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A Controlled, Longitudinal Study of Olfactory Perception and Symptoms of Pregnancy Sickness

by

Farhad N. Dastur

Submitted in partial fulfillment of the requirements

for the degree of Doctor of Philosophy

at

Dalhousie University

Halifax, Nova Scotia

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The undersigned hereby certify that they have read and recommend to the Faculty of Graduate Studies for acceptance a thesis entitled, "Smell Perception and Pregnancy Sickness: A Test of the Pregnancy Sickness as Adaptation Theory" by Farhad N. Dastur in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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DEDICATION

I dedicate this thesis to the pregnant and nonpregnant women who generously gave the gift of their time to participate in my study. The opportunity to work with you was a singular honor and a rare privilege.

> "Out under the moon and the stars, alone with his son that eighth night, Omoro completed the naming ritual. Carrying little Kunta in his strong arms, he walked to the edge of the village, lifted his baby up with his face to the heavens, and said softly, 'Fend kiling dorong leh warrata ka iteh tee.' Behold—the only thing greater than yourself."
>
> —Alex Haley (1976), Roots.

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STRUCTURED ABSTRACT

Background: Pregnancy sickness—food/odor aversions, nausea and vomiting—affects 50-90% of women during early pregnancy. Very little data exists on changes in olfactory perception as part of the pregnancy sickness symptomatology.

Objectives: To document changes in olfactory sensitivity and identification, food aversions and cravings, and nausea and vomiting at each trimester and postpartum.

Design: A controlled, longitudinal, quasi-experimental study.

Participants: Nineteen pregnant and 18 nonpregnant healthy women volunteers.

Main Outcome Measures: Odor detection thresholds, olfactory identification ability, number of food aversions and cravings, total symptomatic distress over a 12-hour period from nausea and vomiting.

Results: Olfactory sensitivity was heightened at each trimester, but not postpartum, relative to nonpregnant women and was greatest at first trimester. Olfactory identification did not differ between groups or between the three trimesters and postpartum. Food aversions did not differ between pregnant and nonpregnant women, but, first trimester aversions were higher than second trimester, third trimester, and postpartum. Food cravings did not differ between groups or between the three trimesters and postpartum. First trimester women had more vegetable aversions and more fruit cravings than controls. First trimester distress from nausea and vomiting was greater than controls.

Conclusions: Olfactory sensitivity, vegetable aversions, fruit cravings, and nausea and vomiting increased during the first trimester relative to nonpregnant women. Following independent replication of these results, consideration should be given to broadening the definition of pregnancy sickness to include increased first trimester olfactory sensitivity.

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"...When from a long-distant past nothing subsists, after the people are dead, after the things are broken and scattered, still, alone, more fragile, but with more vitality, more unsubstantial, more persistent, more faithful, the smell and taste of things remain poised a long time, like souls..."

—Marcel Proust, Remembrance of Things Past (A la Recherche du Temps Perdu).

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Q.E.D.

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The Participants

Final acknowledgment goes to the women whose rich experiences are partially recorded in this document. Respect for their confidentiality precludes the printing of their names. To them I say, "you are fondly remembered and deeply appreciated."

CHAPTER ONE

INTRODUCTION

1.0. General Introduction

Pregnant women frequently report experiencing alterations in their olfactory perceptions, such as increases in olfactory sensitivity and changes in odor preferences. These reports have been predominantly anecdotal in nature; very little empirical evidence exists that documents specific pregnancy-related olfactory changes (e.g., Cooksey, 1995; Doty, 1986; 1995; Gilbert & Wysocki, 1991; Laska, Koch, Heid, & Hudson, 1996). Published studies on changes in olfactory perception during pregnancy, particularly the early studies, are few in number, small in sample size, and rely on weak experimental designs and imperfect measurement methods (e.g., Hansen & Glass, 1936; Schmidt, 1925). Thus, the present state of our knowledge is characterized by an inconsistent and incoherent picture of the specific nature and consequences of potential pregnancy-related olfactory changes.

Understanding the nature of olfactory changes is important for at least six reasons. First, olfaction serves as an early warning system for the detection and recognition of harmful environmental substances such as smoke, rancid food, and noxious fumes and chemicals (Doty, 1979b; Doty & Kimmelman, 1986). For example, sulphurous-smelling mercaptans are added to natural gas (which humans cannot perceive) so that natural gas leaks may be detected.

Second, olfactory disturbances can impede performance in certain occupations such as food preparation, product testing in the food and beverage industries, water works

utilities, and the perfume industry (Doty, 1995). Normal olfactory functioning is also important in occupations where certain odors signal danger. Some fire-fighting departments screen their workers for their ability to identify smoke and burning electrical wires; some public utilities screen their workers for their ability to identify leaking natural gas (Doty, 1995).

Third, olfaction plays a critical role in determining food palatability and intake (Booth, 1990; Le Magnen, 1992; Mozell, Smith, Smith, Sullivan, & Swender, 1969; Wysocki & Pelchat, 1993). The full sensory experiences involved in food consumption are not reducible to the five discrete tastes of sweet, sour, bitter, salty, and "umami" (Japanese for "savory") (Brand, 1997); rather, olfactory perception appears to be a significant mediator in determining flavor (Mattes & Cowart, 1994; Rozin, 1982). A comprehensive study of 750 patients from the University of Pennsylvania Smell and Taste Center revealed that complaints of taste loss typically reflect loss of olfactory not gustatory function (Deems et al., 1991). Out of 586 patients reporting olfactory loss, 74% believed that they also suffered from gustatory loss; however, results showed that fewer than 4% actually had a demonstrable gustatory deficit.

Fourth, olfactory disturbances can lead to nutritional problems through shifts in food palatability, the development of learned food aversions, altered dietary preferences, and, more indirectly, changes in caloric intake (Cowart, Young, Feldman, & Lowry, 1997; Doty & Kimmelman, 1986; Doty, 1977; Ferris, Schlitzer, & Schierberl, 1986; Friedman & Mattes, 1991; Goodspeed, Gent, & Catalanotto, 1987; Mattes, 1995; Mattes & Cowart, 1994; Schiffman, 1983). Given the established link between olfaction and dietary selection and the literature on pregnancy's influence on dietary selection (Hook, 1980;

Rodin & Radke-Sharpe, 1991), it is germane to ask whether pregnancy-related changes in olfaction may underlie pregnancy-related shifts in dietary selection

Fifth, substances in the maternal diet can cause changes in the composition of the amniotic fluid which can influence the *in utero* olfactory, gustatory, and trigeminal experiences of the developing fetus (Bartoshuk & Beauchamp, 1994; Beauchamp, Cowart, & Schmidt, 1991; Hauser, Chitayat, Berns, Braver, & Muhlbauer, 1985; Mennella & Beauchamp, 1997). A remarkable placebo-controlled experiment by researchers at the Monell Chemical Senses Center showed that the scent of garlic was present in the amniotic fluid of pregnant women who consumed capsules containing the essential oil of garlic (Mennella, Johnson, & Beauchamp, 1995). Later in gestation, the fetus swallows large amounts of amniotic fluid and has open airway passages that are exposed to amniotic fluid (Pritchard, 1965; Renfree, Hensleigh, & McLaren, 1975; Schaffer, 1910); thus, the fetus encounters changeable olfactory and gustatory stimuli. Animal studies have also established that olfaction occurs *in utero* (Schaal & Orgeur, 1992), and have taken the human findings one step further by showing that certain odors experienced *in utero* were preferred postnatally (Hepper, 1987; 1988; Smotherman, 1982a,b).

Sixth, much evidence now links maternal malnutrition to adverse fetal outcomes such as fetal growth retardation, congenital malformations, spontaneous abortion, premature birth, and low birthweight (Committee on Nutritional Status during Pregnancy and Lactation, 1990; Hurley, 1980; Seller, 1987; Stein, Susser, Saenger, & Marolla, 1975). For example, dietary folate deficiencies are associated with neural tube defects (American Academy of Pediatrics, 1993) which can be prevented by periconceptional

vitamin supplementation (Czeizel & Dundas, 1992; Forman et al., 1996). In addition to folate, pregnant women relative to nonpregnant women require higher intakes of iron, protein, vitamins E, K, C, B_6, B_{12}, magnesium, iodine, niacin, riboflavin, thamin, zinc, and selenium in order to have healthy pregnancies (Whitney & Rolfes, 1996). Given the importance of maternal nutrition on embryonic and fetal health, and given the influences of olfaction on nutrition (e.g., Mattes, 1995; Mattes & Cowart, 1994), it becomes apparent that significant changes in olfactory perception may be part of a web of causal links connected to pregnancy outcomes.

Clinically, it is important to know whether changes in olfactory function might place some pregnant women—and their developing babies—at nutritional risk. Understanding the nature of pregnancy-related olfactory changes thus becomes a clinically meaningful and theoretically interesting research question. The attempt to provide an initial answer to that question provides the central justification of this thesis.

Pregnancy sickness is a physically uncomfortable, psychologically distressing condition characterized by nausea, and/or vomiting, and/or food aversions and cravings, and experienced by 50-90% of all pregnant women world-wide (Baylis, Leeds, & Challacombe, 1983; Biggs, 1975; Brandes, 1967; Brown, Kahn, & Hartman, 1997; Cruikshank & Hays, 1991; Crystal, Bowen, & Bernstein, 1999; Dickens & Trethowan, 1971; DiIorio, 1985; Edwards, McSwain, & Haire, 1954; Fairweather, 1968; Finley, Dewey, Lonnerdal, & Grivetti, 1985; "First International Conference on Nausea and Vomiting of Pregnancy," 1998; Fitzgerald, 1984; Gadsby, Barnie-Adshead, & Jagger, 1993; Giles, 1893; Harries & Hughes, 1958; Hook, 1976; 1978; 1980; Jarnfelt-Samsioe, Samsioe, & Velinder, 1983; Klebanoff, Koslowe, Kaslow, & Rhoads, 1985; Lacroix,

Eason, & Melzack, 2000; Leduc, 1988; Loewen, 1988; Macy, 1986; Marcus, 1965; Melzack, Rosberger, Hollingsworth, & Thirwell, 1985; Mintum & Weiher, 1984; National Research Council, 1992; O'Brien & Naber, 1992; O'Brien & Newton, 1991; O'Brien & Relyea, 1999; O'Brien & Zhou, 1995; Petitti, 1986; Pope, Skinner, & Carruth, 1992; Posner, McCottrey, & Posner, 1957; Profet, 1988; 1992; Rainville, 1998; Rodin & Radke-Sharpe, 1991; Rofe, Blittner, & Lewin, 1993; Taggart, 1961; Tierson, Olsen, & Hook, 1986; Vellacott, Cooke, & James, 1988; Walker, Walker, Jones, Verardi, & Walker, 1985; Weigel & Weigel, 1989a,b; Willson & Carrington, 1979; Worthington-Roberts, Little, Lambert, & Wu, 1989).

The symptoms of pregnancy sickness—often inappropriately called "morning sickness"—may occur at any time of the day, and though the prevalence is greatest during early pregnancy, symptoms may persist throughout the pregnancy until birth (Lacroix et al., 2000). The principal symptoms of pregnancy sickness, as commonly understood, are nausea and vomiting; however, this thesis uses an expanded definition of pregnancy sickness which will be delineated later.

A relatively recent and controversial theory by evolutionary theorist Margie Profet (1988; 1992) views pregnancy sickness as an adaptation designed to protect the embryo from toxins found in the maternal diet. It is a controversial theory, partly because it views pregnancy sickness as a normal feature of pregnancy rather than as a pathology, and partly because it proposes that pregnancy sickness has been shaped by evolutionary forces to meet the unique needs of the embryo, and is not merely an epiphenomenon secondary to pregnancy-related hormonal changes. A key prediction of Profet's theory is that olfactory sensitivity will increase during first trimester as a mechanism for detecting

even minute levels of food-associated toxins (e.g., plant insecticides, bacterial break-down products, molds, rancid food). Because Profet's pregnancy sickness theory makes an explicit prediction about olfactory sensitivity during pregnancy, this thesis also sets out to examine whether first trimester women experience increased olfactory sensitivity relative to nonpregnant women.

None of the previous studies have taken a theoretical approach to the study of pregnancy-related olfactory change. The theory-testing approach of this thesis is significant because the science of psychology is best advanced when we have theories to guide our experiments and data to test our theories.

Chapter 1 provides a general introduction to the thesis, its structure and scope. Chapter 2 reviews the literature on pregnancy-related olfactory changes and highlights problems with these studies. Chapter 3 reviews the literature on pregnancy-related food aversions, cravings, and pica and highlights problems with these studies. Chapter 4 discusses pregnancy sickness including prevalence estimates, historical context, etiology, treatments, and the special case of hyperemesis gravidarum. Chapter 5 discusses Profet's theory of pregnancy sickness as an adaptation, states the logic of her argument along with supporting evidence, and places the theory within the context of Darwinian medicine. Discussions on toxicology, teratology, and embryonic development provide background information for understanding the theory and its specific predictions. Chapter 6 describes the research motivating this thesis: a case-controlled, longitudinal study primarily investigating olfactory changes at each trimester, with secondary investigations of food aversions and cravings, and nausea and vomiting. This description includes the study's objectives, predictions to be tested, and significance. Chapter 7 documents the study's

methods, while chapter 8 documents the results. Chapter 9 is a general discussion that integrates the study's findings with existing data and theory. Problems and limitations with the study are examined, alternative theories are discussed, and suggestions for future research are proposed. Eight figures and nine tables appear in the thesis. Appendices document the study's raw data, clinical information forms, and data collection forms. A reference section containing 575 references concludes the thesis.

The stylistic format of this thesis follows the latest guidelines set by the Faculty of Graduate Studies of Dalhousie University, and the guidelines of the Publication Manual of the American Psychological Association (1995). In the event of a discrepancy between the two styles, the Faculty of Graduate Studies guidelines took precedence.

1.1. Publication Search Strategies

The studies cited in this thesis cover a wide range of disciplines. The principal method used for uncovering relevant publications involved computerized searches of the PsycLIT™ database (Jan. 1974 to April, 2000) and the MedLine™ database (Jan. 1966 to April, 2000). A more modest search was undertaken using Dissertation Abstracts International, Section B, The Sciences and Engineering (Jan. 1990 to Jan. 1998). The following keywords (or their close variants) were used in the index search: "olfaction," "pregnant," "morning sickness," "nausea," "hyperemesis gravidarum," and "food aversions." References were also found by recovering those references cited in relevant publications. Some references were obtained from participation in the following conferences: The Fourteenth Biennial Conference of the International Society for Human Ethology (Vancouver, August, 19-23, 1998), The Fifth National Health Promotion Research Conference (Halifax, 1997), The Ninth Annual Human Behavior and Evolution

Society Conference (Tucson, 1997), and The Animal Behavior Society Conference (Seattle, July, 1994). Publications were also obtained through informal methods such as word-of-mouth, or by mailing or e-mailing researchers to obtain their most recent or difficult-to-find publications.

1.2. General Note on Definitions & Terminology

The many technical terms used in this thesis have been drawn from the diverse fields informing the thesis: developmental biology, neurobiology, toxicology, evolutionary biology, nutritional science, obstetrics, physiology, and perceptual psychology. Attempts have been made to define these terms using the most widely accepted definitions within the relevant discipline. Where multiple definitions exist or where definitions are in contention, efforts have been made to be clear about which definition is being used here. During the literature review, studies reporting statistically significant or non statistically significant findings (i.e., differences or associations) are often summarized. When reporting significant findings, the standard convention of statistical significance (i.e., $p < .05$) is used unless otherwise stated.

CHAPTER TWO

2.0. Olfactory-Related Terminology

"Olfactory function" is a global concept subsuming several dissociable subcomponents (Doty & Kobal, 1995; Duncan & Smith, 1995): (a) olfactory sensitivity, (b) olfactory discrimination, (c) olfactory recognition, (d) olfactory identification, and (e) olfactory perception.

"Olfactory sensitivity" reflects the lowest concentration of a stimulus that can be discerned (i.e., the absolute olfactory threshold). Qualitative odor sensations are rarely perceived at very low odor concentrations; instead, the ephemeral presence of an odor is detected. The detection threshold is the lowest odorant concentration where such a presence is reliably detected; the recognition threshold is the lowest concentration of odorant required to activate olfactory receptor neurons which results in the reliable perception of that odor quality (e.g., lemon-like). Olfactory sensitivity may be increased or decreased, and these alterations may be limited to some odors or to all odors. It should be noted that olfactory sensitivity and olfactory acuity are synonyms, and both are inversely related to odor detection thresholds: increased sensitivity (or acuity) necessarily implies lower odor detection thresholds.

"Olfactory discrimination" requires individuals to decide whether two odor stimuli have the same or different quality. A time-consuming variant of this procedure is called multidimensional scaling (Schiffman, Reynolds, & Young, 1981). "Olfactory recognition" requires the individual to recognize but not identify an odor stimulus within a presented set. A variant of this test presents the individual with a target odor and requires them to then select the target from a larger set of odor stimuli.

"Olfactory identification" is a commonly used procedure for assessing olfactory function. Three variants of this procedure exist: (a) identifying an odor stimulus by name (this involves a verbal memory component), (b) indicating whether the odor stimulus is similar to an object named by the examiner (e.g., does this smell like lemon?), and (c) identifying the odor from a list of names.

"Olfactory perception" involves assessing the subjective experiences associated with odors such as their intensity, familiarity, evocativeness, and pleasantness. The study of qualitative olfactory perception is not yet refined and relies largely on indirect measures such as similarity scaling and odor naming (Lawless, 1997; Schiffman, 1974).

The following olfactory terms are generally accepted, although inconsistencies in terminology still exist (Amoore, 1977; Cowart et al., 1997; Duncan & Smith, 1995; Leopold, 1995; Snow, Doty, Bartoshuk, & Getchell, 1991). "Anosmia" (also called general or total anosmia) refers to an inability to detect any odor sensation. "Hyposmia" or "microsmia" refers to a decreased sensitivity to or a decreased identification of some or all odorants. Sometimes "anosmia" is used more broadly to refer to anosmia, as defined above, and to hyposmia. "Specific anosmia" refers to an inability or difficulty in detection of a specific odor compound or limited class of compounds in the presence of preserved general olfactory functioning. "Dysosmia" refers to distorted olfactory perception and can take two forms: "phantosmia" or "olfactory hallucination" which is the perception of an odor (usually unpleasant) that does not exist, and "parosmia" or "troposmia" which is a distortion in perception of an odor that does exist.

The terms "alterations," "disturbances," and "changes," with respect to olfactory function, are synonymous for the purposes of this thesis. These terms imply functioning that is out of the range of that normally expected, and could include both increased and decreased performance on standard tests of olfactory function. The reference point "normal" is used in its statistical sense. Terms such as "deficit," "deterioration," "impairment," and "damage" almost always refer to decreased test performance. These terms have negative connotations and are largely avoided in recognition of the

connotative assumptions embedded within scientific language—assumptions that exert subtle yet powerful influences on data interpretation, theorizing, and critical thought (Bernstein, 1971; Martin, 1992; Scheman, 1993).

2.2. Pregnancy-Related Changes in Olfactory Function

Changes in olfactory perception are frequently reported by pregnant women (Cooksey, 1995; DiIorio, 1985; Doty, 1986; Erick, 1993; 1995; Gilbert & Wysocki, 1991; Laska et al., 1996; Tao & Claude, 1994). However, little information exists on the incidence, prevalence, nature, function, and clinical implications of pregnancy-related changes in olfaction. A number of reasons account for this absence of data. First, investigating olfactory changes across pregnancy is a methodologically difficult, long, and labor-intensive endeavour (R. Doty, personal communication, 1994). Recruiting pregnant women can be difficult because of their legitimate concerns regarding the safety of their fetuses during experiments. Second, until quite recently, human olfactory studies have received little scientific recognition or financial support (Cowart et al., 1997). This is because many scientists and physicians believe that humans rely chiefly on visual and auditory input, and consider olfactory problems to be unimportant (Hastings, 1990). Methodological and theoretical problems also exist, as highlighted by Berne & Levy (1988), "Hence, investigations of the olfactory pathways are often carried out without a theoretical framework built on specific functional questions" (p. 189).

Until recently, it has been difficult to produce, control, and deliver olfactory stimuli—and to then measure the human perceptual responses to those stimuli (Berne & Levy, 1988; Hastings, 1990). Withal, the olfactory pathways themselves tend to be

diffuse and difficult to characterize—although modern imaging technologies have made remarkable progress in redressing this problem.

