undercooked meat (Kapperud et al. 1996)—rarely causes toxoplasmosis in immunocompetent individuals (Smith 1997). Toxoplasmosis is a serious risk factor for individuals with compromised cell-mediated immunity, however, such as pregnant women (Smith 1997).

Maternal immunosuppression also creates risks for the embryo. Miscarriages and birth defects can result if, in the first trimester, the woman contracts a febrile illness (Shaw et al. 1998), including viruses (Dickinson and Gonik 1990; Kurppa et al. 1991), respiratory infections (Kricker et al. 1986), and influenza (Saxén 1975; Lynberg et al. 1994). Foodborne pathogens can also directly affect the viability of the embryo. For example, gestational toxoplasmosis has been linked to congenital neurological birth defects (Fichera and Roos 1997), spontaneous abortions, neonatal diseases, and ocular defects (Holliman 1995). Dickinson (1994) has estimated that 3% of congenital deformities result from gestational infections.

In view of all these dangers, we maintain that the embryo protection hypothesis must be expanded. We suggest that NVP protects both the mother and her embryo from infections by foodborne microorganisms and poisoning from their toxins, in addition to protecting the embryo from teratogens and abortifacients in the mother's diet. This expanded hypothesis would explain the high frequencies of aversions to "meats, fish, poultry, and eggs" (Figure 7) in pregnant women, especially during the first trimester of pregnancy. Decreases in these aversions as pregnancy progresses (Figure 8) are consistent with increasing maternal and embryo protection. In the first trimester, embryonic tissues are so vulnerable to disruption (Figure 3c) that even fat- and protein-rich foods are rejected. As pregnancy progresses,

however, nutrient requirements increase and fetal vulnerability decreases, so the possible costs to the woman and fetus of ingesting animal products are exceeded by the benefits of consuming these nutrient-dense foods.

It is puzzling that women should ever crave animal products during the first trimester (Figure 7). Perhaps in some populations these foods are the principal or only sources of protein, fats, iron, folate and other vitamins, and other kinds of nutrients. Adequate protein intake is crucial to normal development (especially later in pregnancy); low protein diets have been linked to decreased placental and birth weights (Campbell et al. 1996; Godfrey et al. 1996). Also, fresh meat that is boiled thoroughly (so no teratogens are produced via cooking), and to which no spices are added, would pose little threat to a woman or her developing embryo. In fact, sterilized meat products probably contain fewer dangerous compounds than many vegetables (Profet 1992, 1995).

We have argued that NVP causes the expulsion of foods that contain microorganisms and toxic chemicals, and also encourages pregnant women to eliminate the offending foods from their diet. Nausea and vomiting do cause individuals to subsequently dislike the foods that triggered gastrointestinal distress (Milgram et al. 1977; Pelchat and Rozin 1982; Rozin and Vollmecke 1986), and the adaptive value of such food aversion learning is obvious (Letarte et al. 1997). Consistent with this hypothesized "prophylactic" function, multiple studies have reported a connection between NVP and learning food aversions (Nobmann and Adams 1970; Hook 1976, 1978; Ojofeitimi et al. 1982; Finley et al. 1985; Al-Kanhal and Bani 1995), and between aversions and reduced consumption of those foods (Tierson et al. 1985; Brown and Toma 1986). For example, Rodin and Radke-Sharpe (1991:334) commented that "[f]or the most part, the food groups that were more commonly avoided among pregnant than nonpregnant women were strongly related to the symptoms of NVP"; Finley et al. (1985:684) stated that "[t]he most common aversions were directed toward vegetables, usually onions or members of the *Brassica* family, strongly spiced or strong-smelling mixed dishes (usually of Chinese, Italian, or Mexican ethnic origin), or 'greasy' foods. Usually the foods were reported aversive because they provoked nausea."

The maternal and embryo protection hypothesis predicts that the frequency of NVP should be affected by the characteristic diet of a population. There were wide variations in frequencies of NVP among countries (i.e., 35–84% in 16 countries; Figure 1) and subpopulations. In the United States alone, the range in NVP frequencies was 27–89% in 22 samples. The frequency of NVP in the United Kingdom was significantly higher than in the United States and elsewhere. We tried to relate these differences to diet, i.e., by determining whether study subjects in the United Kingdom consumed more meats or more pungent vegetables than subjects in the United States or elsewhere. Appropriate dietary information was unavailable, however.

Dietary data were available in the Human Relations Area Files for the 27 nonindustrial cultures with information on NVP. Minturn and Weiher (1984) reported that societies in which NVP symptoms were not observed had corn as a staple food significantly more often than societies where NVP occurred. They also reported that societies with no symptoms consumed significantly more fats and green vegetables, and that NVP was more prevalent in the Insular Pacific (91% of the societies) than in their overall sample (73%). Minturn and Weiher found no associations between NVP and altitude, latitude, longitude, the type or intensity of agriculture, presence of food taboos, importance of women in the subsistence economy, settlement patterns, or the sizes of communities.

Our results (Tables 2 and 3) extend those of Minturn and Weiher (1984). We found that the seven societies in which NVP symptoms were not observed were significantly less likely to have meat as a dietary staple, and significantly more likely to have only plants as dietary staples, than the 20 societies in which symptoms occurred. Moreover, societies without NVP were significantly more likely to have corn as a dietary staple (and corn as the only staple) than societies with NVP. Of course our analyses, as well as those of Minturn and Weiher (1984), may be questioned because societies are not independent data points—owing to possible recent common ancestry or diffusion of dietary preferences. Independence is statistically desirable but, as discussed by Ember and

Otterbein (1991) and Mace and Pagel (1994), independence of specific cultural practices is often impossible to assess. Use of cladistic methods to infer independence of cultures has been suggested, but as pointed out by several respondents to Mace and Pagel (1994:557-564) as well as Mace and Pagel themselves (1997: 305), it may be inappropriate to infer cultural "phylogenies" by applying maximum parsimony techniques that were developed for investigating evolutionary histories. Hartung (1997:347) argued that variations in independence among cultures are "like noise in a signal . . . more likely to obscure true relationships than to generate false ones," and Otterbein (1994:559) stated he "certainly would not cease using worldwide samples in comparative research because of the alleged difficulties that arise from the nonindependence of cases." Following his advice, we analysed (Table 3) all 27 cultures for which information on NVP symptoms were available in the HRAF.

There are two possible explanations for the HRAF results. First, pregnant women in corn-based societies may rarely eat foods that trigger NVP and subsequent aversions. Domesticated corn is bland-tasting, and some strains have minimal (Darnetty et al. 1993) or no chemical resistance to bacteria and fungi (Guo et al. 1998). This does not mean that corn is always safe, because some corn-dwelling spoilage microorganisms produce teratogens (e.g., *Penicillium*, *Fusarium* and *Aspergillus* spp.; Reddy and Reddy 1993). However, fresh cultivated corn and unspoiled, dried corn contain minimal teratogens. The alternative hypothesis is that corn-based diets are nutritionally deficient in some way that specifically disrupts the physiological mechanisms underlying NVP. For example, corn contains so little lysine, tryptophan and niacin that malnutrition would occur in societies with corn-based diets, were it not for alkali processing (Katz et al. 1974). Of the corn-based societies in which NVP symptoms have not been observed, information on food preparation was available only for two: the Tarahumara treat corn with alkali, but the Papago do not (Katz et al. 1974). In the Tarahumara at least, nutritional deficiency is unlikely to account for the absence of morning sickness.