Studies on olfactory sensitivity during pregnancy conflict with each other. Several early studies reported a general increase in olfactory sensitivity during the first trimester (Henssge, 1930; Le Magnen, 1952; Luvara & Murizi, 1961; Steiner, 1922; Zwaardemaker, 1895); however, some have reported maximum sensitivity during the second or third trimesters (Good, Geary, & Engen, 1976; Laska et al., 1996). Schmidt (1925) reported anosmia during the first trimester while others have reported decreased sensitivity during late pregnancy (Hansen & Glass, 1936; Luvara & Murizi, 1961; Noferi & Giudizi, 1946).

In the largest assessment of olfactory perception during pregnancy ever undertaken, Gilbert & Wysocki (1991) investigated 13,610 pregnant and 277,228 nonpregnant U.S. women. The results of this study derived from a much larger mail-in "Smell Survey" conducted on behalf of the National Geographic magazine (September, 1986), and distributed to 10.7 million society members worldwide. A world-wide total of 1,420,000 (13% response rate) usable Smell Surveys were returned with 1,200,000 (84.5%) coming from the United States. Results from women aged 20 to 40 were analyzed—an age range that accounted for 95% of all pregnant participants. The nonpregnant women were older than the pregnant women (32.23 vs. 30.05 years respectively), and the majority (94.9%) of the combined sample identified their ethnicity as white. The menstrual cycle phase and use of hormone-based contraceptives among the nonpregnant women were not reported. Pregnant women were not asked to report their trimester. The Smell Survey form

contained six microencapsulated odorants chosen to represent a range of pleasantness, familiarity, and food-relatedness.

The researchers concluded that the Smell Survey results provided little evidence that pregnant and nonpregnant women differ in olfactory sensitivity. However, the conclusion is suspect on at least four grounds. First, no objective, psychophysical olfactory sensitivity test was administered to the women. Instead, participants were asked to rate their own sensitivity on a 1 to 5 Likert scale. Second, the participants filled out the survey under uncontrolled and probably very heterogenous "testing" conditions. For example, some women may have completed the survey in the morning while others completed it at night. Third, mail-in survey data is considered unreliable given the uncontrollable biases in the characteristics of the respondents. And fourth, no distinction was made between the three trimesters, thus preventing valid testing of the prediction of increased first trimester olfactory sensitivity.

The Smell Survey also revealed that a pattern of olfactory perceptual differences exist between pregnant and nonpregnant women that are difficult to interpret. The following statistically significant differences were found (all comparisons are relative to the nonpregnant women). Pregnant women more frequently detected the odor of eugenol (a spicy, pleasant-smelling odor and the major constituent of clove oil) and this difference persisted across the age range tested. This result is consistent with increased olfactory sensitivity but should not be interpreted as such for the four reasons outlined above. Pregnant women found isoamyl acetate (a banana-like fruity odor) and mercaptans (an unpleasant "warning" odor added to natural gas) more intense, but they found androstenone (a volatile steroid naturally produced in humans that smells pleasantly

musky to some people and like stale urine to others) and Galaxolide (a pleasant, synthetic musk note extensively used in the perfume industry) less intense than nonpregnant women. Eugenol, mercaptans, and Galaxolide were rated as less pleasant, but androstenone's musky/urinous odor was rated as more pleasant than nonpregnant women. Hedonic ratings for a given pleasant-rated odor typically show an inverse-U relationship: as odor intensity increases, the odor becomes increasingly pleasant, reaches a maximum, and then becomes increasingly unpleasant. However, no consistent relationship between odor intensity and hedonic ratings were found in this study.

Tao and Claude (1994) investigated food aversions and olfactory sensitivity during each trimester in a group of 195 French women. Sixty-one percent of the women developed food aversions, defined as a complete refusal of one or several foods which were usually consumed prior to pregnancy. Fifty-eight percent of these women thought that their specific food refusal was due to odor alone or to both the odor and taste of these foods. Seven percent thought that the food texture and appearance were important. Sixty-seven percent of all the women thought that their olfactory sensitivity had increased during the period of food aversions. Unfortunately, once again olfactory sensitivity was not assessed using objective methods.

Erick's (1995) paper on "hyperolfaction" (presumably increased olfactory sensitivity) and hyperemesis gravidarum (see definition in section 4.5) speculated that hyperolfaction serves to cue the pregnant woman to seek a cleaner, quieter, more temperate environment. Erick did not provide any objective data on the olfactory function of hyperemetic pregnant women to substantiate her claim of hyperolfaction.

Cooksey (1995) coined the term "olfactory craving of pregnancy" to describe a behavior in which pregnant women develop a "craving" to smell certain non-food substances. These substances include gasoline, bleach, ammonia, aerosol air freshener, aerosol disinfectant, pine oil cleaning solution, rubbing alcohol, nail polish remover, powder cleanser; chalk, body powder, concrete chips, crushed bricks, and powder detergent. These olfactory cravings occur in conjunction with or independently of pica, a pregnancy-associated practice in which women crave and consume nonfood substances such as dirt, clay, cigarette ashes, ice, freezer frost, flour, baking soda, baking powder, cornstarch, and powdered milk (Edwards et al., 1954; Horner, Lackey, Kolasa, & Waren, 1991; Pope et al., 1992). Cooskey's observational report was based on semi-structured discussions with 300 U.S. women shortly after they had given birth (within 48 hours for vaginal births and within 4 days for cesarean births). This method is weaker than interviewing the women during their experience of olfactory pica because it relies on memory for events that occurred months ago, and elicits those memories shortly after the physically and emotionally intense experience of childbirth (Coleman, 1969; Tobin, 1957). The women interviewed were described as low-income and from many ethnic groups, but predominantly African American; however, actual quantitative demographic data were not reported. Cooksey reported that several of the women commented that pregnancy had made their "nose" more sensitive; unfortunately, these reports were not documented with careful qualitative methods nor were they complemented by objective tests of olfactory function.

Laska et al. (1996) published what is perhaps the best study of pregnancy-related olfactory function to date. These researchers investigated 20 pregnant women (mean age

= 27.5 years) during each trimester (8-11 weeks, 20-23 weeks, and 32-36 weeks postconception) and once postpartum (2-3 months postpartum). Pregnant women were compared to a group of 20 (mean age = 26.2 years) age-matched, nonpregnant women tested in parallel. The menstrual cycle phase that the nonpregnant controls were in during testing was not reported; nor was it reported whether the controls were taking hormone-based contraceptives. All of the women were healthy, non-smokers, recruited from a gynecological clinic in southern Germany. The pregnant women had uncomplicated deliveries and pregnancies.

The women were evaluated for olfactory sensitivity, odor intensity perception, hedonic evaluation, and olfactory identification. In their abstract these researchers claimed, "no consistent differences in olfactory sensitivity or odor evaluation were found between the two groups" (Laska et al., 1996; p. 567). However, a closer examination of their results reveals that a number of statistically significant findings were obtained (all comparisons involve pregnant women versus nonpregnant controls). First trimester pregnant women had lowered olfactory sensitivity as measured by the *n*-butanol olfactory sensitivity test, while third trimester women had increased olfactory sensitivity. Pregnant women rated the odor of androstenone as more intense (first session), and rated the following odors as less familiar: clove (third session), aniseed (third and fourth session), peanut (first session), banana (second, third, and fourth sessions), a 12-component odor mixture (second and fourth session), and musk (fourth session). Pregnant women were also less often able to provide exact verbal descriptions for the following food-associated odors: peanut, aniseed, lemon, and banana. Pregnant women judged peanut less pleasant (first, second, and third sessions) and clove more pleasant (all sessions). These

researchers viewed these positive findings as theoretically uninteresting because the findings did not represent a "systematic shift" in olfactory function.

2.3. Problems with the Research on Pregnancy-Related Olfactory Function

When taken together, the relatively few published studies on pregnancy-related olfactory changes have presented a complex and sometimes contradictory profile, largely a consequence of unclear conceptual definitions and inconsistent or weak methodologies. Many of the published studies failed to include a control group. The best control group are nonpregnant women tested in parallel and matched on relevant variables such as age, smoking history, and health. Within this control group, the menstrual cycle poses an interesting problem: which phase of the menstrual cycle is most appropriate for comparison? This issue is important because changes in olfactory sensitivity as a function of menstrual cycle phase have been found, with sensitivity peaking at ovulation and again just before menses (Doty, 1986). To date, none of the studies that used nonpregnant women as controls reported or discussed whether menstrual cycle phase was controlled—leading one to assume that it was not.

The studies failed to report, reported ambiguously, or failed to control for stage of pregnancy. Stage of pregnancy is an important variable because collapsing across trimesters may even-out subtle but relevant differences specific to the physiologically, hormonally, nutritionally, psychologically, and developmentally different periods of pregnancy.

Most studies have been based on small sample sizes (except Gilbert & Wysocki, 1991) or have been clinical case studies which provide for a potential richness of qualitative detail, but do not allow for the detection of systematic statistical effects. Some

studies used cross-sectional or partially longitudinal designs, but their failure to test at each trimester—with the exception of Laska et al. (1996)—means that the pattern of olfactory changes across pregnancy remains unclear.

Another significant problem has been the general failure to use objective psychophysical tests of olfactory function that possess good psychometric properties. The phenyl ethyl alcohol odor detection threshold test and the University of Pennsylvania Smell Identification Test are two of the best and most commonly used tests of olfactory function (see Method section), yet none of the studies used either of these tests.

All of the published research on olfaction during pregnancy has been conducted on North American or European women. The absence of cross-cultural data precludes complete testing of theories that postulate universal biological or psychological mechanisms that operate in the face of diverse environmental and cultural conditions.

The studies reviewed neither proposed nor tested predictive conceptual models of how or why olfactory function changes during pregnancy. Conceptual models are important because they generate hypotheses that lead to testable predictions, they give a rationale for test selection, and they help frame and contextualize the interpretation of data (Cimino, 1994). This lack of a theoretical framework is very likely the reason why Gilbert & Wysocki (1992) and Laska et al. (1996) both concluded that systematic changes in olfaction were absent or difficult to interpret.

Taken together, the studies reviewed here lack literal replication: replication of results by independent investigators using the same measures, methods, conditions, and samples. They also lack compelling constructive replication (Lykken, 1968), in the sense of producing convergent results through the use of different measurement procedures,

experimental conditions, and samples. Thus, the state of the field is both data poor and theory poor. The attempt to overcome some of these criticisms informed the design of the study reported in this thesis.

CHAPTER THREE

3.0. Pregnancy-Related Food Aversions and Cravings: Definition of Terms

Presently, there are no objective, validated measures of food aversions or cravings in humans. Instead, studies have relied on self-reports in response to experimenter-defined descriptions. The following definitions illustrate this variability. Mattes (1991) defined food aversion as, "If a person becomes sick after eating a certain food, he/she may develop an intense dislike for that food, called an 'aversion,' whether or not the food was responsible for the illness" (p. 500). A study on dietary cravings and aversions in the postpartum period defined food cravings and aversions as, "A very unusual, unexplained desire or dislike for a food" (Worthington-Roberts et al., 1989, p. 648). Logue, Ophir, and Strauss (1981) defined food aversion as, "Whether they had ever eaten or drunk something and felt nauseated and then not wanted to eat or drink that thing afterwards" (p. 321). Blank and Mattes (1990) defined food craving as, "Have you ever had a craving or strong desire to eat or drink a food, beverage, or other substance (including spices, herbs, seasonings or items not usually thought of as edible) such that you simply could not resist consuming the item?" (p. 194).

In broad terms, pregnancy-related food aversions involve the rejection of foods consumed prior to the pregnancy. Typically, the rejection is so strong that consumption of the food or the mere thought of consumption leads to nausea or vomiting. Pregnancy-

related food cravings involve an overwhelming desire to consume foods not desired before pregnancy. Typically, the desire is so strong that actions are taken to satisfy the craving. Pregnancy-related pica is a relatively rare form of craving in which the substances desired for consumption are not typically thought of as foodstuffs. Table 1 lists some of the pregnancy-related food aversions, cravings, and pica that have been reported in the literature.

3.1. Pregnancy-Related Food Aversions and Cravings: Duration, Prevalence, and Sensory Aspects

Many studies have reported the development of food aversions, cravings, and pica during pregnancy (Baylis et al., 1983; Crystal et al., 1999; Dickens & Trethowan, 1971; Hook, 1978; Marcus, 1965; National Research Council, 1992; Pope et al., 1992; Rainville, 1998; Rodin & Radke-Sharpe, 1991; Taggart, 1961; Walker et al., 1985; Worthington-Roberts et al., 1989). Studies have also documented the existence of food aversions and/or cravings in other populations including the general population (Garb & Stunkard, 1974), university faculty (Bender & Matthews, 1981), college students (Logue et al., 1981; Logue, Logue, & Strauss, 1983), alcoholics (Logue, Logue, & Strauss, 1983), cancer, radiotherapy, and chemotherapy patients (Brewin, 1980; Mattes, Arnold, & Boraas, 1987; Mattes, Curran, Powlis, & Whittington, 1991), and women with premenstrual dysphoric disorder (Bancroft, Cook, & Williamson, 1999; Cohen, Sherwin, & Fleming, 1987; Evans, Foltin, & Fischman, 1999).

One of the interesting findings from this literature is that food cravings are typically more intermittent or short duration than food aversions which tend to be continuous and more persistent (Blank & Mattes, 1990). In support of this general finding, Tierson et al.

Table 1

Examples of Pregnancy-Related Food Aversions, Cravings, and Pica

Food Aversions	**Food Cravings**	**Pica Substances Ingested**
Meats	Fruit and fruit juices	Baking powder and soda
Eggs	Sweet desserts	Toothpaste
Pizza	Ice cream	Chalk
Fried Foods	Chocolate	Cigarette ashes
Cooked vegetables	Fast foods	Cornstarch
Poultry	Pickles	Clay
Italian foods and sauces	Italian foods and sauces	Cough drops
Coffee	Raw vegetables	Powdered detergent
Tea	Bread	Soil
Cola drinks	Sandwiches	Flour
Milk	Milk	Freezer frost
Non-chocolate sweets	Nuts	Ice (crushed, cubed, chopped)
Juice	Plain or fried potatoes	Match tips
Seafood	Salads	Powdered milk

Note. Adapted from Cooksey, 1995; Dickens & Trethowan, 1971; Hook, 1978; 1980; Horner, Lackey, & Kolasa, 1991; Loewen, 1988; Osman, 1985; Pope et al., 1992; Skinner, & Carruth, 1992; Taggart, 1961; Walker et al., 1985.

(1985) reported that pregnancy-related food cravings typically range between 2 and 20 weeks postconception whereas aversions may last throughout the pregnancy. Dickens and Trethowan (1971) noted that cravings begin later than aversions but that aversions persist longer. Craved items tend to be sweet tasting and pleasant smelling, while aversions tend to be bitter tasting, bad tasting (e.g., soapy, mealy, or dusty), and unpleasant smelling items.

Data from the general population seem to indicate a high prevalence of food cravings even among nonpregnant women. Blank & Mattes (1990) found cravings in 56% of their nonpregnant women with no history of pregnancy and 75% in nonpregnant women with a history of pregnancy. Dickens and Trethowan (1971) found cravings in 51% of their sample of pregnant women, while Tierson et al. (1985) found cravings in 76% of their sample of pregnant women. The prevalence of aversions in pregnancy is also quite high, with two studies both finding that 66% of pregnant women reported food aversions (Pope et al., 1992; Taggart, 1961). A longitudinal study of 129 American women found a significant association between experiencing food aversions and cravings before pregnancy and after pregnancy (Crystal et al., 1999).

Studies that have examined the sensory influences underlying food aversions have highlighted the importance of olfaction and gustation, with appearance (e.g., colour, shape, size), texture (e.g., consistency, temperature, moisture), and trigeminal stimulation playing smaller roles (Blank & Mattes, 1990; Booth, 1990). Thus, an aversion to a specific food may involve aversions to one or more of the following sensory features: odor, taste, appearance, texture, and/or trigeminal stimulation. Unfortunately, some researchers have conflated the term "food aversion" with the term "taste aversion." This

confusion occurs when using the colloquial definition of "taste" which is a global construct that includes the food's odor, temperature, appearance, and texture in addition to its taste in the strict sense of that term.

3.2. Pregnancy-Related Food Aversions

Early studies found that tea, coffee, fried food, the odor of food frying, and eggs were common pregnancy-related food aversions (Edwards et al., 1954; Harries & Hughes, 1958; Posner et al., 1957; Taggart, 1961). A study of 31 third trimester, adolescent (aged 11-17) American women found that the most frequently reported aversions were to meats, eggs, and pizza (Pope et al., 1992). Hook (1978) reported aversions for over 25 food items, based on interviews with 250 American women within days of delivery. The top five aversions were: (a) meats (16.8%), (b) Italian food sauces (9.6%), (c) vegetables in general (9.2%), (d) poultry (8.4%), and (e) fried foods (7.2%).

It is interesting to note that a number of studies have reported aversions to vegetables, typically of the Brassica type (e.g., cabbage, turnips, radishes). Reported frequencies of aversions to vegetables follow: 6% (Walker et al., 1985), 9% (Hook, 1978), 17% (Loewen, 1988), 18% (Dickens & Trethowan, 1971), and 35% (Finley et al., 1985).

In the Yale Pregnancy Study, 80 pregnant women and 80 nonpregnant women were followed from pre-pregnancy, through the trimesters, until delivery (Rodin & Radke-Sharpe, 1991). Participants were 160 American women recruited from health maintenance organizations and represented a broad section of the community. The presence of food aversions and cravings was determined prospectively by responses to a series of standardized questions. Participants were queried as to whether they had craved,

or avoided any particular food during the past two weeks, and then asked why. Over the three trimesters, the prevalence of food aversions ranged from 62-95% while the prevalence of food cravings ranged from 71-87%. These frequencies parallel findings from other studies (e.g., Walker et al., 1985) and underscore the ubiquity of pregnancy-related food aversions and cravings.

3.3. Pregnancy-Related Food Cravings

In a comparison of four early studies which examined the kinds of foods pregnant women craved, the most frequent food craving was for fruits, the number two item was sweet things other than fruit, vegetables came third, and—with the exception of one study—meat, fish, and eggs came in last (Dickens & Trethowan, 1971; Edwards et al., 1954; Harries & Hughes, 1958; Posner et al., 1957). Taggart (1961) found that approximately two-thirds of the women she studied manifested some food craving during pregnancy, with the most common craving being fruit. Hook's (1978) study (described in section 3.2) found that the top five food items craved were:
(a) ice cream (18.4%), (b) chocolate (15.6%), (c) citrus fruits and fruit juices (12%), (d) other fruits and fruit juices (12%), and (e) candy (11.6%). In Pope et al.'s (1992) study of pregnant adolescents, the most frequently reported cravings were for sweets, fruits and fruit juices, fast foods, pickles, ice cream, and pizza.

Food cravings were also found to lead to increased food intake, while aversions led to decreased food intake. Loewen's (1988) longitudinal study of 60 Canadian women revealed that the most common cravings were for ice cream, chocolate, non-chocolate desserts, and fruit. Seventy percent of the women reported at least one craving to sweet foods.

3.4. Problems with the Research on Pregnancy-Related Food Aversions and Cravings

Unlike the data on pregnancy-related olfactory function, the data set on pregnancy-related food aversions, cravings, and pica (cravings and consumption of nonfood items) consists of some cross-cultural data, data on adolescent and adult pregnant women, and a larger set of studies (Cooksey, 1995; Danford, 1982; Darwish, Amine, & Abdulla, 1982; Hook, 1978; Horner et al., 1991; Loewen, 1988; Dickens & Trethowan, 1971; Finley et al., 1985; Pope et al., 1992; Posner et al., 1957; Walker et al., 1985). However, this data is still limited by inconsistent definitions of what constitutes a food aversion, craving, or pica. Words such as "craving" and "aversion" have been criticized because they lack standardized, operational definitions and often fail distinguish between the hedonic-affective components of these words and their behavioral components (Reid, 1992; Weingarten & Elston, 1990).

Some of the studies have been limited by their retrospective designs. Thus, postpartum women would be asked to recall their food aversions, cravings, or pica during their pregnancy, a difficult memory task which involves recall for events several months after they occurred. For example, Cooksey (1995), Dickens and Trethowan (1971), and Hook (1978) all interviewed postpartum women within days of delivery, while Worthington-Roberts et al. (1989) interviewed women one month after delivery. The absence of instruments with good psychometric properties for assessing these phenomena raise concerns about the reliability and validity of much of this data, especially the quantitative aspects of it. Withal, it is likely that this data set underestimates the prevalence of these phenomena given the strongly negative attitudes that family, friends,

physicians, and the pregnant women themselves hold against dramatic changes in dietary practices. This is particularly true for pica, with many women self-describing their recently altered food selection practices as "crazy" (Cooksey, 1995; Crosby, 1976; Danford, 1982; Horner et al., 1991; Lackey, 1978).

CHAPTER FOUR

4.0. Pregnancy-Related Terminology

The average length of human gestation (from conception to birth) is 38 weeks (266 days) (Yu, 1994). In this thesis all pregnancy-related dates are defined from the time of conception (i.e., gestational age) unless otherwise specified. This definition is important because many obstetricians date a pregnancy from the last day of the woman's last menstrual period (LMP), rather than the actual date of conception. The difference in time between the last menstrual period and conception, is generally two weeks, although considerable variation is possible. Therefore, the urine test for human chorionic gonadotropin or ultrasound confirmation of pregnancy are considered better estimates.

Pregnancy is traditionally divided into three phases: first trimester (0-12 weeks), second trimester (12-28 weeks), and third trimester (28 weeks to birth) (Stoppard, 1993). These three divisions are somewhat arbitrary because they are not based on developmental criteria (Profet, 1995). Three pregnancy-related divisions that do make developmental sense are the "zygote" or "pre-implantation" phase (0-2 weeks postconception), the "embryo" phase (2-8 weeks), and the "fetal" phase (8 weeks to birth). This thesis uses the trimester scheme to facilitate comparisons with previously

published studies; however, it recognizes the greater conceptual validity of the developmental scheme, and incorporates that scheme for theoretical discussions.

The zygote phase is the period before the fertilized egg attaches to the placental wall, a process called "implantation." Implantation involves a complex series of interactions between the zygote and the epithelial cells of the endometrium. These steps include attachment, fusion with the uterine epithelium, and decidualization of the endometrium (Yu, 1994).

The embryonic phase (week 4-8) is the period of most intense organogenesis, when cells of the major organ systems are differentiating, proliferating, and migrating. Most of the organs are developed from three embryonic germ layers: the ectoderm, mesoderm, and endoderm. Cells from the ectoderm eventually form the nervous system, skin, external sensory epithelia, mammary gland, pituitary gland, and teeth enamel. Cells from the mesoderm develop into somites—a primitive segmental unit including muscle, skeletal elements, and connective tissues—which will be combined later in development. Cells from the endoderm form the alimentary canal, the epithelial linings of the bladder, urethra, and respiratory tracts, and the parenchymal tissues of the thyroid gland, thymus, liver, and pancreas.

The fetal stage involves some cellular development, but is principally the period of fetal growth and weight gain, rather than major organ system development (Yu, 1994). The internal organs of the fetus are well formed during this phase, however, the fetus is still not viable if removed from the mother. Fetal growth is the most dominant feature of most of the second and all of the third trimesters. During the first month of the second trimester, the fetus' lateral eyes become ventral as the head enlarges. The limbs become

more proportional to the body, and the face develops into a recognizable human form. By week 12, the external genitalia become visible and identifiable. The crown to rump length increases considerably, and the first fetal movements can be felt by the mother. Fetal growth rapidly accelerates during the third trimester with half of the fetal weight being gained in the last 2-3 months before term. At birth, the mean neonatal weight is 3200 g and the mean length is 36 cm (Yu, 1994).

The terms "nausea," "vomiting," and "retching" are used extensively in this thesis and follow the definitions used by Rhodes, a leader in the development of measurement tools of nausea and vomiting (Rhodes, 1990; Rhodes & Watson, 1987; Rhodes, Watson, & Johnson, 1984). "Nausea" is defined as:

> A subjective, unobservable phenomenon of an unpleasant sensation experienced in the back of the throat and the epigastrum that may or may not culminate in vomiting; it is synonymously described as feeling 'sick at stomach.' It is usually known through self-report but also may have some objective elements because of its intensity. (Rhodes, 1990, p. 888)

"Vomiting" is defined as, "the forceful expulsion of the contents of the stomach, duodenum, or jejunum through the oral cavity" (Rhodes, 1990, p. 888). "Retching" is defined as, "the attempt to vomit, without bringing anything up; it is also called 'dry heaves'" (Rhodes, 1990; p. 888).

4.1. Pregnancy Sickness: Assumptions & Definitions

It is the position of this thesis, and that of several leading researchers, that pregnancy sickness is a normal, nonpathological feature of pregnancy (O'Brien & Zhou, 1995; Petitti, 1986; Weigel & Weigel, 1989a,b). Indeed, clinicians increasingly view the

symptoms of pregnancy sickness as favorable indices reflecting the presence of hormonal and other factors that will sustain the pregnancy (Petitti, 1986; Stein & Susser, 1991). As a syndrome, pregnancy sickness exists as a highly prevalent condition with individual variations. In terms of symptomatology, pregnancy sickness lies on a continuum: there is no threshold above which one has pregnancy sickness and below which one does not.

In the literature, pregnancy sickness is usually referred to as, "morning sickness," or "nausea and vomiting of pregnancy." The first term is a misnomer because the condition can manifest itself at anytime of the day. The second term is more descriptive but does not address other symptoms of "pregnancy sickness," the preferred term used in this thesis. In their study of 435 British women, Gadsby et al. (1993) noted the episodic nature of symptom occurrence and the finding that 95% of women had symptoms before and after midday—only 4% had symptoms exclusively confined to morning (i.e., 6:00 am to 11:59 am). They suggested that a more appropriate term might be, "episodic daytime pregnancy sickness" (p. 248). Profet (1988, 1992) has argued for a comprehensive multisymptomatic definition of pregnancy sickness that includes both food and odor aversions. She states that:

> Pregnancy sickness is a collection of symptoms—food aversions, nausea, and vomiting—one or all of which occur in women during the first trimester of pregnancy. Pregnancy sickness is a physiological/psychological mechanism that influences eating behavior... Many tastes and smells that women normally find palatable become intolerable to them during the first trimester of pregnancy; and these aversive tastes and smells frequently trigger nausea and vomiting as well. (Profet, 1992; p. 327)

Profet's definition of pregnancy sickness is the one used in this thesis. Erick (1993) goes even further, and includes aversions to bright lights, loud noises, snug-fitting clothes, and a sensitivity to invasions of personal space (low-level claustrophobia).

4.2. Pregnancy Sickness: Duration and Prevalence Estimates

Pregnancy sickness usually begins two to four weeks postconception, peaks at about eight weeks postconception, and disappears at about 14 to 16 weeks postconception—although symptoms may persist throughout pregnancy (Cruikshank & Hays, 1991; Gadsby et al., 1993; Willson & Carrington, 1976). Prevalence estimates of pregnancy sickness differ widely among studies and probably reflect the following: (a) different operational criteria used by each study (e.g., nausea alone, vomiting alone, nausea and vomiting); (b) use of objective recording tools versus diary or recall procedures; (c) different time sampling periods (e.g., early pregnancy versus the entire pregnancy); and (d) heterogeneous samples (e.g., predominantly Caucasian versus mixed ethnicity). Biggs (1975) estimated that at least 50% of women suffer from nausea and vomiting during the first 12-16 weeks of pregnancy. A study of 7027 pregnant women found that 73% experienced nausea and vomiting (Brandes, 1967), while a study of 9098 pregnant women found that 56% experienced vomiting alone. Other studies found that 50% of women experienced at least one episode of vomiting or retching (DiIorio, 1985; Klebanoff et al., 1985), while 70-90% experienced some nausea (Jarnfelt-Samsioe et al., 1983; Tierson et al., 1986). Self-reported nausea, vomiting, or both during the first two months postconception were found in 79% of a U.S. sample of women (Brown et al., 1997). An American study of 78 pregnant teenagers (aged 14-19) found that 56% of teenagers experienced nausea and vomiting during first trimester (DiIorio, 1985).

DiIorio's sample consisted of 73% (n = 57) black women and 27% (n = 21) white women. Of the 44 women who experienced nausea and vomiting, 55% (n = 24) were black and 45% (n = 20) were white. Her sample also consisted of 27% (n = 21) married women, 70.5% (n = 55) single women, and 2.5% (n = 2) other. Of the 44 women who experienced nausea and vomiting, 41% (n = 18) were married, 57% (n = 25) were single, and 2% (n = 1) were "other." In Canada, pregnancy sickness affects approximately 200,000 pregnant women each year (Leduc, 1998); world-wide pregnancy sickness affects approximately 100 million women per year ("First International Conference on Nausea and Vomiting of Pregnancy," 1998).

4.3. Pregnancy Sickness: A Trans-Historical and Cross-Cultural Phenomenon

The symptoms of pregnancy sickness have been recorded trans-historically (Fairweather, 1968; Giles, 1893, Guinagh, 1965). The earliest recording of vomiting in early pregnancy dates back to 2000 B.C. in an Egyptian papyrus (reported in Fairweather, 1968). In 300 B.C. Hippocrates noted this aspect of pregnancy and described it as, via French translation, "mauvais coucher," or "a bad bed fellow, touchy and querulous" (Guinagh, 1965). The second-century Roman physician Soranus described how the sickness of pregnancy appeared at around the sixth week and persisted for four months (Fairweather, 1968). In 1706, Kekring reported that pernicious vomiting (probably hyperemesis gravidarum) led to the death of the pregnant woman, while Muenoit described a fatality incidence of 39% (46 deaths out of 118 cases) of women with pernicious vomiting (Fairweather, 1968).

Nausea and vomiting during pregnancy was found in 31 societies representing diverse global geographic areas excluding Europe (Minturn & Weiher, 1984). In 23

(73%) of these societies, nausea and vomiting was isolated as an identifiable pregnancy-related phenomenon. Ten out of 11 (91%) Pacific Rim societies identified pregnancy-related nausea and vomiting, despite early reports that this condition was nonexistent in these societies (Mintum & Weiher, 1984; Theobald, 1930). Retrospective interview data from a South African study revealed that the total frequency of all levels of nausea alone and nausea and vomiting together differed according to ethnosocial group: 56% in rural black women (n = 560), 57% in urban black women (n = 412), 62% in coloured women (n = 225, European-African-Malay), 65% in white women (n = 256), and 69% in Indian women (n = 318) (Walker et al., 1985). Anthropological data collected on the !Kung peoples of the Kalahari Desert suggest that the !Kung recognize nausea, vomiting, and unexplained dislikes for certain foods as signs of pregnancy (Shostak, 1981). In contrast, Wulf Schiefenhövel of the Max-Planck Institute could not recall seeing a single case of hyperemesis gravidarum in over 30 years of fieldwork in Melanesia (W. Schiefenhövel, personal communication, October 24, 1998). Importantly, he did not claim that pregnancy sickness was absent, just that he did not observe the much rarer and more extreme condition of hyperemesis gravidarum. Further, it is not clear if a Western anthropologist would have had access to information about indigenous women's experiences with pregnancy-related symptoms (O'Brien & Relyea, 1999).

4.4. Pregnancy Sickness: Impact, Etiology, and Treatments

Pregnancy sickness is a physiologically and psychologically distressing experience which can negatively affect family, social, and occupational functioning (O'Brien & Naber, 1992; O'Brien & Zhou, 1995; Rofe et al., 1993). It has been estimated that 25% of women experiencing pregnancy sickness require time off work, and that nearly 50% of

employed women feel that their work efficiency has been reduced by pregnancy sickness (Vellacott et al., 1988).

Many theories have been proposed to explain pregnancy-related nausea and vomiting; although the precise causes are still unclear (O'Brien & Newton, 1991; O'Brien & Relyea, 1999). These theories have suggested that pregnancy sickness is due to rising levels of human chorionic gonadotropin (hCG), estrogens, progesterone, and/or CCK, hypoglycemia, adrenal dysfunction, vitamin B6 deficiency, CCK-induced gastric hypofunction, fluid and electrolyte imbalance, psychological maladaptations to the pregnancy, disturbed sexual functioning, a psychiatric conversion disorder, genetic factors, hormonal levels associated with fetal gender, cultural factors, reduction of maternal energy intake to stimulate early placental growth, or that it is a protection from sexual activity (Depue, Bernstein, Judd, & Henderson, 1987; Deutsch, 1994; DiIorio, 1988; El-Mallakh, Liebowitz, & Hale, 1990; Fairweather, 1968; Frick, Bremme, Sjogren, Linden, & Uvnas-Moberg, 1990; Huxley, 2000; O'Brien & Newton, 1991; Profet, 1988; 1992; Reid, 1962; Uddenberg, Nilsson, & Almgren, 1971; Zhou, O'Brien, & Relyea, 1999).

The number of theories seeking to explain pregnancy-related nausea and vomiting is exceeded only by the number of treatments for the same. Table 2 lists some of the historical and current theories of pregnancy sickness. In general, the diverse treatments have not been rigorously investigated, and where specific interventions have been investigated, they have not been found to prevent symptoms with potent and widespread efficacy (Leduc, 1998). Rather, some symptomatic relief for a percentage of women has been reported for each treatment, though even this effect must be separated from a

placebo effect. Indeed, half of the antiemetic effect of acupressure in De Aloysio and Penacchioni's (1992) study could be accounted for by a placebo effect.

From the 1930's to the 1960s, treatments for pregnancy-related nausea and vomiting, including hyperemesis gravidarum (see Section 4.5.), included vitamin therapy, mineral and hormonal therapies, intravenous honey infusions, inductive electric current therapy, sleep therapy, and injections of the mate's blood (Fairweather, 1968). More recently a range of antiemetic drugs have been brought to bear on this condition including doxylamine/pyridoxine, dimenhydrinate, diphenhydramine, meclizine, metocloramide, prochlorperazine, and thiethlyperazine (Burmucic & Weiss, 1987; Vutyavanich, Wongtra-ngan, & Ruangsri, 1995). Nonpharmacological interventions have included vitamin B6 therapy (Sahakian, Rouse, Sipes, Rose, & Niebyl, 1991; Vutyavanich et al., 1995; Willis, Winn, Morris, Newsom, & Massey, 1942), powdered ginger root (Fischer-Rasmussen, Kjaer, Dahl, & Asping, 1990), hypnotherapy (Apfel, Kelley, & Frankel, 1986; Baram, 1995; Fuchs, Paldi, Abramovici, & Peretz, 1980; Stanford, 1994), sensory afferent therapy (Evans, Samuels, Marshall, & Bertolucci, 1993), and acupressure (De Aloysio & Penacchioni, 1992; Dundee, Sourial, Ghaly, & Bell, 1988; Hyde, 1989; O'Brien, Relyea, & Taerum, 1996). A randomized, sham-controlled, double-blinded study of 60 American first trimester pregnant women found that acupressure at the PC-6 anatomical site—on the anterior surface of the forearm, 5 cm proximal to the wrist crease—was effective in reducing symptoms of nausea but not the frequency of vomiting (Belluomini, Litt, Lee, & Katz, 1994). This acupressure point is the same point that the SeaBands™ anti-motion sickness wrist bands are designed to target.

Table 2

Historical and Current Theories of Pregnancy Sickness by Category of Explanation

Category	Theory
Psychological	"Unconscious" rejection of the baby (primary gain)
	Attention-seeking behavior (secondary gain)
	Psychological maladaptations to pregnancy
	Conversion disorder
Hormonal /	Rising hormone levels:
Nutritional	human chorionic gonadotropin, estrogens, progesterone, CCK
	Adrenal dysfunction
	CCK-induced gastric hypofunction
	Hormonal levels associated with fetal gender
	Vitamin B6 deficiency
	Hypoglycemia
	Fluid and electrolyte imbalance
Evolutionary	Reduced maternal energy intake to stimulate early placental growth
	Protection from coital frequency in early pregnancy
	Defense against potential dietary embryotoxins
	Epiphenomenon

Note. Sources: Biggs, 1975; Burmucic & Weiss, 1987; Depue et al., 1987; Deutsch, 1994; Dilorio, 1985; El-Mallakh, Liebowitz, & Hale, 1990; Erick, 1993; Fairweather, 1968; Frick, Bremme, Sjogren, Linden, & Uvnas-Moberg, 1990; Huxley, 2000; O'Brien & Newton, 1991; Profet, 1988; 1992; Uddenberg, Nilsson, & Almgren, 1971; Zhou, O'Brien, & Relyea, 1999.

4.5. Hyperemesis Gravidarum: Definition, Prevalence, and Impact

Hyperemesis gravidarum (HG) is a maladaptive extreme of pregnancy sickness, defined as pernicious vomiting that occurs for the first time before the 20th week of gestation and is of sufficient severity to cause persistent nausea, inability to perform activities of daily living, sleep disturbances, dehydration, apathy, constipation, weight loss of at least 5%, ketosis, acetonuria with eventual neurological disturbance, liver damage, retinal hemorrhage, renal damage, and electrolyte imbalance (Fairweather, 1968; Mannor, 1981; Reid, 1962). Excessive vomiting in pregnancy has been defined by the World Health Organization (1992) into five subtypes: (a) mild hyperemesis gravidarum, (b) hyperemesis gravidarum with metabolic disturbance, (c) late vomiting of pregnancy, (d) other vomiting complicating pregnancy, and (e) vomiting of pregnancy, unspecified.

Hyperemesis gravidarum can lead to maternal malnutrition; feelings of guilt, depression, isolation, hopelessness, and fear; relationship stress, a decision to undergo therapeutic abortion; fetal prematurity and lower birth weight (Chin & Lao, 1988; First International Conference on Nausea and Vomiting of Pregnancy, 1998; Godsey & Newman, 1991; Gross, Librach, & Cecutti, 1980; Hod, Orvieti, Kaplan, Friedman, & Ovadia, 1994; Källén, 1987; Mazzotta, Magee, & Koren, 1996). Weight loss of greater than 5% of pre-pregnant weight has been associated with slowed fetal growth (Gross et al., 1980), and severely malnourished pregnant women have an increased risk for spontaneous abortion (Wong, Leader, & Deitel, 1981).

Approximately 1% (Walters & Humphrey, 1980) to 5% (Soules et al., 1980) of pregnant women will experience HG during their pregnancy. Women with HG typically require hospitalization, rehydration therapy with intravenous fluids (e.g., isotonic (5%)

dextrose), and antiemetic medication such as Diclectin™ (doxylamine and vitamin B6) or Bendectin™.

The intensely debilitating and emotionally devastating nature of HG was illustrated in a study conducted by the Motherisk Program at Toronto's Hospital for Sick Children which revealed that some women experiencing HG elect to abort their pregnancies (Mazzotta et al., 1996). In a 2 month period, 17 of the 1100 (1.6%) women interviewed terminated an otherwise wanted pregnancy because of HG. In none of these cases were other causes of termination identified such as medical, socioeconomic, or life threatening complications. A telling case from the Motherisk study was that of a 30-year-old university student who experienced bouts of nausea every 30 minutes and vomited an average of 15 times per day. She lost 12 kg of body weight, lost consciousness three times, required hospitalization during the first three months of her pregnancy, and lost four months of university studies. Though the pregnancy was planned, she elected therapeutic abortion.

The impact of hyperemesis gravidarum on society is also significant. A Canadian study demonstrated that withdrawal of the antiemetic pyridoxine/doxylamine (Bendectin™) from the market because of the threat of litigation due to drug-induced congenital limb defects resulted in a 50% increase in hospital admissions for nausea and vomiting over a two year period (Neutal & Johansen, 1995). It should be noted that studies have concluded that no risk of congenital limb defects is associated with the use of pyridoxine/doxylamine (McCredie, Kricker, Elliott, & Forrest, 1984).

This thesis adopts the position that hyperemesis gravidarum represents a maladaptive extreme of pregnancy sickness. For this reason, and because conducting lengthy olfactory

testing of women suffering from HG is practically and ethically difficult, this thesis does not focus on this important condition.