Additional evidence derives from studies of geophagy. Clay eating is widespread in traditional societies. Many types of clay contain compounds that (i) coat the mucous membranes of the digestive tract and protect them from damage by toxins, and (ii) bind and prevent absorption of ingested phytochemicals, microbial toxins, and microorganisms (Vermeer and Ferrell 1985; Phillips et al. 1990; Johns and Duquette 1991a). Even acorns and wild potatoes can be made edible by preparing them with certain clays (Johns and Duquette 1991b; Diamond 1999).

If absence of NVP is associated with lack of dietary toxins, rather than nutritional deficiencies, then in cultures exhibiting NVP women should be able to reduce symptoms through practices that remove or detoxify dietary teratogens. In support, Wiley and Katz (1998) found that women in many traditional African societies practice geophagy in early pregnancy to relieve NVP symptoms. They also reported that geophagy was more prominent in non-dairying societies, and that this was likely due to the higher levels of phytochemicals in the diets of these societies.

Geophagy also has been shown to serve a protective function in nonhumans. Chimpanzees in Uganda and Tanzania practice geophagy, and Mahaney et al. (1996, 1997) found that the soils they eat have a high content of metahalloysite, a partially hydrated clay mineral with antidiarrheal properties like the pharmaceutical Kaopectate™. Mahaney et al. suggested that the chimpanzees were medicating themselves in response to gastrointestinal distress. Geophagy also occurs in many other herbivorous mammals and seed-eating birds; in parrots at least, it reduces absorption of toxic phytochemicals into the bloodstream (Gilardi et al. 1999). These comparative observations support the hypothesis that it was the absence of toxins, rather than nutritional deficiency, that eliminated NVP in certain traditional societies (Table 2).

A more decisive test of the alternative explanations for the HRAF data would involve comparing miscarriage rates. The maternal and embryo protection hypothesis predicts that miscarriage rates of women in corn-based societies (or women in any society who eat nothing but bland-tasting vegetables and do not exhibit NVP) should be as low as miscarriage

rates of women who exhibit NVP in societies where meats and strong-tasting vegetables are dietary staples (e.g., Figure 4). In contrast, the nutritional deficiency hypothesis predicts that miscarriage rates of women in corn-based societies (or bland vegetarians) should be as high as miscarriage rates of women who do not exhibit NVP in societies where meats and strong-tasting vegetables are dietary staples. Unfortunately, HRAF sources gave no indications of relative miscarriage rates in corn-based and meat-based societies, and there are no data on miscarriage rates for women who ate only bland-tasting vegetables (e.g., corn, grains).

Two other findings are less consistent with the maternal and embryo protection hypothesis. First, although NVP was clearly associated with reduced miscarriage rates, its occurrence did not reduce the chances of low birth weight or birth defects. These negative outcomes can result from environmental insults that occur in the first trimester (Smith et al. 1998), so under the maternal and embryo protection hypothesis, NVP should have been associated with reduced frequencies of both outcomes. Second, if NVP indeed serves a protective function, then artificially alleviating the symptoms should leave the mother and embryo more vulnerable. However, Kullander and Källén (1976) reported that pregnant women who used antiemetic drugs (mainly antihistamines) to alleviate NVP were less likely to miscarry than women who did not use antiemetics. Many other investigators have studied the effects of antinauseant drugs on congenital malformations. Seto et al. (1997) conducted a meta-analysis of such studies. They reported that pregnant women who had taken antiemetics in the first trimester were slightly but significantly less likely to bear children with major malformations than women who had not taken antiemetics.

Although these findings appear to contradict our hypothesis, they may only indicate that women with the most severe symptoms (i.e., those least likely to miscarry anyway: Figure 6) were the most likely to use antiemetics. Indeed, Kullander and Källén (1976:105) argued that the correlation "is probably completely due to less frequent and possibly less severe morning sickness complaints in pregnancies ending in miscarriage," and Seto et al. (1997) noted that their results could indicate either that eliminating vomiting reduces anomalies by creating better metabolic conditions for fetal development, or that women who experienced NVP severe enough to seek drug relief were bearing the healthiest embryos. In addition, since women in these studies took antiemetics to alleviate symptoms, they may have already developed aversions to potential pathogen- or teratogen-containing foods, thereby protecting themselves and their embryos by a judicious selection of diet before NVP symptoms were suppressed.