CHAPTER FIVE

5.0. Pregnancy Sickness in a Darwinian Medicine Context

Darwinian medicine uses the theory of natural selection to make empirically testable predictions about previously unsuspected aspects of human biology and psychology, and to provide fresh insights into the causes of medical disorders (Buss, 1995; Ewald, 1980; Russell & Russell, 1983; Scriver, 1984, Nesse, 1990; Williams & Nesse, 1991; Nesse & Williams, 1994; Nesse & Williams, 1995). As a conceptually coherent paradigm, Darwinian medicine is a recent development in evolutionary thought. Despite its recent genesis, the application of evolutionary theory to medicine has already led to novel theories of health and disease and to empirically testable hypotheses. Darwinian medicine has extended and reconceptualized our thinking about infectious diseases and the evolution of antibiotic and viral resistance (Ewald, 1980), chronic degenerative diseases (Crews & James, 1991), predispositions to obesity (Dulloo, Henry, Ismail, Jacquet, & Girardier, 1994), human nutritional requirements (Eaton, Eaton, Konner, & Shostak, 1988; Eaton & Konner, 1985; Eaton & Nelson, 1991), female reproductive cancers (Eaton et al., 1994), ageing and longevity (Kirkwood & Holliday, 1979), allergic reactions (Profet, 1991), menstruation (Profet, 1993), environmental influences on disease (Southwood, 1987), generalized osteoarthritis (Hutton, 1987), motion sickness (Treisman, 1977), and psychiatric conditions (Allen & Sarich, 1988; Crow, 1995; Glantz & Pearce, 1989; Nesse, 1990; 1991). Given the insights derived by the application of

evolutionary theory to these diverse phenomena, it was only a matter of time before a Darwinian analysis was brought to bear on pregnancy sickness.

The central organizing principle of Darwinian medicine, and one of the central ideas of biology, is the adaptationist program: a theory-driven research agenda that seeks the evolutionarily adaptive value of structures, processes, traits, or behaviors (Alcock, 1989; Buss, Haselton, Shackelford, Bleske, & Wakefield, 1998; Mayr, 1983; Pinker, 1997; Thornhill, 1997; Williams, 1966; 1992). Mayr (1983) places this point in historical context:

> The adaptationist question, 'What is the function of a given structure or organ?' has been for centuries the basis of every advance in physiology. If it had not been for the adaptationist program, we probably would still not yet know the functions of thymus, spleen, pituitary, and pineal. Harvey's question, 'Why are there valves in the veins?' was a major stepping stone in his discovery of the circulation of blood. (p. 328)

The theory that motivates this search for adaptedness is Darwin's theory of natural selection (Darwin, 1859; 1871) as refined and expanded by modern evolutionary thought (Axelrod & Hamilton, 1981; Bowler, 1989; Buss, 1999; Cavalli-Sforza & Feldman, 1981; Cosmides & Tooby, 1994; Daly & Wilson, 1982; Dawkins, 1982; 1986; 1989; Dennett, 1995; Doolittle & Sapienza, 1980; Fisher, 1958; Gould & Eldredge, 1977; Hamilton, 1964; 1980; Maynard Smith, 1976, 1978; Mayr, 1982; Trivers, 1971; 1972; 1974; Williams, 1966; 1992; Wilson, 1975; Zahavi, 1975).

The essence of natural selection is that genes seek to maximize their representation in future generations (Dawkins, 1989). Natural selection acts like a sieve in each generation: genetic variants that are not successful solutions to the problems of survival

and reproduction posed by a changing and hostile environment are filtered out (Dawkins, 1996). Genetic variants that are successful solutions to the adaptive problems pass through the sieve; they get "selected." The problems of life create a situation whereby genes are in perpetual contention with each other, and this conflict, iterated over thousands of generations, results in selection of those genes that can directly or indirectly out-replicate their rivals. This conflict, and the selective sieve that allows adaptive solutions to pass, results in evolutionary change, or adaptations, or, more technically, "descent with modification."

Descent with modification is a useful phrase in its simplicity and absence of intentionality or directionality. "Descent" refers to a progression from one generation to another; "modification" refers to any form of change which then becomes available, under appropriate circumstances, for descent to subsequent generations. The emphasis on selection at the "genic" level, that is, the level of the genome, rather than the individual level renders intelligible phenomena that, *prima facie*, appear to be maladaptive to an organism.

The adaptive value of *prima facie* maladaptive phenomena come into focus when viewed at the genic level of analysis (Dawkins, 1979; 1982; 1976/1989). A classic example of a response thought to be maladaptive but then reinterpreted as adaptive is the elevated temperature caused by the fever response to bacterial infection. Conventional, non-Darwinian medical wisdom maintained that the elevated temperature of fever should be reduced. Thinking about fever using the adaptationist program revealed that the elevated temperature created an inhospitable environment for bacterial replication, thus, the fever should be allowed to run its course—unless temperatures reach dangerous levels

or persist too long (Boorstein & Ewald, 1987; Kiester, 1984; Kluger, 1986; 1991; Muller, 1948; Williams & Nesse, 1991). Evolutionary thinking helped us reinterpret what we thought was a maladaptation into an adaptation with limits. This last point is important because evolved mechanisms in the body are not perfect adaptations capable of responding to any and all conditions; they are compromises evolved under multiple, sometimes incompatible selective pressures and shaped by genetic limits, present design constraints, ecological boundaries, and historical pathways (Buss et al., 1998; Dawkins, 1982; Dennett, 1995; Williams, 1992). Thus, elephants' ears will not likely evolve into wings—Dumbo notwithstanding—even though wings would be an adaptive development in the search for food, water, and mates. Any anatomical, physiological, behavioral, or psychological adaptation can be pushed too far or can become maladaptive if placed in a novel environment. Dark skin is adaptive in environments of intense equatorial sun, but when placed in a novel environment such as high latitudes, dark skin becomes maladaptive because it diminishes vitamin D synthesis. Thus, a maladaptive extreme of an evolved mechanism does not invalidate the utility of that mechanism; indeed, it highlights its utility under conditions that historically and currently prevail.

A conceptually useful tool in the search for adaptations is the technique of reverse-engineering (Pinker, 1997). In forward engineering one designs a structure or machine to do something; reverse engineering asks what a structure or machine was designed to do. In evolutionary terms, reverse engineering asks the question: what problem of survival and reproduction does this structure, trait, process, or behavior solve? Evolutionary questions about pathology are conceptually different than the questions asked within traditional medical disciplines. Traditional disciplines search for "proximate" answers:

"*how* does this work?" Darwinian medicine searches for "ultimate" answers: "*why* does this work?" It is important to emphasize that these two types of questions are complimentary to each other: both must be asked before deeper insights can be reached (Alcock, 1989; Tinbergen, 1951; Williams & Nesse, 1991).

5.1. Testing Functional Hypotheses

Evolutionary psychological hypotheses about adaptations are sometimes derided as mere storytelling with no possibility of empirical verification. This accusation can also be leveled at other psychological hypotheses including socialization, learning, and culture as causal explanations. The issue is not whether a hypothesis is a story or not, the issue is what are the necessary and sufficient criteria that a hypothesis must meet to be called scientific, and therefore, testable? Tooby & Cosmides (1992) outlined several criterion questions that adaptive theories within evolutionary psychology must meet in order to be scientifically testable:

(1) Is the evolutionary hypothesis formulated precisely and in an internally consistent manner?

(2) Does the hypothesis coordinate with known causal processes in evolutionary biology?

(3) Can new and specific empirical predictions about behavior or psychological processes be derived from the hypothesis for which data are currently lacking?

(4) Does the hypothesis account for known empirical findings more parsimoniously and compellingly than competing hypotheses?

(5) Is the proposed psychological mechanism capable of solving the hypothesized problem?

Table 3 lists twelve examples of empirical discoveries made about humans that were generated from evolutionary thinking, thus demonstrating that functional/adaptive hypotheses can and have been tested. Many other examples of empirical discoveries made from testing adaptive theories could be drawn from more established fields such as ecology, zoology, paleontology, botany, and ethology (Alcock, 1989; Bowler, 1989; Dawkins, 1989; Dennett, 1995; Kingsbury, 1983; Maynard Smith, 1978; Trivers, 1971; Wilson, 1975; Zahavi, 1975).

5.2. Health and Sickness in a Darwinian Medicine Framework

Some physicians and scientists still view "pregnancy sickness" (the 95-99% of cases not involving HG) as a condition reflecting some underlying pathology, psychological maladjustment, or disease state. This conceptualization has led to two reactions: (a) pregnancy sickness is a distressing condition that simply must be endured; and (b) pregnancy sickness is a pathological condition that should be treated by either pharmacological, dietary, or lifestyle interventions. However, the Darwinian medicine perspective suggests that not all distressing conditions reflect underlying pathology; they may instead represent normal physiological or psychological adaptations to a particular set of endogenous and exogenous factors. This point immediately raises the question: "what is disease?"

While it is not philosophically satisfying or operationally sufficient to define disease as an "absence of health," finding a concise and accurate definition of disease has proved elusive. Clear conceptual criteria for identifying diseases are important for the advancement of medicine and for providing a framework for determining proper functioning and, in the case of dysfunction, appropriate treatment strategies. One virtue

Table 3

Examples of Empirical Discoveries Generated by the Testing of Functional Hypotheses

Example of Empirical Discovery	Reference
Sexually dimorphic mating strategies	Thiessen, 1993; Thiessen, Young, & Burroughs, 1993
Cheater detection procedure in social exchange	Cosmides, 1989
Stepchild abuse at 40 times the rate of nonstepchild abuse	Wilson & Daly, 1987
Relationship-specific sensitivity to betrayal	Shackelford & Buss, 1996
Maternal-fetus conflict	Haig, 1993
Frequentist reasoning in human cognition	Cosmides & Tooby, 1996
Waist-to-hip ratio as a determinant of attractiveness judgments	Singh, 1993
Standards of beauty involving symmetry	Grammer & Thornhill, 1994
Male sexual jealousy as a deterrent to paternity uncertainty	Baker & Bellis, 1995; Buss, 1988; Daly, Wilson, & Weghorst, 1982
Sex-linked shifts in mate preference across the lifespan	Kenrick & Keefe, 1992
Predictable causes of conjugal dissolution in 89 cultures	Betzig, 1989
Perceptual adaptations for entraining, tracking, and predicting animate motion	Heptulla-Chatterjee, Freyd, & Shiffrar, 1996

of Darwinian medicine is that it avoids intuitive appeals about what is desirable and undesirable in terms of body function. Good evolutionary theories are characterized by a set of explicit principles for identifying the presence of a disorder such that once an evolved physiological or psychological mechanism has been described and its proper function identified, a criterion emerges for ascribing dysfunction (Wakefield, 1992). Buss (1999) has defined dysfunction using this evolutionary approach as: "Dysfunction occurs when the mechanism is not performing as it was designed to perform in the contexts in which it was designed to function" (p. 399). An example of a dysfunction using this definition would be if heat-conserving thermoregulatory mechanisms such as reduced blood flow to the extremities, shivering, and postural changes failed to operate in response to significant cold-exposure.

5.3. Pregnancy Sickness as Maternal Adaptation: The Logic of the Argument

An evolved physiological or psychological mechanism (i.e., an adaptation) represents a solution to a specific problem of survival or reproduction that recurred over evolutionary history (Buss, 1995; 1999; Pinker, 1997; Thornhill, 1997; Tooby & Cosmides, 1992; Williams, 1966; 1992). The fact that the period of organogenesis (2 weeks to about 9 weeks postconception) coincides with the typical period of pregnancy sickness (begins at 2 to 4 weeks, peaks at 6 to 8 weeks, and disappears by 14 weeks postconception), combined with other features of pregnancy sickness, led Profet (1988; 1992) to propose that pregnancy sickness may actually be a specific adaptation designed to protect the embryo from the potentially teratogenic compounds found in many natural foods. For historical purposes, it should be noted that the essence of Profet's theory was

first proposed by Hook (1976) who postulated that aspects of pregnancy sickness may serve as a feto-protective mechanism to diminish maternal exposure to embryotoxins.

In evolutionary language, pregnancy sickness solves the survival and reproductive problem of protecting the developing embryo from exposure to potential toxins which could damage the developmental process. As a theoretician, Profet did not conduct any empirical studies in either the development or testing of her theory (M. Profet, personal communication, July, 1994); she did, however, synthesize many empirical and theoretical studies to support the theory. The logic of her argument rests upon several lines of convergent evidence drawn from diverse fields. The logic of Profet's theory follows:

1. Many foods contain toxins, either as naturally produced pesticides or as the infestations from molds, fungi, and bacteria on the food (Ames & Gold, 1989; Ames, Profet, & Gold, 1990a,b; Beier, 1990; Betz, 1996; Huxtable, 1992; Ivie, Holt, & Ivey, 1981; Kumana et al., 1985; Rhoades, 1979; Ridker, 1989; Sheehan, 1998; Shepard, 1980; Wilson, 1977).
2. Those toxins that cross the placental barrier can cause deleterious developmental effects during the period of organogenesis (approximately 14 to 60 days postconception), the embryo's period of maximum susceptibility to developmental damage (Hodgson & Levi, 1987; Lauder & Krebs, 1986; Leavitt, 1995; Persaud, 1985a; 1985b; Seeley, Stephens, & Tate, 1992).
3. Humans reliably detect natural cues of toxicity such as pungent smells, and bitter and sour tastes. Many foods (e.g., rancid milk and yogurt, spoiled fish, overripe potatoes) emit such sensory cues when they "go bad." In general, these sensory cues are avoided by humans and animals alike (Bartoshuk & Beauchamp, 1994; Blank &

Mattes, 1990; Garcia & Hankins, 1975; Hook, 1978; Kingsbury, 1983; Mennella & Beauchamp, 1997; Taggart, 1961).

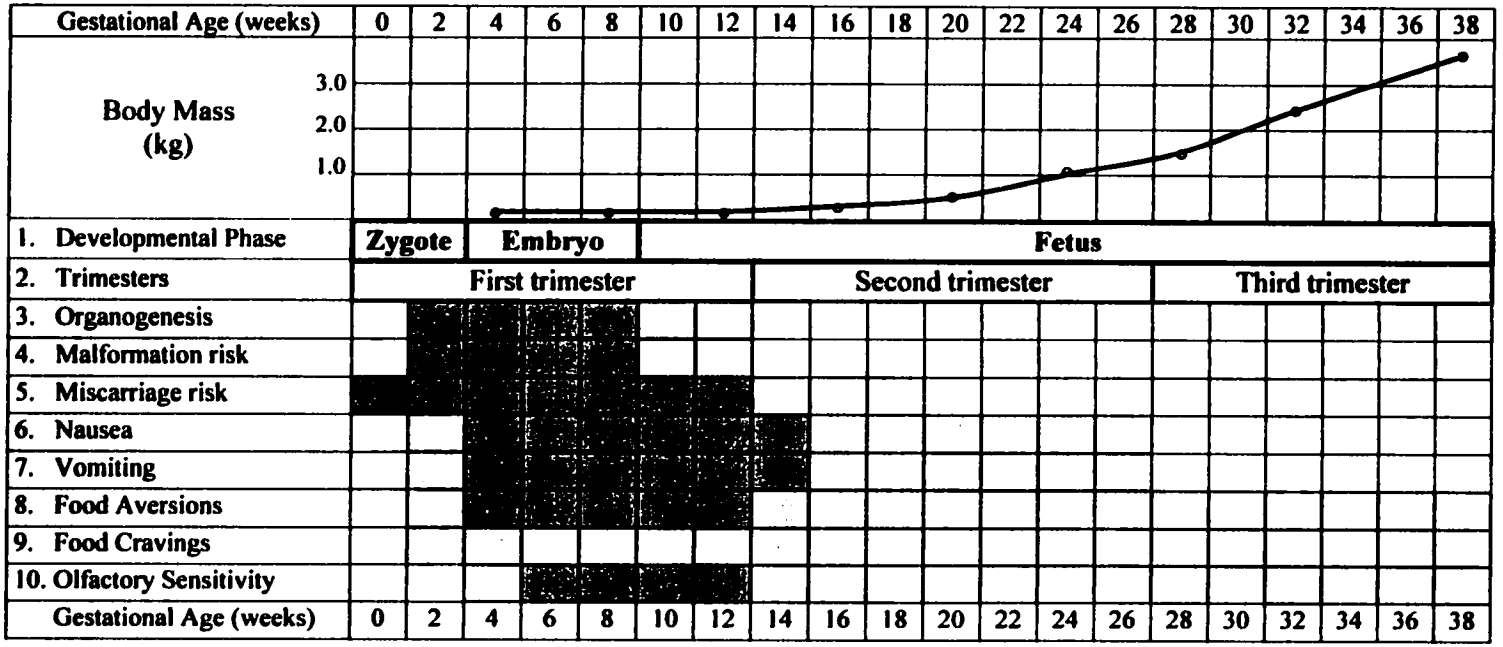
4. The symptoms of pregnancy sickness—food/odor aversions, nausea, and vomiting—coincide with the period of organogenesis (Biggs, 1975; Brown et al., 1997; Cruikshank & Hays, 1991; Gadsby et al., 1993; Hook, 1978; Walker et al., 1985; Willson & Carrington, 1976; Worthington-Roberts et al., 1989) (see Figure 1).
5. Organogenesis is the period of greatest sensitivity to developmental disruption, and coincides with the period when miscarriages and developmental malformations are most frequent (American Medical Association, 1989; Hodgson & Levi, 1987; Leavitt, 1995; Seeley et al., 1992; Wilcox et al., 1985) (see Figure 1).
6. The symptoms of pregnancy sickness diminish during the fetal growth stage when organogenesis is essentially complete and the fetus' need for calories exceeds its vulnerability to toxins (Le Magnen, 1992; Prentice & Whitehead, 1987). As seen in Figure 1, the fetus' body mass increases rapidly around the middle of second trimester.
7. Women with pregnancy sickness use natural sensory cues associated with toxicity to alter their dietary habits (Tao & Claude, 1994). First trimester women report that smoke and food smells were most likely to precipitate nausea and vomiting (DiIorio, 1985).
8. The symptoms of pregnancy sickness have been reported throughout history and in highly diverse cultures world-wide (Darwish et al., 1982; Fairweather, 1968; Minturn & Weiher, 1984).

9. Women with moderate pregnancy sickness—but not hyperemesis gravidarum—have better pregnancy outcomes (i.e., lower incidence of congenital birth defects, particularly cardiac malformations) than women with mild or no pregnancy sickness (Brandes, 1967; Klebanoff et al., 1985; First International Conference on Nausea and Vomiting of Pregnancy, 1998; Weigel & Weigel, 1989a,b).

The conclusion Profet derives from these empirical arguments is that pregnancy sickness is the complex system of defenses that function to protect the embryo from potential food-associated toxins consumed by the mother. Figure 1 provides a graphical illustration of how pregnancy sickness symptoms—nausea, vomiting, food aversions—risk of miscarriages and developmental malformations, and fetal body mass are a function of gestational age and tend to coincide with the period of organogenesis. Also presented in Figure 1, are the data from this thesis showing increased olfactory sensitivity during the period of organogenesis. Figure 2 gives a schematic representation of the factors activating and the pathways leading to the emetic center and the emetic response.

5.4. Plant-Associated Toxins

Virtually all plants synthesize chemicals of varying toxicity as a defense against herbivorous mammals, insects, fungi, and parasites (Beier, 1990, Betz, 1996; Huxtable, 1992; Kumana et al., 1985; Rhoades, 1979; Ridker, 1989; Sheehan, 1998). These chemical defenses make the plants unpalatable and can sicken or kill their predators. It has been estimated that 99.9% (by weight) of dietary pesticides in the American diet are actually naturally occurring chemicals (Ames et al., 1990). Examples of toxins found in natural foods include phytoestrogens in soybean, chlorogenic acid in coffee, saponins from legumes, 8-methoxypsoralen in celery and parsnip, allyl isothiocyanate in cabbage,



■ Highly increased frequency or intensity.

▨ Moderately increased frequency or intensity.

□ No different than nonpregnant women (rows 6-10).

Figure 1. Pregnancy sickness symptoms, malformation/miscarriage risk, and fetal mass are a function of gestational age and developmental phase.

Note. Week 0 = conception. Birth = approximately week 38. Adapted from the results of the present study and the following: Biggs, 1975; Brown, Kahn, & Hartman, 1997; Cruikshank & Hays, 1991; Gadsby et al., 1993; Klebanoff et al., 1985; Lacroix et al., 2000; Leavitt, 1995; Seeley, Stephens, & Tate, 1992; Stoppard, 1993; Willson & Carrington, 1976; Zhou et al., 1999.

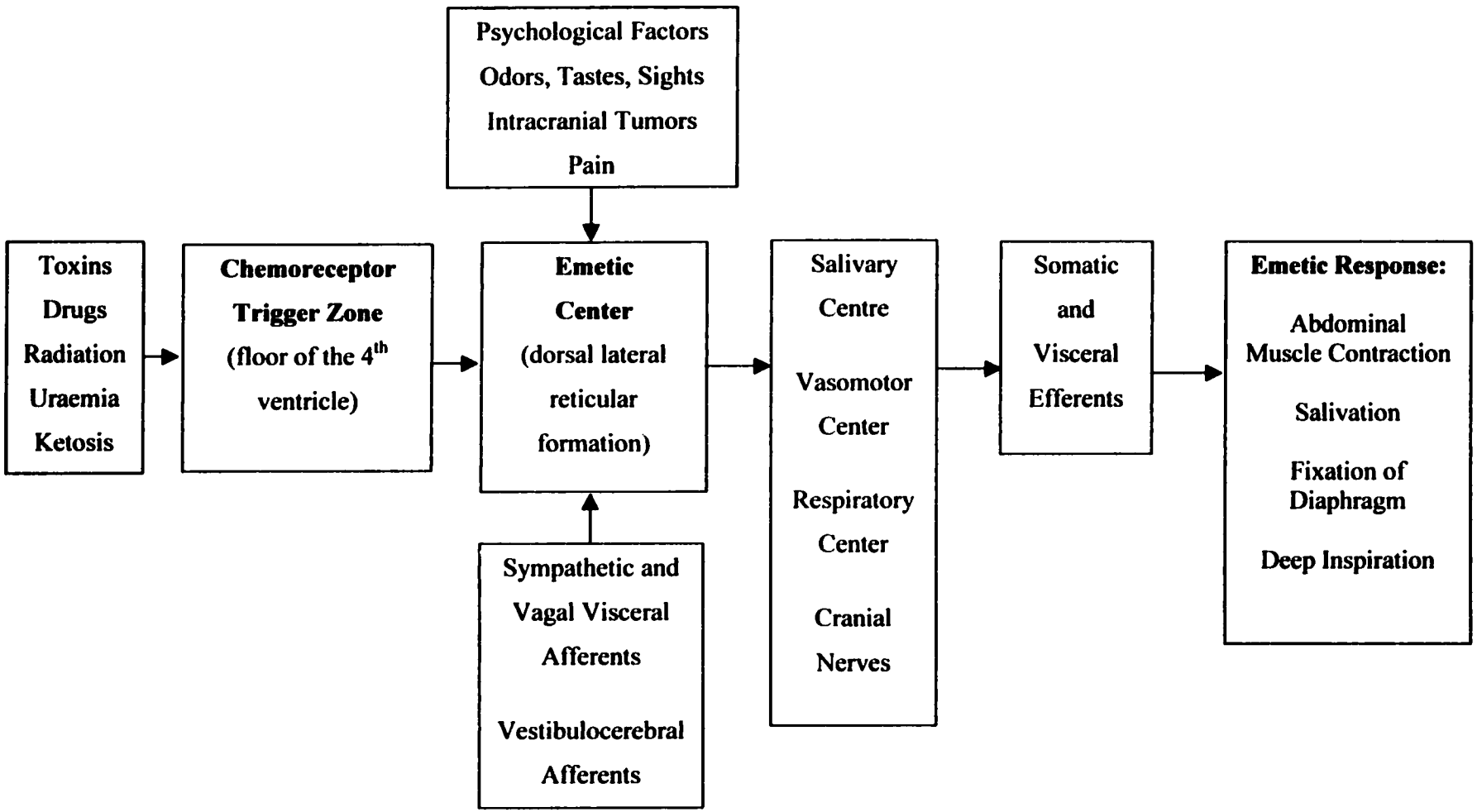


Figure 2. Schematic representation of the factors activating and pathways leading to the emetic center and the emetic response.

Note. Adapted from Biggs, 1975; Rhodes, 1990.

cauliflower, and brussels sprouts, and safrole in black pepper, cocoa, and nutmeg (Ames et al., 1990; Ivie et al., 1981; Sheehan, 1998). Sassafras, which is consumed as a tea in the southeastern United States, can cause diarrhea and displays both hepatotoxicity and hepatocarcinogenicity (Ridker, 1989). Licorice contains glycyrrhizic acid, a metabolic precursor of an 11β-steroid dehyrdrogenase inhibitor which has been linked to primary aldosteronism (Ridker, 1989).

These toxins, also called secondary chemical compounds because they are not involved in primary metabolic processes, are structurally diverse, ubiquitous, and in some cases can comprise up to 10% of the plant's dry weight (Abelson, 1990). Estimates of the number of such toxins are astonishingly large, ranging from 50,000 to 100,000. Approximately 15,000 of these have been chemically characterized.

From an evolutionary perspective, the coupling of a plant's nutrients with its toxins created a selective pressure for humans to evolve physiological and psychological mechanisms for detecting toxic plant compounds, determining dangerous toxic thresholds, and detoxifying and eliminating ingested toxins (Ames et al., 1990; Rhoades, 1979). Convergent evidence exists supporting the existence of such mechanisms. For example, the liver and surface epithelia of the skin and lungs contain enzymes capable of detoxifying many compounds, and the surface layers of the mouth, esophagus, stomach, intestines, colon, skin, and lungs are shed every few days (Ames et al., 1990; Bickers & Kappas, 1980). Even olfactory receptor neurons regenerate—the only known neurons in the adult, along with gustatory receptor neurons and some hippocampal neurons to undergo a cycle of death and regeneration (Briepohl, Mackay-Sim, Grandt, Rehn, & Darrelmann, 1986; Dodd & Castellucci, 1991). Olfactory receptor neurons undergo

regeneration from precursor basal cells approximately every 60 days (Dodd & Castellucci, 1991).

A neural mechanism exists for detecting toxins and inducing nausea and vomiting: the chemoreceptor trigger zone (CTZ), one of the circumventricular organs in the area postrema of the brain stem. The CTZ possesses chemoreceptors that detect many kinds of toxins in the circulation and cerebrospinal fluid, and is one of the few brain regions not subject to the blood brain barrier (Borison, 1986; Rhodes, 1990).

5.5. Toxicology, Teratology, and Embryonic Development

The implications of altered food selection during pregnancy due to olfactory alterations is of concern because the embryo is potentially highly sensitive to toxins and teratogens (Galbraith, Voytek, & Ryon, 1983; Hodgson & Levi, 1987; Marsh et al., 1987; Persaud, 1985a, Tilson, 1995). The term "toxin" is used here in its broad definition: a chemical agent that impairs the biochemical, physiological, or psychological functions of an organism as a function of some dose-response relationship (Parod & Dolgin, 1992; Rosenberg, 1995).

The endogenous and exogenous factors that can lead to abnormal development fall under the general rubric of teratogens, and include a diverse array of influences such as hormones (e.g., excess androgens, diethylstilbestrol), drugs (e.g., thalidomide, aminopterin, phenytoin), radiation (e.g., x-rays), viruses (e.g., rubella, cytomegalovirus), alcohol, cigarette smoking, and industrial chemicals (e.g., methylmercury), and many naturally produced chemicals (discussed earlier) (Beier, 1990; Lenz, 1985; Persaud, 1985b; Schardein, 1985; Shepard, 1986). Studies in pregnant laboratory animals have

shown that over 600 agents cause congenital birth defects, with approximately 25 of these being proven human teratogens (Shepard, 1980).

Early pregnancy is characterized by embryonic organogenesis, a period that lasts from approximately day 14 to day 60 postconception—the end date varies depending on the organ system (Seeley et al., 1992). Organogenesis involves the formation of the limbs, muscles, the major organs, the central nervous system, heart, eyes, ears, external genitalia, and the beginning of ossification. Low molecular weight toxins can diffuse across the placental barrier where they can then interfere with the embryo's normal processes of development. Toxins induce teratogenesis (developmental malformations) by interfering with cell division, proliferation, differentiation, and migration. They can change the characteristics of cell membranes, disrupt chemical signals, interfere with placental or maternal chemicals that regulate nourishment of the embryo, and can exert carcinogenic, clastogenic (chromosomal), or mutagenic effects (Hodgson & Levi, 1987; Waddell & Marlowe, 1981; Williams, 1982). Developmental events are precisely timed and coordinated and, therefore, are highly susceptible to disruption. Even very small alterations during early developmental processes can magnify into large abnormalities at later pre- or postnatal developmental periods. Also, the very low body weight of the embryo relative to the quantities of toxins it potentially encounters increases its vulnerability. Lastly, the embryo does not possess the endogenous detoxification mechanisms that adults do; instead, it must rely on maternal defenses.

A fundamental teratological principle is that embryonic development involves critical periods: stages of development characterized by accelerated tissue differentiation and growth, and an increased vulnerability to certain endogenous and exogenous factors

(Lauder & Krebs, 1986; Persaud, 1985a; 1985b). Embryonic development in general, and during the critical period in particular, is characterized by intense cell proliferation, migration, degeneration, and death (Edelman, 1984). Critical periods tend to coincide with the time of an organ's first appearance; therefore, developing organs are most susceptible to malformations during early organogenesis (Seeley et al., 1992). The peak susceptibility to teratogenesis for various organ systems are given in Table 4.

5.6. Pregnancy Sickness and Reproductive Outcome

A number of studies suggest that the presence of pregnancy sickness is associated with better reproductive outcomes (Weigel & Weigel, 1989b). Brandes (1967) studied 7,027 pregnant women and found that those with nausea or vomiting during the first 20 weeks of pregnancy had a spontaneous abortion rate of 2.8% while women not showing nausea or vomiting had a rate of 6.6% (Brandes, 1967). Klebanoff et al. (1985) studied 9,098 pregnant women and found that women who vomited during pregnancy had a miscarriage and stillbirth rate of 3.4% while women who did not vomit had a rate of 5.3%. Weigel and Weigel (1989a) studied 873 women with pregnancy sickness symptoms before the first 20 weeks of gestation; women who vomited had a spontaneous abortion rate of 1.0%, women with nausea but no vomiting had a rate of 3.6%, and women with no nausea or vomiting had a rate of 7.2%. Yerushalmy and Milkovich (1965) studied 3,853 pregnant women before week 20 of gestation and found that the miscarriage rate for women with pregnancy sickness was 3.8% and rose to 10.4% for women who did not experience symptoms.

A Canadian study that complicates the picture presented above showed that severity of vomiting was related to decreased infant birthweight (Zhou et al., 1999). Participants

Table 4

Peak Susceptibility to Teratogenesis for Various Organ Systems by Developmental Age

Organ System	Developmental age (weeks from conception)	Phase of gestation
central nervous system	2-5	embryonic
heart	2.5-5.5	embryonic
arms and legs	3.5-7	embryonic
eyes	3.5-7.5	embryonic
teeth and palate	6-8	embryonic
external genitalia	6.5-9	embryonic
ear	3.5-8.5	embryonic

Note. Data obtained from Moore (1982).

were 102 symptomatic volunteers (mean age = 30 years) recruited for a clinical trial evaluating the effectiveness of P6 acupressure on reducing the severity of nausea and vomiting during pregnancy. The study used stepwise multiple regression techniques to analyze the relationships between severity of nausea and vomiting (measured with the Rhodes Index of Nausea and Vomiting (Rhodes et al., 1984), demographic variables, and selected pregnancy outcome variables. Results showed that severity of vomiting, parity, and gestational age accounted for 22% of the explained variance in birthweight. These results contradict those found by some researchers (Brandes, 1967; Tierson et al., 1986) but is supported by others (Chin & Lao, 1988; Källén, 1987). The reason for this discrepancy may relate to the fact that all of the participants were symptomatic (i.e., experienced at least some nausea with or without vomiting) whereas other studies may have included a more heterogeneous sample of symptomatic and asymptomatic women.

5.7. Specific Predictions Derived from the Theory

Profet's theory (1988; 1992) views pregnancy sickness as a defensive mechanism designed to avoid embryotoxins that coincides with the particularly critical period of embryonic organogenesis. The theory predicts that pregnancy sickness should be limited to early pregnancy when protecting the developing embryo is the most important adaptive goal. In contrast, second and third trimester pregnancy are characterized by rapid fetal growth, a 30% increase in maternal metabolic rate, and a concomitant increase in food consumption (Le Magnen, 1992; Prentice & Whitehead, 1987). Thus, the most important adaptive goal of late pregnancy involves increasing maternal weight and meeting the fetus' nutritional demands. This may explain why pregnancy sickness tends to disappear

after the first trimester (which subsumes organogenesis). Vomiting that persists into late pregnancy has been associated with decreased birthweights (Zhou et al., 1999).

Profet predicted that early pregnancy should involve increased olfactory sensitivity because this would be the first defensive mechanism by which pregnant women would be able to detect the odor cues associated with toxic substances. A lowering of the threshold for inducing nausea and vomiting by the CTZ is also a prediction of the theory. Studying olfactory function provides an indirect way of assessing if the CTZ threshold has indeed lowered: certain odors should trigger more nausea and vomiting.

The toxins of many plants have alkaloid chemical structures and alkaloids tend to produce a bitter taste or, when volatilized, a pungent odor that signals noxiousness (Kingsbury, 1983). Pungent odors and bitter tastes are perceived to be aversive to the population at large, and to pregnant women in particular (Blank & Mattes, 1990; Fackelmann, 1997; Hook, 1978; Taggart, 1961). Interestingly, many people do consume bitter tasting or pungent-smelling foods and drinks; however, the palatability of such foods is usually acquired through repeated sampling and is typically sustained by other hedonically satisfying properties. For example, the bitter taste of beer is typically rejected initially, and then becomes increasingly pleasurable especially in conjunction with the rewarding effects of alcohol. The bitterness of coffee is offset by the addition of sugar and cream and by the stimulating properties of caffeine.

Developmental studies involving the facial reactions (e.g., grimaces, tongue protrusions, relaxation), sucking movements, and intake behaviors of infants suggest that infants reject sour tastes (e.g., citric acid), reject or are indifferent toward bitter tastes (e.g., urea and quinine), and show a preference for sweet tastes (e.g., sucrose) (Desor,

Maller, & Andrews, 1975; Ganchrow, Steiner, & Munif, 1983; Mennella & Beauchamp, 1997; Rosenstein & Oster, 1990). These reactions are present within hours of birth and suggest genetic predispositions in the reactions toward these tastes.

The advertisement of toxicity via unpleasant odors is a defensive strategy of plants called "olfactory aposematism" (Eisner & Grant, 1980). Its purpose is to deter consumption of the plant by insects and other animals. The strategy is analogous to the visual aposematism employed by animals such as the brightly-coloured and highly poisonous black and yellow Costa Rican tree frog or many butterflies (Alcock, 1989; Brower, 1969; Brower & Brower, 1964; Duffey, 1970; Wiklund & Sillen-Tullberg, 1985). Many meats, seafoods, and other animal products (e.g., dairy products) also contain toxins as a result of the bacteria and molds that infest them (Alcock, 1983). The metabolic breakdown products of these bacteria and molds invariably have a sour or bitter taste and pungent odor. Furthermore, animals studies have shown that bacterial endotoxins can exert teratogenic effects and even fetal reabsorption by the uterus (Gower et al., 1990; Haesaert & Ornoy, 1986; O'Sullivan, Dore, & Coid, 1988).

The odors and tastes generally associated with low levels of toxins include sweet tasting and fruity smelling foods. Both of these patterns make evolutionary sense for it is in the plant's survival interests to "advertise" those parts that are edible—the sweet, nutritious, brightly coloured seed-containing fruits—and those parts that are inedible—the bitter, fibrous, survival-related structures like leaves, stalks and roots (Harvell, 1990; Keeler, 1983).

In summary, pregnancy sickness is a set of mechanisms designed to recognize general cues of toxicity (via changes in olfaction and gustation), lower exposure to toxins

(via changes in food selection and the development of nausea), and eject ingested toxins (via vomiting) if the first two avoidance mechanisms fail. Toxicity, *per se*, cannot be smelled or tasted; instead, perceptual mechanisms evolved to recognize cues reliably associated with toxins in the natural environment. We do not smell bacteria; we smell their breakdown products of their metabolism. The two most common of these cues are pungent smells and bitter tastes. If Profet's theory of pregnancy sickness is correct, then at least several predictions can be made about first trimester pregnant women compared to nonpregnant women: (a) increased olfactory sensitivity; (b) no difference in olfactory identification; (c) increased food aversions; and (d) increased nausea and vomiting. It should be noted that Profet's theory is primarily a theory about early pregnancy, that is, the period of organogenesis—approximately coincident with the first trimester. Therefore, these predictions are focussed only to the first trimester.

CHAPTER SIX

6.0. Objectives and Motivations of the Present Study

The research reported in this thesis is motivated by distinct but interrelated purposes. The first purpose is to provide detailed, longitudinal, and methodologically sound data on the changes in olfactory perception experienced by pregnant women. The study's design improves on previous studies in several distinct ways. First, it uses a controlled design, comparing pregnant to nonpregnant women tested in parallel. The nonpregnant controls are all tested at the same phase of their menstrual cycle, and none of the controls are taking hormone-based contraceptives. Second, the pregnant women are tested at each trimester in recognition of the distinct metabolic, hormonal, physiological, developmental

and dietary changes associated with each trimester, and once again several months postpartum. Testing at each trimester will help determine if distinct changes in olfactory function are related to pregnancy stage. Third, the women are tested longitudinally, a statistically powerful design because each woman serves as her own control (Keppel & Zedeck, 1989). Finally, the study employs two widely used, objective tests of olfactory function and an instrument to measure nausea and vomiting, all of which possess high psychometric reliability and validity (see Method).

The second purpose of this thesis is to examine if a key prediction of Profet's (1988; 1992) pregnancy-sickness as maternal adaptation theory is correct: that first trimester women will be characterized by increased olfactory sensitivity relative to nonpregnant women. Secondary theoretical predictions can also be tested by this thesis. These predictions compare women in their first trimester to their second and third trimesters and first trimester women to nonpregnant women. These predictions follow: (a) increased first trimester food aversions to vegetables, meats, and seafoods; (b) increased first trimester cravings to fruit; and (c) increased first trimester nausea, vomiting, and retching.

6.1. Significance

This research is the first controlled, longitudinal study on pregnancy-related olfactory function to be guided by a biological hypothesis that makes specific predictions about the direction and nature of olfactory change. This thesis is important from a theoretical perspective because it uses insights from Darwinian medicine to conceptualize pregnancy sickness—not including hyperemesis gravidarum—as a normal though distressing feature of pregnancy. To the extent that clear changes in olfactory function are

found, this thesis also underscores the importance of understanding olfactory perceptual changes and their influence on dietary habits, quality-of-life, and potential odor triggers of nausea and vomiting. That information will be useful to scientists and clinicians designing future intervention studies, and for health professionals, pregnant women, and their social supports concerned with management strategies for producing symptomatic relief from pregnancy sickness.

CHAPTER SEVEN

METHOD

7.0. Participants

Forty adult women volunteered as unpaid participants in this study. Twenty of the women (mean age at first trimester = 30.2 ± 0.8 years) were pregnant (primi- or multiparous) with either singletons or twins. A control group of 20 nonpregnant (previously nulli-, primi-, or multiparous) women (mean age = 28.8 ± 1.9 years) were tested in parallel. Thirty-seven women (19 pregnant and 18 controls) completed the study (see 7.4. for details).

Participants were recruited from Halifax, Nova Scotia (approx. 1997 population = 340,000) and nearby communities (e.g., Dartmouth) over a one year period. Recruitment was restricted to Halifax because all of the communities within a 100 km radius of the city are considerably smaller. Recruitment tools included a combination of local newspaper, radio, and community television announcements, notices placed throughout the city, word-of-mouth, hospital newsletters, ads on hospital and university bulletin boards, and brochures given to obstetricians and gynecologists. Multiple recruitment tools were selected including print, radio, and visual informational mediums. Ads were placed in local newspapers. Radio advertisements were aired on the CKDU-FM community radio station. Television announcements were aired on the Community Access Television Station. Brightly coloured brochures were posted throughout the city: in malls, at the ferry terminal, on billboards, at supermarkets, and at the cash registers at drugstores. Five obstetricians and gynecologists agreed to help with recruitment by

informing their patients of the study. Sixty-five percent (n = 13) of the pregnant women were recruited from reading notices or newsletters or brochures within the IWK-Grace Health Centre, 15% (n = 3) were recruited from obstetricians & gynecologists, and the remaining 20% (n = 4) were recruited from all other means combined. Fifty-five percent (n = 11) the nonpregnant women were recruited from word-of-mouth, either directly or via second party contacts, 30% (n = 6) were recruited from reading notices or newsletters within the IWK-Grace, and 15% (n = 3) were recruited from all other means combined.