Given the frequency and significance of NVP in humans, we were surprised to find so little evidence of it among nonhuman mammals. Indeed, one reason the embryo protection hypothesis has not been adequately tested is that no appropriate animal models are available. There are several possible reasons why NVP is unknown outside of dogs, rhesus macaques, and chimpanzees. First, domesticated and captive mammals (e.g., lab animals, household pets, zoo specimens) often receive sterilized and bland diets that are relatively free from microorganisms and toxic phytochemicals, so NVP might seldom be triggered. Alternatively, females that exhibited malaise (nausea and vomiting) during gestation may have been artificially selected against in captive breeding programs. Second, NVP may be unnecessary for maternal and embryo protection in mammals that have efficient physiological mechanisms for destroying ingested bacteria and fungi, and detoxifying secondary metabolites of plants and microorganisms (e.g., pegastric fermentation in brocket deer, *Mazama* spp.: Bodmer 1991). Alternatively, herbivorous mammals may simply avoid eating the most toxic plants during gestation, and pregnant carnivores may pass up carrion that has been heavily infested with especially virulent or toxic bacteria or fungi. Third, NVP may actually be more widespread, but it has gone unnoticed owing to difficulties of detection. Free-living female mammals would have to be observed pre- and postconception, and detailed time budgets of foraging behavior and food preferences would have to be assembled to reveal subtle changes in dietary habits.

Two general hypotheses alternative to maternal and embryo protection have been pro-

posed to explain NVP. First, it may simply be a side effect of viable pregnancies. Stein and Susser (1991:165) argued that "nausea is affected by the outcome [of pregnancy]. It manifests with differing frequencies according to whether a pregnancy will terminate either as a miscarriage or as a live birth." Haig (1993, 1996) agreed that nausea and vomiting might be effects rather than causes, either of some placental factor that itself reduces the chances of miscarriage, such as human chorionic gonadotropin (hCG), or of genetic conflicts of interest between a fetus and its mother. The latter idea, which originated with Trivers (1974), is that because the fetus is more related to itself than to its future siblings, especially if they have different fathers, it is selected to take more nutrition from the mother than is optimal for her to give to any one offspring. According to Haig (1993), the more healthy and vigorous the fetus, the more capable it is of competing effectively for maternal resources, resulting in reduced chances of being miscarried but with more obvious indications of physiological conflict with its mother.

Five facts do not accord with these side-effect hypotheses. First, NVP is *not* a necessary concomitant of a viable pregnancy, nor is it only associated with viable pregnancies. In our sample of 5,235 pregnancies in which NVP did not occur (Figure 4), only 535 (10%) resulted in miscarriages, and in our sample of 13,192 pregnancies in which NVP did occur, 509 (4%) resulted in miscarriages. Second, no consistent differences in types or levels of reproductive hormones between emetic and nonemetic viable pregnancies have been discovered. Although reproductive hormones are necessary for the expression of NVP, they are not, by themselves, sufficient to trigger NVP symptoms (Andrews and Whitehead 1990). Third, there are seven societies in which NVP symptoms have never been reported (Table 3), although viable pregnancies routinely occurred. Complete absence of NVP obviously runs contrary to the side-effect hypotheses. Fourth, these hypotheses do not predict either (i) specificity of food aversions or (ii) patterns of change in aversions across the course of pregnancy (Figures 7–9), whereas both phenomena are consistent with protecting the mother and embryo.