7.1. Ethical Approval

This protocol received approval by the Research Ethics Committee of the IWK-Grace Health Centre on July 5, 1994, and by the Human Subjects Ethical Review Committee of Dalhousie University on August 27, 1994. Amendments to the original proposal received approval on December 5, 1995. The protocol was renewed with modifications by the IWK-Grace Health Centre on January, 27, 1997. The project was audited as part of the Health Centre's new policy of random audits by the IWK-Grace Research Ethics Board on April 3, 1997, by a committee headed by R. Bortolussi, Chief of Research. The project successfully passed the audit in July, 1997.

Informed, written consent was obtained from all participants. Participants were informed that their participation was voluntary and that they could withdraw at any time, for any reason, and without any consequences. The participants were told that their participation and all the results obtained from them would be treated confidentially, and that individual names would be re-coded to avoid identification of specific individuals.

The investigator verbally informed the participants about the study's purpose, but not specific hypotheses, and gave each participant an information brochure before receiving

participation consent. The information brochure was a briefer version of a comprehensive Clinical Information Form which was available upon request. The brochure and Clinical Information Form contained the following information: introduction, study goals, inclusionary criteria, significance, test descriptions, risk/benefits, fate of information collected, time commitments, location of study, statement of ethical approval, assurance that participation was voluntary, and a contact name and phone number.

7.2. Inclusionary Criteria

7.2.1. Pregnant women. Women were deemed pregnant after self-reported confirmation by either a urinary and/or blood pregnancy test. Conception date was collected from each woman. The most accurate method was ultrasound determination, followed by estimated date of conception/ovulation based on reliable history coupled with the results from methods of determining ovulation (e.g., ovulation kits) and the typical length of her cycle. In cases where objective or estimated procedures were not used, conception date was defined as two weeks after the last menstrual period (LMP), a time that approximates ovulation (Stoppard, 1993). However, the duration between ovulation and LMP shows individual variability and should not be considered a precise measure. Data on the percentages of women employing each of these date-of-conception determining methods were not collected; thus, it is unlikely that the exact postconception date of the pregnant women within each trimester group were all the same.

7.2.2. Nonpregnant women. Women with menstrual cycles between 24 and 35 days were invited to participate. The menstrual cycle is counted from the first day of menstrual bleeding to the last day before the next menstrual period. The menstrual cycle lasts between 24 days and 35 days in 95% of women (American Medical Association, 1989),

with a mean length of 29.1 days and a standard deviation of 7.5 days (Chiazze, Brayer, Macisco, Parker, & Duffy, 1968). Menstrual flow typically lasts from 2 to 8 days (Treloar, Boynton, Behn, & Brown, 1967).

7.3. Exclusionary Criteria

Certain conditions, treatments, and experiences are associated with altered olfactory function (e.g., decreased olfactory identification ability, dysosmia, or hyposmia) (Duncan & Smith, 1995; Leopold, 1995) and, therefore, were justified as exclusionary criteria.

7.3.1. Exclusionary criteria specific to pregnant women.

Hyperemesis gravidarum. Women diagnosed with hyperemesis gravidarum were excluded. Hyperemesis gravidarum is pernicious vomiting that occurs for the first time before the 20th week of gestation and is of sufficient severity to cause persistent nausea, inability to perform activities of daily living, sleep disturbances, dehydration, apathy, constipation, weight loss of at least 5%, ketosis, acetonuria with eventual neurological disturbance, liver damage, retinal hemorrhage, renal damage, and electrolyte imbalance (Erick, 1993; 1995; Fairweather, 1968; Mannor, 1981; Reid, 1962). The severe nature of hyperemesis gravidarum justifies exclusion of women on this basis. Because only 1% (Walters & Humphrey, 1980) to 5% (Soules et al., 1980) of pregnant women experience hyperemesis gravidarum, this criteria was not considered overly restrictive.

Nausea/vomiting interventions. Women receiving pharmacological or nonpharmacological treatment for nausea and/or vomiting were excluded. Pharmacological interventions include drugs like (a) doxylamine/vitamin B6 (e.g., Diclectin—the only drug approved by Health Canada for this indication), (b)

pyridoxine/doxylamine (e.g., Bendectin), (c) the H_1 histamine antagonists dimenhydrinate (e.g., Dramamine, Gravol), hydroxyzine (e.g., Atarax), and meclizine (e.g., Antivert), (d) diphenhydramine (e.g., Benadryl), and (e) the phenothiazines chlorpromazine (e.g., Largactil) and prochlorperazine (e.g., Stemetil) (Smith & Reynard, 1992). Nonpharmacological interventions include acupressure, hypnotherapy, vitamin B6 therapy, and ginger therapy (Apfel, Kelley, & Frankel, 1986; Belluomini et al., 1994; Sahakian et al., 1991). Women using either pharmacological or nonpharmacological interventions were excluded because reductions in nausea and vomiting resulting from the intervention or a placebo effect would confound our data on distress from nausea and/or vomiting.

Fertility drugs. Women whose conception was aided by the use of fertility drugs (e.g., clomiphene) were excluded. These women were excluded because fertility drugs are sometimes prescribed to treat an underlying hormonal disturbance—a disturbance which may affect the dependent measures of interest in this study.

7.3.2. Exclusionary criteria specific to nonpregnant women.

Absence of menstrual cycles. Women who did not have menstrual cycles were excluded. These include women with chronic amenorrhea (greater than or equal to 180 days without menstrual flow), women with hysterectomies, and postmenopausal women (i.e., women who have ceased menstruating for at least one year and whose age is compatible with menopause) (Abraham, 1978). Anosmia has been found in women with primary amenorrhea (Marshall & Henkin, 1971). Although postmenopausal women do not have olfactory identification deficits (Kopala, Good,

& Honer, 1993), they may have other olfactory or dietary changes due to the significant postmenopausal drop in estradiol levels.

Hormone-based contraceptives. Women currently using hormone-based contraceptives such as ethinyl estradiol, norgestrel, diethylstilbestrol, or norethindrone were excluded. Doty et al. (1981) found similar fluctuations in olfactory sensitivity in women taking or not taking a hormone-based contraceptive. They concluded that the olfactory changes were not directly dependent on circulating gonadal or gonadotropic hormones. However, hormone-based contraceptive use may affect food aversions and cravings, or symptoms of nausea and vomiting; therefore, their use was deemed a justifiable exclusionary criteria.

7.3.3. Exclusionary criteria for both pregnant and nonpregnant women.

Head injury. Women with a history of head injury with a significant loss of consciousness (e.g., more than one minute) were excluded. The amount of olfactory damage resulting from head injury is positively correlated with the severity of head injury (Costanzo & Becker, 1986; Duncan & Seiden, 1995). Posttraumatic anosmia occurs in about 20-30% of patients with severe head injury (e.g., producing unconsciousness) (Costanzo & Becker, 1986). Olfactory dysfunction is caused by posterior-anterior coup or contra-coup forces that rapidly shift the brain parenchyma, thus tearing or shearing the olfactory nerve filaments at the point at which they pass through the tiny foramina in the cribriform plate at the base of the skull (Costanzo, DiNardo, & Zasler 1995; Jafek, Eller, Esses, & Moran, 1989).

Medical conditions. Many medical conditions are associated with changes in olfactory sensitivity, identification, or dysosmias. Current presence or history of any of the following conditions justified exclusion:

(a) Endocrine disorders: untreated primary hypothyroidism (Lewitt, Laing, Panhuber, Corbett, & Carter, 1989; Mackay-Sim, 1991; McConnell, Menendez, Smith, Henkin, & Rivlin, 1975), adrenal cortical insufficiency (Mackay-Sim, 1991; Henkin & Bartter, 1966), congenital adrenal hyperplasia (Henkin & Bartter, 1964), chromatin-negative gonadal dysgenesis (Henkin, 1967), and hypogonadotropic hypogonadism (sometimes seen in women) (Tagatz, Fialkow, Smith, & Spadoni, 1970).

(b) Neurological/Psychiatric conditions: epilepsy (West & Doty, 1995), schizophrenia (Kopala, Clark, & Hurwitz, 1989; 1992; Kopala et al., 1995), Alzheimer's disease (Doty, Reyes, & Gregor, 1987; Serby, Larson, & Kalkstein, 1991), idiopathic Parkinson's disease (Doty, Deems, & Stellar, 1988), Huntington's disease (Doty, 1991), chronic alcohol addiction (Kesslak, Profitt, & Criswell, 1991; Shear et al., 1992), Pick's disease (Doty, 1991), and depression (Serby et al., 1990) although Amsterdam, Settle, Doty, Abelman, & Winokur (1987) did not find olfactory disturbances in depression.

(c) Nasal and/or sinus disease: nasal polyposis, chronic sinusitis, allergic rhinitis, and chronic viral upper respiratory tract infection (Cowart, Flynn-Rodden, McGready, & Lowry, 1993; Deems et al., 1991; Duncan & Smith, 1995; Fein, Kamin, & Fein, 1966; Henkin, Larson, & Powell, 1975).

(d) Chronic occupational exposure to chemicals: examples include benzene, benzol, butyl acetate, carbon disulfide, ethyl acetate, formaldehyde, hydrazine, menthol,

methyl bromide, trichloroethylene, cadmium, nickel (Amoore, 1986; Doty, 1979; Duncan & Smith, 1995).

(e) Nutritional disorders: pernicious anemia (Rundles, 1946).

(f) Tumors: intranasal or intracranial tumors (Doty, 1979; Feldman, 1986).

Hormone replacement therapy. Women taking hormone replacements (e.g., thyroxine) were excluded given the possibility that such hormones may affect the dependent measures of this study.

Present or past chronic smokers. Women who presently smoke or were chronic smokers in the past were excluded. Cigarette smoking adversely influences odor identification ability (Doty et al., 1984; Frye, Schwartz, & Doty, 1990). This adverse effect is dose-related and exists in both present and past smokers (Frye et al., 1990). This rigorous criterion (i.e., present or past chronic smokers) was used because even though cessation of smoking produces improvements in olfactory function, the improvements require approximately the same number of years as the number of years smoked (for a two-pack per day smoker) (Frye et al., 1990). Another difference between smokers and nonsmokers involves the higher threshold for reflexive apnea (a measure of trigeminal sensitivity) among smokers (Dunn, Cometto-Muniz, & Cain, 1982). Smoking has also been associated with decreased nausea and vomiting during pregnancy (Jarnfelt-Samsioe et al., 1983; Klebanoff et al., 1985). Women who previously smoked only intermittently, as in social settings, and less than one pack a week, but who currently did not smoke, were included to avoid too restrictive a criterion.

Drug use. In the week prior to testing, use of drugs known or suspected to affect olfaction. Examples of drugs with documented olfactory effects include:

(a) Amebicides and anthelmintics: metronidazole and niridazole (Prata, 1969; Strassman, Adams, & Pearson, 1970).

(b) Local anesthetics: benzocaine and procaine hydrochloride (von Skramlik, 1963).

(c) Anticoagulants: phenindione (Scott, 1960).

(d) Antimicrobials: ampicillin and streptomycin (Jaffe, 1970; Zilstorff & Herbild, 1979).

(e) Immunosuppressives: vincristine sulfate (State, Hamed, & Bondok, 1977).

(f) Goitrogens: methimazole and propylthiouracil (Grossman, 1953).

(g) Diuretics: captopril and ethacrynic acid (Rollin, 1978).

(h) Muscle relaxants and medications for Parkinson's: baclofen and levodopa (Rolin, 1978).

(i) Vasodilators: oxyfedrine and bamifylline hydrochloride (Whittington & Raftery, 1980).

Dental work. Significant dental work (e.g., root canal) within the week prior to testing.

7.4. Information on Participant Exclusions

A total of 72 pregnant and nonpregnant women indicated interest in participating in the study. Thirty-two (44%) of these women (12 pregnant and 20 nonpregnant) were excluded. The study began with an initial sample of 40 women (20 pregnant and 20 nonpregnant). One of the pregnant women miscarried during early first trimester and, therefore, was excluded from the study. Two of the nonpregnant women withdrew from

the study because they moved to distant cities. Postpartum data on one of the women could not be obtained because the woman moved.

7.5. Demographic Data

Participants were asked to provide the following demographic information: (a) age in years; (b) body mass index (weight (kg) divided by height squared (m^2)); (c) most recent level of formal education in years; (d) self-identified ethnicity; and (e) current employment status. Demographic data can be found in Table 5 in the Results.

7.6. Procedure

All participants were tested in the same quiet testing room at the IWK-Grace Health Centre for Children, Women & Families (Halifax, Nova Scotia). Testing occurred any day of the week between 10:00 a.m. and 5:00 p.m. Early morning and evenings were avoided to control for potential circadian rhythmic effects on olfactory function. Participants were requested not to consume food or drink (except water or juice) one hour before testing. Before each session, participants were informed of the nature of the testing and the anticipated duration. Participants were informed that they could ask questions on an *ad hoc* basis. Before testing, a fan was used to circulate room air and an air purifier (Bionaire™ model LP-1000) was used during testing to filter small particles.

7.7. Testing Schedule

Pregnant women were tested at each trimester: (a) first trimester, 6-10 weeks postconception; (b) second trimester, 16-20 weeks postconception; (c) third trimester, 30-34 weeks postconception; and (d) postpartum, 6-18 months following delivery.

Nonpregnant women were tested at approximately equivalent intervals as the pregnant women and within the week following the onset of their menstrual cycle.

Testing at this point in the cycle provides consistency across nonpregnant participants and is convenient because each woman knows with relative certainty when menstruation has begun. Also, this period largely avoids the luteinizing hormone, follicle stimulating hormone, and estrogen surges associated with pre-ovulation and ovulation.

The examiner administered each test to each participant to ensure accuracy, understanding, and attention. Women received the same tests in the same order during each visit. The order of test administration was as follows: (a) the Phenyl Ethyl Alcohol olfactory threshold test, (b) the food aversions and cravings questionnaire, and (c) the University of Pennsylvania Smell Identification Test. The Rhodes Index of Nausea and Vomiting (Form 2) questionnaire was completed by participants at home after receiving instructions from the examiner. Although this procedure did not randomize order effects, it did allow for the most sensitive olfactory testing to occur first, followed by a test with no olfactory component to reduce olfactory fatigue effects, before presentation of the final olfactory test. A few minutes of rest was provided between each test and whenever a woman requested a break. Each test session required approximately two hours, but each woman determined the actual duration. In sessions where fatigue was an issue, testing was divided into two 1-hour sessions over two consecutive days. Data were collected on the number of women who requested that the sessions be divided: (a) Nonpregnant women: first visit (16%), second visit (21%), third visit (11%), fourth visit (0%); (b) Pregnant women: first trimester (28%), second trimester (11%), third trimester (53%), postpartum (0%).

Consistency in testing conditions and procedures was attempted, however, sometimes conditions or procedures were modified so that each individual woman could

meet the objectives of the test session in a comfortable and convenient way. Vanderploeg (1994) outlined nine interview and testing principles to be used during the data collection phase of neuropsychological evaluations; these principles or modified versions of them were used wherever appropriate.

7.8. Tests and Questionnaires

7.8.1. Phenyl ethyl alcohol odor detection threshold test. The rose-smelling compound phenyl ethyl alcohol (PEA; Aldrich Chemical Co., Milwaukee, WI) dissolved in propylene glycol (Aldrich) was used in a single staircase (transformed up-down methods), forced-choice procedure to measure odor detection thresholds (see Doty, Burlingame, & McKeown, 1993; Doty et al., 1988; Doty, Gregor, & Settle, 1986; Wetherill & Levitt, 1965).

Phenyl ethyl alcohol was chosen as the target odor because it is pleasant smelling at higher concentrations and can be diluted in a liquid diluent (i.e., propylene glycol). Phenyl ethyl alcohol has little trigeminal activity (Silver & Moulton, 1982) and, therefore, is thought to predominantly assess the functional integrity of the first cranial nerve. Phenyl ethyl alcohol detection thresholds correlate well with detection thresholds for many other odorants such as acetic acid, diallyl sulfide, camphor, phenol, skatole, cyclopentadecanolide, and isovaleric acid (Yoshida, 1984); therefore, insensitivity to PEA probably indicates general olfactory insensitivity. The test-retest reliability of the PEA test is $r = .88$, $p < .001$ ($n = 57$) (Doty, McKeown, Lee, & Shaman, 1995).

The testing procedures used in this study were based on those developed by Doty and colleagues (e.g., Doty & Kobal, 1995; Smith, Doty, Burlingame, & McKeown, 1993), and were confirmed during a 1996 personal visit to Dr. Richard Doty at the Smell

and Taste Center at the University of Pennsylvania, and during a 1996 personal visit to Dr. Charles Wysocki at the Monell Chemical Senses Centre in Philadelphia. Solutions of PEA dissolved in propylene glycol were prepared in 100 ml glass vials that were 8.0 cm high and had an internal diameter of 4.0 cm. The opening diameter affects the determination of thresholds because larger openings allow for a greater surface area for the odorants to evaporate (Doty et al., 1986). Previous studies have used either glass bottles or plastic bottles for the PEA test. Plastic sniff bottles require the examiner to squeeze the bottle so that an odor sample is directed to the examinee's nose. Glass bottles require the examinee to place their nose over the bottle opening and sniff the sample under their own control. The glass bottle method was chosen because R. Doty suggested it was a better procedure (R. Doty, personal communication, 1994) since it allowed for a finer control of odorant exposure.

The concentration series ranged from –20.00 to –2.00 $\log_{10}$ in half-log steps (vol/vol). A given trial consisted of sequential and random presentation of two vials, one containing a given PEA concentration and the other containing diluent alone. The vials were held close to and under the participants' nostrils, and participants were requested to report which of the two bottles smelled stronger, and to guess if they reported perceiving no difference (forced-choice paradigm). The initial trial was presented at the -6.50 log vol/vol concentration, and if a correct response occurred on this trial, additional trials were presented at that concentration until either a miss occurred or five consecutive correct responses occurred. If a miss occurred, the procedure was repeated at a concentration one log step higher. This procedure was continued until five consecutive correct responses occurred, at which point the next trial was presented at a half-log

concentration step lower. From this point, only one or two trials were presented at a given concentration before moving to the next concentration pair: up, if the first or second trial was missed, down if neither trial was missed. This procedure continued until seven reversals of the "up-down staircase" occurred.

The dependent measure was the geometric mean of the last four staircase reversal points out of seven of the log concentration (vol/vol) of PEA.

7.8.2. Olfactory identification test. The University of Pennsylvania Smell Identification Test (UPSIT; commercially available as the Smell Identification Test™, Sensonics, Inc., Haddonfield, NJ) was used to test olfactory identification. The UPSIT is a quantitative, standardized, microencapsulated test of olfactory identification. The test consists of four envelope-sized booklets each containing ten synthetic "scratch and sniff" stimuli (for a total of 40 stimuli) embedded in 10- to 50 μm urea-formaldehyde polymer microencapsules fixed in a proprietary binder and positioned on brown strips at the bottom of the test booklets (Deems et al., 1991; Doty, 1995; Doty, Shaman, & Dann, 1984). The UPSIT is the most widely used olfactory test in the world and has been administered to over 35,000 people in North America (Doty, 1995; Doty et al., 1995). Normative data based on a sample of nearly 4,000 men and women ranging in age from 4-99 years is available (Doty, 1995). This database makes it possible to provide normative data down to the 5th percentile in each 5-year category. The UPSIT has found wide use in clinical settings and has been used as a validation criterion for other clinical olfactory tests (Wright, 1987).

The UPSIT's long-term test-retest reliability was measured for tests administered 6 or more months apart ($r = .90$, $p < .001$, $n = 57$) (Doty et al., 1984), and the short-term

test-retest reliability was measured for tests administered two weeks apart (r = -.95, p < .001, n = 69) (Doty, Newhouse, & Azzalina, 1985). Split-half reliability coefficients for the UPSIT as measured by the Spearman-Brown formula for the UPSIT are also high (r = 0.93) (Doty et al., 1989).

The UPSIT permits classification of respondents into the following discrete categories, from normal olfactory identification ability to increasingly poorer ability: normosmia, mild microsmia, moderate microsmia, severe microsmia, total anosmia, and probable malingering. Additionally, it has been used to detect the influence of various pathologies on olfactory function (e.g., Doty & Kobal, 1995; Doty et al., 1987; Doty et al., 1988; Kopala et al., 1992).