Fifth, under Haig's (1993, 1996) genetic conflict hypothesis, manifestations should be more pronounced in younger women because they should withhold more resources from current offspring since they have greater future reproductive opportunities than older women. Conflict should be especially evident in adolescent mothers because they themselves are still growing and would directly compete with the embryo for key resources (e.g., Wallace et al. 1996). Most studies, however, have found no relationship between maternal age and NVP (e.g., Medalie 1957; Järnfelt-Samsioe et al. 1983; Vellacott et al. 1988; Chin 1989; Paarlberg et al. 1996; Gadsby et al. 1997; but see Klebanoff et al. 1985; Jinadu and Daramola 1990), and in a study of 78 pregnant 14–19 year olds, DiIorio (1985) reported that the youngest women (ages 14–15) had the lowest incidence of NVP (27% vs. 61% of 16–19 year olds). Finally, Haig's conflict hypothesis suggests that NVP symptoms should also be more pronounced later in pregnancy because an older, larger fetus requires more resources and may be more effective in competing for them. NVP symptoms peak early in pregnancy, however, when the embryo is tiny (Figure 3).

Rather than dismissing Stein and Susser's (1991) and Haig's (1993) hypotheses, we suggest that it may be more appropriate to view them as mechanistic complements to maternal and embryo protection (i.e., hypotheses at different levels of analysis). Under this interpretation, reproductive hormones that accompany viable pregnancies set the physiological stage for the expression of NVP by sensitizing the neural pathways that trigger nausea and vomiting (Andrews and Whitehead 1990). A likely candidate is hCG, whose concentration in maternal blood peaks during weeks 8 to 10 of pregnancy and declines dramatically by weeks 14 to 18 (Riley 1959; Tulchinsky and Hobel 1973; Kauppila et al. 1984), thus closely paralleling the time-course of NVP (Figure 3). A rise in estradiol coincides with the onset of NVP, but its concentration continues to increase after NVP symptoms have diminished (Buster and Simon 1989). Although these hormones (and others) are necessary to support pregnancy, their association with nausea and vomiting, especially in response to specific dietary triggers (Figures 7–10), requires a func-

tional analysis. This reemphasizes the complementarity of hypotheses about fitness effects and their underlying mechanisms (e.g., Tinbergen 1963; Sherman 1988).

The second alternative hypothesis was proposed by Deutsch (1994:277), namely that "pregnancy sickness and mastalgia have evolved to reduce frequency of sexual intercourse in early pregnancy." The idea is that NVP alerts a woman's partner to her pregnancy, thereby discouraging behavior that might harm the embryo. NVP also might signal a woman's partner and her kin of the impending need for additional food and protection. There are three reasons to doubt this "communication" hypothesis, however. First, intercourse does not affect the viability of a pregnancy, except possibly during the final 4 to 6 weeks before birth (Pritchard and MacDonald 1980:319), by which time NVP has typically waned (Figure 3). Second, the communication hypothesis does not predict the absence of NVP in any society, unless pregnant and lactating women always live alone (i.e., there is no one to communicate with). This certainly does not occur in the seven societies in which morning sickness has not been observed (Table 2). Most importantly, NVP peaks after 8 weeks of gestation, well after other less costly and uncomfortable indications of pregnancy have become apparent. The most obvious of these is cessation of menstruation, which occurs some 4 weeks earlier. Our perusal of HRAF files revealed that this is a universally recognized indicator of pregnancy. For example, in the Okinawa (Maretzki and Maretzki 1963:456), the "[c]essation of menstrual periods signals the start of pregnancy," and in the Gond (Grigson 1949:263) "all women know when they miss their first menstruation that they are probably starting to bear a child." In the Alor (DuBois 1944:28–29), "the wife knows she is pregnant . . . when she ceases to have monthly periods," and a Tongan woman "uses several signs as an indication of pregnancy. She finds herself without much appetite and feels physically weak. She is also abnormally sensitive to bad smells. Menstruation ceases" (Beaglehole and Beaglehole 1941:78). And in the Terena (Oberg 1949:38), "a woman becomes aware that she is pregnant when her menses cease and she has spells of nausea and is particular about her food."