The forty UPSIT odor stimuli were designed in accordance with several criteria. The odors were chosen to represent a number of previously established qualitative odor classes (Amoore, 1962; Harper, Bate-Smith, & Land, 1968). These classes included disparate sectors of a multidimensional perceptual space (Davis, 1979). The odors also consisted of single and multiple component chemicals. For example, the licorice stimuli was composed of the single chemical anethole, while the chocolate odorant was composed of several chemicals.

Each odor is released by scratching the odor strip with a pencil or coin and holding the scratched strip near the nostrils. Above each odorant is a multiple-choice question with four alternative responses, one of which is correct. An example of a test item reads as follows: "This odor smells most like: (a) chocolate; (b) banana; (c) onion; or (d) fruit punch." Participants took as long as they needed to choose an answer, but they had to choose one of the responses even if they reported perceiving no odor (i.e., this is a

forced-choice test). The four answer choices were covered with paper while participants smelled the odor. Dr. Richard Doty, the developer of this test, confirmed that this procedural variation (i.e., covering the answers with paper) would not change the validity or reliability of the test. After completing the ratings, the four choices were revealed and a decision was made.

The dependent measure was the total number of odors correctly identified out of a maximum score of 40.

7.8.3. Food aversions and cravings questionnaire. Participants were read a list of 142 food items divided into 11 categories: fruit, vegetables, snack foods, dairy, grains, condiments, beverages, desserts, miscellaneous, herbs & spices, and main dishes. These food groups were adapted from the basic food groups of the Canadian Dietary Information System, a software database developed specifically for work on nutrition surveys (as reported in the Nova Scotia Heart Health Program, 1993). Presently, there do not exist any food aversion or food craving questionnaires with good psychometric properties. This absence led to the construction of the present questionnaire, the psychometric properties of which are unknown. Therefore, data collected from this questionnaire needs to be interpreted as exploratory.

For each item, participants were asked if they experienced a food aversion, a food craving or neither anytime during the past two weeks. An "aversion" was defined as "A dislike for a food so strong that consuming it would make you feel sick to your stomach." A "craving" was defined as "A desire to consume a food so strong that you had to have it right away." Aversions and cravings involve a psychic component—repulsion or desire—and a behavioral component—action to remove the aversive stimulus or fulfill the desire.

The dependent measures were the mean number of food aversions and the mean number of food cravings.

7.8.4. Nausea, vomiting, and retching questionnaire (Rhodes INV Form 2). The total distress experienced from nausea, vomiting, and retching was measured with the Rhodes Index of Nausea and Vomiting Form 2 (INV Form 2). The INV Form 2 is an 8-item, 5-point, Likert-type self-report instrument. Detailed psychometric properties of the INV Form 2 have been described (Rhodes, Watson, & Johnson, 1983; 1984; 1985). The internal reliability of the form has been estimated by two statistical procedures: the split-half correlation (.90), and the Cronbach's Alpha (.98). Concurrent validity was assessed by comparing the ratings of chemotherapy patients with the rating of a family member the evening following chemotherapy, a procedure that yielded a Spearman's correlation coefficient of $r_s = .87$, $p < .001$ ($n = 18$). Construct validity was assessed by the ability of the instrument to discriminate between well people and cancer patients. Factor analysis supported the three experience subscales—nausea, vomiting, retching—as unique and distinct. The INV Form 2 has been used mostly in studies of chemotherapy-related nausea and vomiting (e.g., Rhodes et al., 1987); however, the form has been used in several studies with obstetrical populations (Belluomini et al., 1994; O'Brien & Zhou, 1995; O'Brien, Relyea, & Taerum, 1996; Stainton & Neff, 1994; Zhou, O'Brien, & Relyea, 1999). The INV Forms 2 is a paper-and-pencil format questionnaire and requires two to three minutes to complete. Each questionnaire asks eight questions about nausea, vomiting, and retching during the last 12 hours. A total of six identical INV Form 2 questionnaires were given to each woman to complete at home. Women were requested to begin the questionnaires that evening and to fill out the remaining questionnaires

consecutively, that is, every 12 hours. The six questionnaires thus provided symptomatic data over a period of three days (i.e., 6 questionnaires x 12 hours per questionnaire = 3 days).

The dependent measure was the total distress from nausea, vomiting, and retching during an average 12-hour period.

7.9. Study Design, Sample Size, and Data Analysis

This study used a longitudinal, controlled design. For each woman, data on nine dependent measures were analyzed: (1) olfactory detection thresholds; (2) odor identification scores; (3) the correlation between PEA thresholds and UPSIT scores; (4) total number of food aversions; (5) number of food aversions to vegetables; (6) number of food aversions to meats & seafoods; (7) total number of food cravings; (8) number of food cravings to fruits; (9) number of food cravings to desserts; and (10) total distress from nausea, vomiting, and retching.

The initial sample size ($\underline{n} = 40$) was determined with the assistance of a statistician within the Psychology Department. The PEA olfactory sensitivity test was chosen as the most important test and a difference of 0.2 log units was chosen as a clinically meaningful difference. The 0.2 log unit criteria was suggested by Dr. Charles Wysocki at the Monell Chemical Senses Center. The suggested sample size was computed to be $\underline{n} = 32$ which was increased by eight to $\underline{n} = 40$ to take into account participant drop-out. Also, the study reported by Laska & Hudson (1996) possessed a similar between and within subjects design, and its sample size of $\underline{n} = 40$ was consistent with our computation.

Before performing the analyses, the data were assessed for normality, heterogeneity of variance, and outliers. Non-normal data were subjected to power transformations (e.g.,

logarithmic, Y^q, square root) adapted from Tukey's (1977) "ladder of powers." Appropriate power transformations systematically change data distribution shape by minimizing positive or negative skew, pulling in statistical outliers, and making the distribution more symmetrical (Hamilton, 1992). Heterogeneity of variance—which the data transformations tended to reduce—was tested using the Levene Median test, while normality was tested using the Kolmogorov-Smirnov normality test (Siegel & Castellan, 1988). A data distribution that fails the Kolmogorov-Smirnov test indicates that the data varies significantly from the pattern expected if the data were drawn from a population with a normal distribution.

The data were analyzed using 2 x 4 mixed factorial ANOVAs ($\alpha = .05$), with "condition" (nonpregnant vs. pregnant) as the between-subjects factor, and "visit" (first, second, and third trimester, and postpartum) as the within-subjects variable. Post hoc comparisons were made using the Student Newman-Keuls test to correct for familywise type I error rate.

Nonparametric tests were used in those cases where the data displayed a non-normal distribution and unequal variances which data transformations were not able to correct. For within-group comparisons the Friedman repeated measures analysis of variance on ranks was used to determine if a single group of individuals was affected by a series of different experimental treatments, where each individual received each treatment. For between-group comparisons the Mann-Whitney rank sum test (a.k.a. the Mann-Whitney U-test) was used to test the null hypothesis that two samples were not drawn from populations with different medians. The Mann-Whitney rank sum test is a nonparametric procedure which does not require the assumptions of normality or equal variance.

Chi-square tests were used to analyze discrete variables except in cases where the expected frequency of more than 20% of the cells in the 2 x 2 contingency table were less than 5, in which case the Fisher Exact Probability test was used (Siegel & Castellan, 1988). Data on specific categories of food aversions and cravings comparing first trimester women to first visit nonpregnant women were analyzed using t-tests for independent samples (two-tailed).

Descriptive and inferential statistical analyses were computed using the *SigmaStat* Version 1.01 (Jandel Corporation, San Rafael, CA) statistical software.

7.10. Risks/Benefits

There were no immediate health benefits of participation. None of the tests involved any harm or distress to the subjects. The substances used in the olfactory tests have been safely used in previous studies (e.g., Doty et al., 1993). Participants were informed that certain odors may be transiently unpleasant or may trigger nausea.

7.11. Funding

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CHAPTER EIGHT

RESULTS

8.0. Analysis of Demographic Data

Demographic comparisons were made between first visit nonpregnant controls and the first trimester women to assess the similarities between the two groups on potentially relevant variables (see Table 5). Student's t-tests for independent samples revealed that there was no difference in age between the two groups, and no difference in body mass index between the two groups. Body mass index (BMI) is a construct calculated by dividing a person's body weight (kg) by the square of their height (m^2). The BMI correlates with disease risks and is often used by health professionals to determine appropriate weight ranges (Bray, 1992). For adult women, "underweight" is defined as a BMI less than 20, "normal weight" as a BMI between 20 and 25, and "overweight" as a BMI between 25 and 30 (Whitney & Rolfes, 1996). As seen in Table 5, the mean (±SEM) BMI of both the first trimester (24.8 ±1.3) and the nonpregnant (24.1 ±1.2) women was within the weight range considered normal. In a nutritional study of 2212 Nova Scotian women (stratified probability sample drawn from the Nova Scotia Medical Services Insurance Plan File), 53% of nonpregnant women aged 18-34 years and 42% of nonpregnant women aged 35-49 years had a BMI of 20-25 (Report of the Nova Scotia Heart Health Program, 1993). Though widely used, the BMI should be interpreted cautiously because it does not take into account body frame size, age, physical activity levels, or the fact that muscle outweighs fat.

Table 5

Demographic Data Comparing the First Visit Nonpregnant Women to First Trimester Women

Variable (Mean ±SEM) or number of cases and %	Nonpregnant (n = 18)	First Trimester (n = 19)	Statistical Analysis	p-value
Age in years	28.8 ±1.9	30.2 ±0.8	t(35) = -0.74	ns
Body Mass Index (kg/m^2)	24.1 ±1.2	24.8 ±1.3	t(35) = -0.40	ns
Education				
9-16 years (high school to college)	14 (78%)	16 (84%)	Fisher Exact	ns
>16 years (advanced training)	4 (22%)	3 (16%)	Test	
Self-Identified Ethnicity				
White	14 (78%)	17 (89%)	Fisher Exact	ns
Nonwhite	4 (22%)	2 (11%)	Test	
Employment				
Full or Part Time				
(at home or outside)	7 (39%)	16 (90%)	$\chi^2(1) = 6.26$	$p < .01$
Other				
(Student, Seeking employment)	11 (61%)	3 (10%)		

Note. Group comparisons for continuous variables used Student's t-test for independent samples (two-tailed). Group comparisons for nominal data used the Chi-square test for independence; however, the Fisher Exact Probability test was used in cases where the expected frequency of more than 20% of the contingency table cells was less than 5.

Fisher Exact Probability tests revealed no difference in the proportion of women at each education level (9-16 years versus >16 years) between the two groups, nor any difference in self-identified ethnicity (white versus non-white) between the two groups. The Chi-square test revealed that a relationship existed between group status and employment: significantly more first trimester women were employed in full- or part-time jobs (at home or outside) than nonpregnant women. Some variables frequently included in demographic assessments (e.g., marital status) were not included in this study because they were not considered relevant to the research questions.

8.1. Phenyl Ethyl Alcohol Olfactory Threshold Test

The distribution of the PEA data passed the Kolmogorov-Smirnov test (K-S Distance = 0.07, p = .05, skew = 0.37). The data passed the equal variance test (p = .63). Table 6 contains the means, standard deviations, standard errors, and the range of the data; Appendix A contains the raw data. Table 7 summarizes the results of the Newman-Keuls post hoc pairwise multiple comparisons.

As seen in Figure 3, the pregnant women had higher olfactory sensitivity (i.e., lower odor detection thresholds) than the nonpregnant women ($F(1, 104) = 25.80$, $p < .0001$, n = 37). The mean (±SEM) PEA (-log concentration (vol/vol)) odor threshold of the nonpregnant women collapsed across the four visits was 6.83 (±0.16) compared to 8.56 (±0.20) for the pregnant women.

Test session also had a significant effect on olfactory threshold scores ($F(3, 104) = 15.61$, $p < .0001$, $n = 37$).

A statistically significant interaction between group and visit was found ($F(3, 104) = 9.85$, $p < .0001$, $n = 37$).

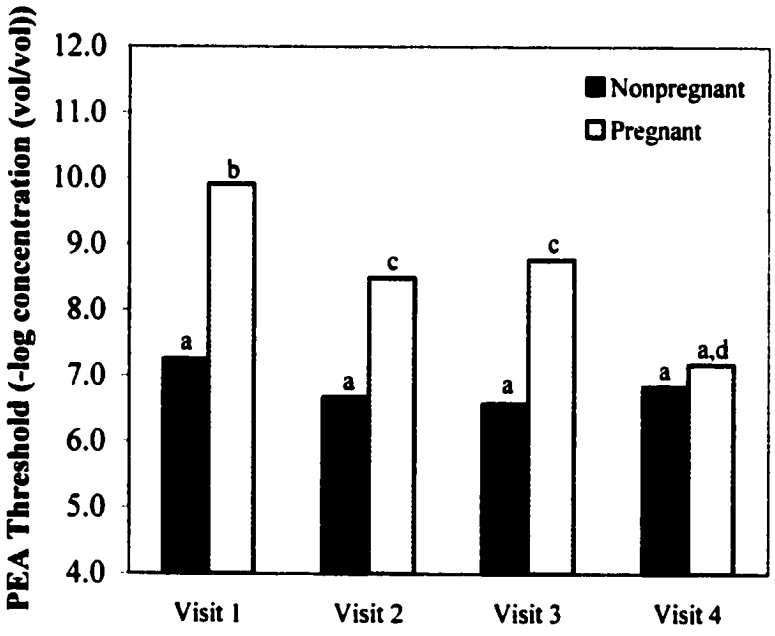

Figure 3. The mean (SEM) PEA odor detection thresholds (-log concentration (vol/vol)) for nonpregnant and pregnant women at each visit.
Letters that differ from each other indicate a statistically significant difference at the $p < .05$ level.

Table 6

Summary Statistics for the Phenyl Ethyl Alcohol (PEA) Olfactory Threshold Test

	PEA threshold -log concentration (vol/vol)			
	Visit 1	Visit 2	Visit 3	Visit 4
	Nonpregnant Women (n = 18)			
Mean	7.25	6.68	6.58	6.84
SD	1.69	1.27	1.05	1.33
SEM	0.41	0.31	0.25	0.32
Range	4.37 – 10.71	4.62-8.62	4.87-8.12	4.62-8.54
	Pregnant Women (n = 19)			
Mean	9.92	8.49	8.76	6.98
SD	1.71	1.37	1.38	1.36
SEM	0.40	0.32	0.33	0.32
Range	6.25-12.35	5.24-11.00	6.50-11.87	6.00-10.70

Comparisons of pregnant versus nonpregnant women at each visit showed that the greater olfactory sensitivity of pregnant women was maintained across each of the three visits: (a) visit one ($\underline{d} = 2.67$, $\underline{p} < .05$); (b) visit two ($\underline{d} = 1.82$, $\underline{p} < .05$); (c) visit three ($\underline{d} = 2.19$, $\underline{p} < .05$), but disappeared by (d) visit four ($\underline{d} = 0.15$, $\underline{ns}$).

Comparisons among the four test sessions within the pregnant group showed that olfactory sensitivity in first trimester pregnant women was greater than second trimester ($\underline{d} = 1.43$, $\underline{p} < .05$), third trimester ($\underline{d} = 1.15$, $\underline{p} < .05$), or postpartum women ($\underline{d} = 2.93$, $\underline{p} < .05$). Second and third trimester women did not differ from each other ($\underline{d} = 0.27$, $\underline{ns}$), but both groups had greater olfactory sensitivity than postpartum women ($\underline{d} = 1.51$, $\underline{p} < .05$ and $\underline{d} = 1.78$, $\underline{p} < .05$, respectively).

There were no differences in olfactory sensitivity in nonpregnant women among the four test sessions: (a) visit one vs. two ($\underline{d} = 0.57$, $\underline{ns}$); (b) visit one vs. three ($\underline{d} = 0.67$, $\underline{ns}$); (c) visit one vs. four ($\underline{d} = 0.41$, $\underline{ns}$); (d) visit two vs. three ($\underline{d} = 0.10$, $\underline{ns}$); (e) visit two vs. four ($\underline{d} = 0.16$, $\underline{ns}$); and (f) visit three vs. four ($\underline{d} = 0.26$, $\underline{ns}$).

The treatment magnitude (i.e., effect size) of the olfactory sensitivity difference between first trimester pregnant women and first visit nonpregnant women was calculated by the alternative eta squared statistic (η^2_{alt}) to be 0.60. The η^2_{alt} statistic corrects for the tendency of the η^2 statistic to underestimate the effect size of experimental designs more complicated than the one-way ANOVA design (see Tabachnick & Fidell, 1989).

Table 7

Results of the Newman-Keuls Post Hoc Pairwise Multiple Comparisons for the Phenyl Ethyl Alcohol (PEA) Olfactory Threshold Test

Comparison	Difference of Means (d)	Significant ($p < .05$)
N1 vs. P1	2.67	yes
N2 vs. P2	1.82	yes
N3 vs. P3	2.19	yes
N4 vs. P4	0.15	no
P1 vs. P2	1.43	yes
P1 vs. P3	1.15	yes
P1 vs. P4	2.93	yes
P2 vs. P3	0.27	no
P2 vs. P4	1.51	yes
P3 vs. P4	1.78	yes
N1 vs. N2	0.57	no
N1 vs. N3	0.67	no
N1 vs. N4	0.41	no
N2 vs. N3	0.10	no
N2 vs. N4	0.16	no
N3 vs. N4	0.26	no

Note. N = nonpregnant group; P = pregnant group; 1 = visit 1; 2 = visit 2; 3 = visit 3; and 4 = visit 4. P4 = postpartum women.

8.2. The University of Pennsylvania Smell Identification Test

The data distribution from the University of Pennsylvania Smell Identification Test was not normally distributed (K-S distance = 0.14, $p < .0001$), displayed negative skewness (-0.38), and failed the equal variance test ($p < .0001$). A series of exponential data transformations were applied but these were not effective in eliminating the non-normality or the unequal variance. Therefore, between group comparisons within a given test session were performed using the nonparametric Mann-Whitney U-test, while within-group comparisons were performed with the nonparametric Friedman Repeated Measures Analysis of Variance by Ranks test.

Table 8 contains the medians, inter-quartile range, means, standard deviations, standard errors, and the range; Appendix B contains the raw data.

As seen in Figure 4, Mann-Whitney U-tests revealed no significant differences in olfactory identification scores between the nonpregnant control group and the pregnant group during any session: (a) first visit nonpregnant vs. first trimester ($T = 348.5$, $p = .86$, $n = 37$); (b) second visit nonpregnant vs. second trimester ($T = 359.0$, $p = .62$, $n = 37$); (c) third visit nonpregnant vs. third trimester ($T = 351.5$, $p = .78$, $n = 37$); and (d) fourth visit nonpregnant vs. postpartum ($T = 326.0$, $p = .84$, $n = 37$).

Test session had no significant effect on olfactory identification scores among the nonpregnant controls. The differences in the ranked median values among the four visits (visit 1 = 37.0, visit 2 = 37.0, visit 3 = 37.5, visit 4 = 38.0) were not statistically significant ($\chi(3) = 5.05$, ns, $n = 37$). Nor was their any significant effect on olfactory identification scores within the pregnant group across sessions. The differences in the

ranked median values among the four visits (visit 1 = 38.0, visit 2 = 36.0, visit 3 = 37.0, visit 4 = 38.0) were not statistically significant ($\chi(3) = 7.18$, ns, $n = 37$).

Post hoc comparisons were not made due to the absence of statistically significant main effects.

The administration manual of the University of Pennsylvania Smell Identification Test defines normal olfactory identification ability, "normosmia," for nonpregnant women as an UPSIT score between 35-40 (Doty, 1995). Normative data on pregnant women are not available so the data for nonpregnant were used as the closest approximation. The manual goes on to define "mild microsmia" (i.e., mildly lowered olfactory identification ability) as a score between 31-34, and moderate microsmia as a score between 26-30. Using these criteria, there were 7 scores out of the 72 UPSIT test sessions (9.7%) for nonpregnant women in which a score fell within the mild microsmic range. There were 7 scores out of the 75 UPSIT test sessions (9.3%) for pregnant women in which a score fell within the mild microsmic range. None of the women scored any lower than mild microsmia.

8.2.1. Pearson correlation coefficients between PEA (-log concentration) scores and UPSIT scores for both groups at each visit.

The Pearson product moment correlation between PEA thresholds and UPSIT scores for both nonpregnant and pregnant women collapsed over all sessions was $r = -.16$, $p < .05$, $n = 37$. None of the correlations for nonpregnant women per visit were statistically significant, nor were any of the correlations for pregnant women. The correlation coefficients for both groups per visit are given in Table 9.