Haig (1993:509) stated that "various hypotheses . . . have been proposed to account for nausea during pregnancy, but I am unable to come to clear conclusions because the evidence remains equivocal." Table 4 summarizes information that supports, contradicts, and is equivocal regarding the three major alternatives. Available information is most consistent with the hypothesis that NVP protects the mother and her embryo from dangerous substances in food. Protection is provided by immediately eliminating the offending foods—especially animal products and plant toxins—from the woman's body (vomiting), and learning to avoid the nauseating tastes subsequently. More thorough testing of this hypothesis could be accomplished by comparing NVP symptoms and pregnancy outcomes among women from the same society who ate very different diets (e.g., meats and vegetables vs. vegetables only vs. grains and cereals only). Such studies must be conducted before specific dietary practices based on the maternal and embryo protection hypothesis are adopted.

Nonetheless, our results have two practical implications. First, there is no reason to believe that alleviating the symptoms of normal NVP (e.g., excluding hyperemesis gravidarum) will improve the outcome of a pregnancy. Indeed, doing so could have the opposite effect, if it interferes with the expulsion of potentially dangerous foods, or with learning to avoid them. Second, there is no reason to believe that discouraging pregnant women from avoiding foods to which they develop aversions will improve their pregnancy outcome. In fact, forcing women to eat aversive foods could be detrimental if it increases the embryo's exposure to foodborne illnesses and teratogenic or abortifacient chemicals. Of course, experiencing NVP does not guarantee that a pregnancy will have a positive outcome, nor does a lack of NVP symptoms portend pregnancy failure. An overwhelming majority of women carry their pregnancies to term and have healthy babies, whether they experience NVP or not (in developed countries, at least). Our key point is that "morning sickness" apparently has served a useful protective function, and should therefore be considered and treated as an adaptation.

TABLE 4

Evidence for and against three alternative hypotheses to explain NVP

Hypothesis	Supporting evidence	Contradictory evidence	Equivocal findings[1]
Maternal and embryo protection	• Women with NVP are less likely to miscarry • Pregnant women who vomit are less likely to miscarry than those who only are nauseated • NVP and aversions peak when embryonic tissues are most susceptible to harm from teratogens (weeks 6–18) and decrease thereafter (as embryonic susceptibility declines) • Foods commonly found aversive are potential sources of teratogens and pathogens • Pregnant women are immunosuppressed, and the greatest number of aversions are to the foods most likely to contain pathogens (i.e., animal products) • Among societies, absence of NVP is related to increased corn and decreased meat in the diet	• NVP is not consistently associated with lower risk of severe birth defects, low birth weight, or preterm birth	• NVP is not consistently associated with lower risk of minor anomalies or neonatal mortality • Taking certain antihistamines reduces NVP, but does not increase chances of birth defects
Epiphenomenon of a viable pregnancy or of genetic conflict	• Women with NVP are less likely to miscarry but are not at lower risk of anomalies, preterm birth, or low birth weight • Taking certain antihistamines to relieve NVP does not increase chances of birth defects or miscarriages	• NVP is absent in 7 cultures • 90% of women without NVP have viable pregnancies • NVP is not consistently associated with levels of hormones that are necessary for the maintenance of pregnancy • NVP is not reliably associated with age (conflict hypothesis) • NVP and aversions decrease as pregnancy progresses (conflict hypothesis)	• NVP is associated with diet • There are clear and consistent patterns in types of foods that pregnant women find aversive
Prevent sexual intercourse/ Communicate to mate or kin that she is pregnant	• NVP is recognized as a sign of pregnancy	• NVP occurs early in pregnancy, but any risk from intercourse occurs later • NVP is absent in 7 cultures • Other well-recognized, less costly signs of pregnancy are apparent early in pregnancy	• NVP is associated with diet • There are clear and consistent patterns in types of foods that pregnant women find aversive

[1] "Equivocal findings" are findings not predicted by the hypothesis, but also not contradictory to critical predictions of the hypothesis.

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