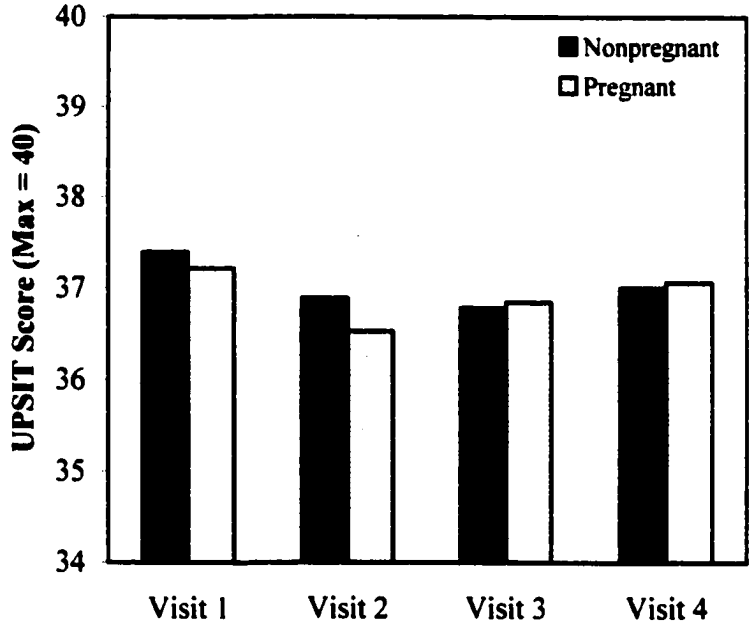

Figure 4. The mean (SEM) University of Pennsylvania Smell Identification Test scores (Max = 40) for nonpregnant and pregnant women at each visit. None of the between group or within group differences were statistically significant.

Table 8

Summary Statistics for the University of Pennsylvania Smell Identification Test (UPSIT)

Statistic	UPSIT Scores			
	Visit 1	Visit 2	Visit 3	Visit 4
	Nonpregnant Women (n = 18)			
Median	37.0	37.0	37.5	38.0
Interquartile Range	37.0-39.0	36.0-38.0	35.0-38.0	36.0-39.0
Mean	37.39	36.89	36.78	37.00
SD	1.65	2.00	2.34	1.50
SEM	0.40	0.48	0.57	0.36
Range	34-40	34-40	31-40	34-40
	Pregnant Women (n = 19)			
Mean	37.21	36.53	36.84	37.06
Median	38.00	36.00	37.00	38.00
Interquartile Range	36.0-38.8	35.0-38.0	36.0-38.0	36.0-38.0
SD	1.81	2.14	1.77	1.51
SEM	0.43	0.51	0.42	0.36
Range	33-40	33-40	34-40	35-40

Table 9

Pearson Correlation Coefficients Between PEA (-log concentration)

Scores and UPSIT Scores for Both Groups at Each Visit

Group	Visit 1	Visit 2	Visit 3	Visit 4
Nonpregnant (n = 18)	-.14	-.26	-.14	-.35
Pregnant (n = 19)	-.35	-.23	-.29	.04

Note. None of the correlations were statistically significant at the $p < .05$ level.

8.3. Number of Food Aversions Questionnaire

The distribution of the food aversion data was not normally distributed (K-S distance = 0.16, $p < .0001$), displayed positive skew (2.13), and did not pass the equal variance test. A power transformation ($Y^{0.2}$) solved the unequal variances problem ($p = .29$), but failed to normalize the data sufficiently. The ANOVA was computed despite the unequal variances because ANOVA has been shown to be robust to violations of equal variance or normality but not both (Keppel & Zedeck, 1989). Table 10 contains the means, standard deviations, standard errors, and ranges; Appendix C contains the raw data. As seen in Figure 5, there was no difference between nonpregnant and pregnant women in the total number of food aversions recalled over a two-week period ($F(1, 104) = 1.00$, $p = .33$, $n = 37$). The mean (±SEM) number of food aversions of the nonpregnant women collapsed across the four visits was 9.44 (±2.02) compared to 7.04 (±1.39) for the pregnant women.

Test session had a significant effect on the total number of food aversions recalled ($F(3, 104) = 4.57$, $p < .005$, $n = 37$).

No statistically significant interaction between group and visit were found ($F(3, 104) = 0.97$, $p = .41$, $n = 37$).

Although the main effect of participant group and the interaction between group and visit were not statistically significant, the pattern of means seen in Figure 5 suggested that pregnant women may have experienced more food aversions than nonpregnant women, and, therefore, justified further analytical comparisons of means using Student-Newman-Keuls post hoc multiple comparisons.

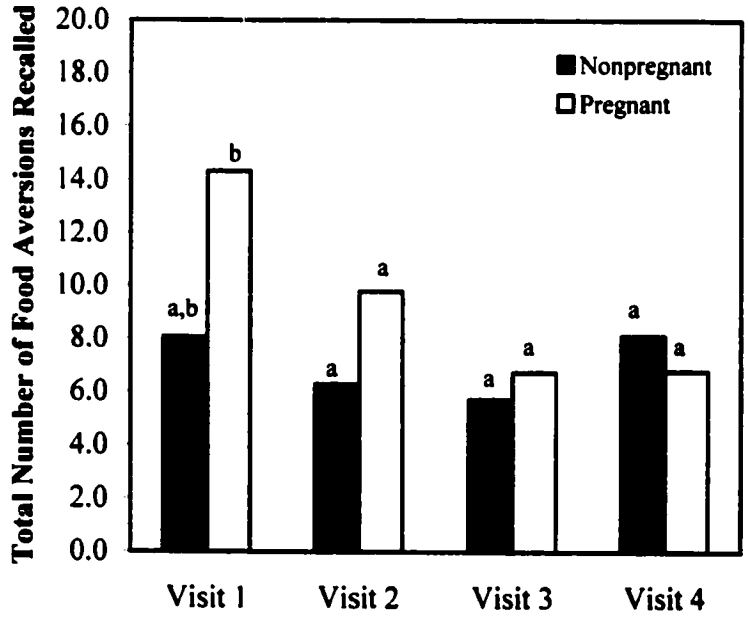

Figure 5. The mean (SEM) total number of food aversions recalled over a two-week period for nonpregnant and pregnant women at each visit. Letters that differ from each other indicate a statistically significant difference at the $p < .05$ level.

Table 10

Summary Statistics for the Number of Food Aversions Questionnaire

Statistic	Number of Food Aversions Recalled			
	Visit 1	Visit 2	Visit 3	Visit 4
	Nonpregnant (n = 18)			
Mean	8.06	6.28	5.72	8.11
SD	6.57	5.45	4.56	6.26
SEM	1.59	1.32	1.11	1.52
Range	0-23	0-23	0-17	0-25
	Pregnant (n = 19)			
Mean	14.32	9.80	6.74	6.78
SD	10.67	10.59	4.90	3.72
SEM	2.52	2.50	1.15	0.88
Range	1-41	0-44	0-18	2-16

Newman-Keuls post hoc analyses showed that there were no differences between pregnant and nonpregnant women during each visit: (a) visit one (d = 0.23, ns); (b) visit two (d = 0.05, ns); (c) visit three (d = 0.10, ns); and (d) visit four (d = 0.05, ns).

However, within the pregnant group, first trimester women had more food aversions than second trimester (d = 0.25, p < .05), third trimester (d = 0.28, p < .05), and postpartum women (d = 0.18, p < .05). No differences were found between second and third trimesters (d = 0.03, ns), second trimester and postpartum (d = 0.08, ns), or third trimester and postpartum (d = 0.10, ns).

Within the nonpregnant group, there were no differences among visits: one vs. two (d = 0.07, ns); one vs. three (d = 0.14, ns); one vs. four (d = 0.01, ns); two vs. three (d = 0.07, ns); two vs. four (d = 0.08, ns), or three vs. four (d = 0.15, ns).

8.3.1. Aversions to Vegetables, Meats, & Seafood.

A more refined analysis of the food aversions data examined the number of aversions to the food categories "vegetables" and "meats and seafoods." The 24 vegetable items in this category are as follows: cooked broccoli, raw broccoli, brussels sprouts, green peppers, asparagus, sweet potatoes, green beans, cauliflower, raw tomatoes, french fries, baked potato, raw carrots, fried onions, raw spinach, lettuce, squash, radishes, frozen corn, cabbage, zucchini, cucumber, raw mushrooms, frozen peas, and baked beans. The 11 items in the meats category and the 10 items in the seafood category are as follows: sausages, baked ham, bacon, steak, pork chops, fried chicken, lamb, hamburger, liver, hard-boiled egg, fried egg, salmon, canned tuna, crab, lobster, mussels, oysters, clams, whitefish (e.g., cod, haddock, halibut), shrimp, and sardines.

The data on aversions to vegetables violated both the normality and equal variance assumptions; therefore, the nonparametric Mann-Whitney Rank Sum Test was used. There was no difference in the number of aversions to vegetables between first trimester and first visit nonpregnant women (Mann-Whitney Rank Sum Test, T(35) = 297.0, ns, n = 37), although there was a trend in the direction of increased aversions among first trimester women.

Data on aversions to meats and seafoods failed the normality test ($p = .04$) but passed the equal variance test ($p = .19$). A t-test for independent samples revealed that there were a greater number of aversions to meats and seafoods among first trimester women than first visit nonpregnant women ($t(35) = -2.23$, $p < .05$, $n = 37$). Table 11 gives data on incidence of food aversions to vegetables, meats, & seafoods between first visit nonpregnant and first trimester pregnant women. Table 12 gives the results of the Newman-Keuls analyses.

8.4. Number of Food Cravings Questionnaire

The distribution of the total number of food cravings recalled was not normally distributed (K-S distance = 0.10, $p < .005$), displayed positive skew (0.25), and failed the equal variance test ($p < .0001$). A power transformation ($Y^{1.5}$) normalized the data but did not solve the unequal variances. Table 13 contains relevant summary statistics: means, standard deviations, standard errors, and the range; Appendix D contains the raw data.

As seen in Figure 6, there was no difference between pregnant and nonpregnant women in the number of food cravings experienced during a two-week period ($F(1, 104) = 0.09$, ns, $n = 37$).

Test session had no significant effect on the number of food cravings ($F(3, 104) = 1.62$, ns, $n = 37$).

No statistically significant interactions between group and visit were found ($F(3, 104) = 1.95$, ns, $n = 37$).

Table 11

Incidence of Food Aversions to Vegetables, Meats, & Seafoods Between First Visit Nonpregnant and First Trimester Pregnant Women

Food Group	1st Visit Nonpregnant Group (n = 18)	1st Trimester Group (n = 19)	Statistical Outcome
Vegetables	24 (M = 1.33, SD = 1.64) (MD = 0.50)	47 (M = 2.47, SD = 2.37) (MD = 2.00)	t(35) = 297.0, ns
Meats & Seafoods	41 (M = 2.28, SD = 2.97)	100 (M = 5.26, SD = 4.89)	t(35) = -2.23, p < .05

Table 12

Results of the Newman-Keuls Post Hoc Pairwise Multiple Comparisons for the Total Number of Food Aversions Questionnaire

Comparison	Difference of Means (d)	Significant ($p < .05$)
N1 vs. P1	0.23	no
N2 vs. P2	0.05	no
N3 vs. P3	0.10	no
N4 vs. P4	0.05	no
P1 vs. P2	0.25	yes
P1 vs. P3	0.28	yes
P1 vs. P4	0.18	yes
P2 vs. P3	0.03	no
P2 vs. P4	0.08	no
P3 vs. P4	0.10	no
N1 vs. N2	0.07	no
N1 vs. N3	0.14	no
N1 vs. N4	0.01	no
N2 vs. N3	0.07	no
N2 vs. N4	0.08	no
N3 vs. N4	0.15	no

Note. N = nonpregnant group; P = pregnant group; 1 = visit 1; 2 = visit 2; 3 = visit 3; and 4 = visit 4. P4 = postpartum women.

8.4.1. Cravings to Fruits and Desserts.

A more refined analysis of the food cravings data examined the number of cravings to the food categories "fruits" and "desserts." The 9 items in the fruit category are as follows: apples, oranges, bananas, grapes, pears, berries, kiwi fruit, grape fruit, and melons. The 9 items in the dessert category are as follows: ice cream, chocolate, cookies, pudding, candy, pies, cake, doughnuts, and pastries.

Data on food cravings to fruits passed the normality and equal variance tests. Evidence of an increased number of food cravings to fruits among first trimester women compared to controls was found (t-test for independent samples, $t(35) = -2.47$, $p < .05$, $n = 37$). Data on the food cravings to desserts also passed the normality equal variance tests. There was no evidence of a difference in cravings to desserts between first trimester women and nonpregnant controls ($t(35) = 0.55$, ns, $n = 37$).

8.5. Total Distress from Nausea and Vomiting (Rhodes INV Form 2)

The distribution of the distress from nausea and vomiting data were not normally distributed (K-S distance = 0.240, $p < .0001$), displayed positive skew (2.52), and failed the equal variance test. A series of exponential data transformations were applied but these were not effective in eliminating the non-normality or the unequal variance. Between group comparisons within a given test session were performed using the nonparametric Mann-Whitney U-test, while within-group comparisons were performed with the nonparametric Friedman Repeated Measures Analysis of Variance by Ranks test. Table 15 contains the medians, inter-quartile range, means, standard deviations, standard errors, and the range; Appendix E contains the raw data.

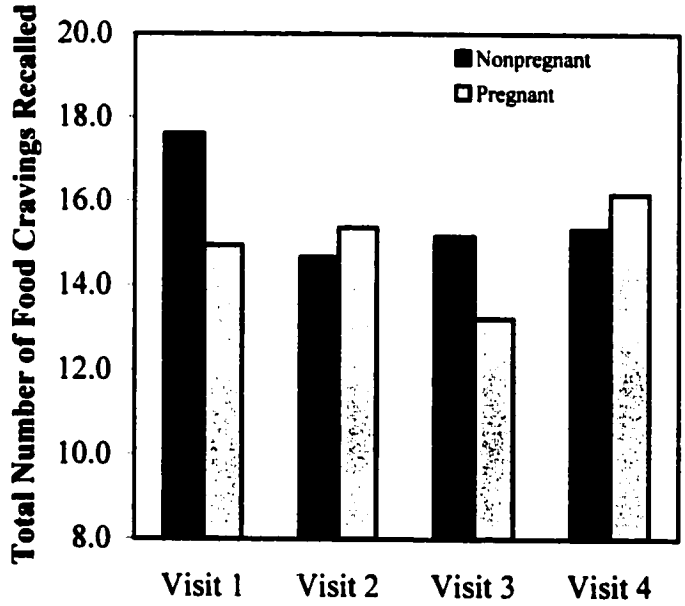

Figure 6. The mean (SEM) total number of food cravings recalled over a two-week period for nonpregnant and pregnant women at each visit. None of the between group or within group differences were statistically significant.

Table 13

Summary Statistics for the Number of Food Cravings Questionnaire

Statistic	Number of Food Cravings Recalled			
	Visit 1	Visit 2	Visit 3	Visit 4
	Nonpregnant Women (n = 18)			
Mean	17.61	14.67	15.17	15.33
SD	9.25	8.49	8.94	7.69
SEM	2.24	2.06	2.17	1.86
Range	4-34	2-30	3-28	4-30
	Pregnant Women (n = 19)			
Mean	14.95	15.37	13.21	16.17
SD	8.54	9.09	8.96	7.84
SEM	2.01	2.14	2.11	1.85
Range	3-28	1-33	0-35	4-32

Table 14

Incidence of Food Cravings to Fruits and Desserts Between First Visit Nonpregnant and First Trimester Pregnant Women

Food Group	1st Visit Nonpregnant Group (n = 18)	1st Trimester Group (n = 19)	Statistical Outcome
Fruits	46 (M = 2.56, SD = 2.09)	83 (M = 4.37, SD = 2.36)	$t(35) = -2.47$. $p < .05$
Desserts	48 (M = 2.67, SD = 1.94)	45 (M = 2.37, SD = 1.30)	$t(35) = 0.55$, ns

As seen in Figure 7, Mann-Whitney U-tests revealed a significant difference in distress from nausea and vomiting between the first visit nonpregnant controls and the first trimester women ($T = 229.5$, $p < .0001$, $n = 37$). The differences in the median values between the controls and the pregnant group for all other sessions was not significant: (a) second visit nonpregnant vs. second trimester ($T = 292.5$, $p = .14$); (c) third visit nonpregnant vs. third trimester ($T = 345.5$, $p = .93$); and (d) fourth visit nonpregnant vs. postpartum ($T = 343.0$, $p = .76$).

Test session had no significant effect on the total distress from nausea and vomiting among the nonpregnant controls. The differences in the ranked median values among the four visits (visit 1 = 0.67, visit 2 = 1.00, visit 3 = 0.92, visit 4 = 0.92) were not statistically significant ($\chi(3) = 1.98$, ns, $n = 37$).

Test session did have a significant effect on the total distress from nausea and vomiting within the pregnant group. The differences in the ranked median values among the four visits (visit 1 = 3.33, visit 2 = 2.17, visit 3 = 0.50, visit 4 = 0.50) were statistically significant ($\chi(3) = 21.70$, $p < .0001$, $n = 37$).

To isolate which sessions within the pregnant group differed from each other, Newman-Keuls pairwise multiple comparisons were computed. The following significant differences were found: (a) first trimester greater than second trimester (difference of ranks = 17.00, $p < .05$); (b) first trimester greater than third trimester (difference of ranks = 26.00, $p < .05$); and (c) first trimester greater than postpartum (difference of ranks = 29.00, $p < .05$). No other significant differences were found.

Prevalence data on the total distress from nausea, vomiting, or retching were calculated for the two groups per visit. The INV Form 2 has a basement score of 0 and a

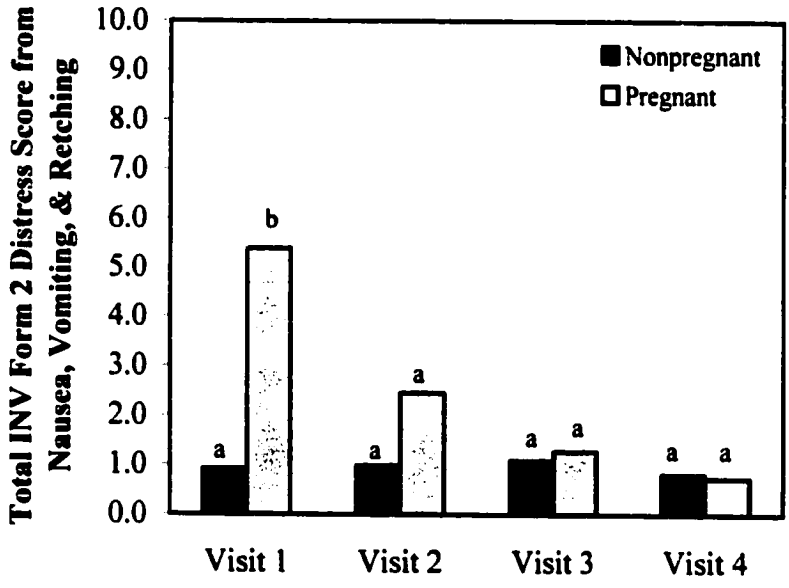

Figure 7. The mean (SEM) total INV Form 2 distress scores from Nausea, Vomiting, & Retching during a 12-hour period for nonpregnant and pregnant women at each visit.
Letters that differ from each other indicate a statistically significant difference at the $p < .05$ level.

Table 15

Summary Statistics for the Total Distress from Nausea, Vomiting, & Retching (Rhodes Index of Nausea and Vomiting Form 2)

	Total Distress from Nausea, Vomiting, & Retching			
Statistic	Visit 1	Visit 2	Visit 3	Visit 4
	Nonpregnant Women (n = 18)			
Mean	0.92	0.98	1.08	0.81
SD	1.07	0.72	1.00	0.63
SEM	0.26	0.17	0.24	0.15
Range	0.00-3.00	0.00-2.00	0.00-3.33	0-1.83
	Pregnant Women (n = 19)			
Mean	5.39	2.46	1.27	0.73
SD	4.35	2.44	1.54	0.70
SEM	1.03	0.57	0.36	0.16
Range	0.00-13.00	0.00-7.83	0.00-5.00	0-1.67

ceiling score of 32. To aid in the interpretation of between and within group comparisons, two quasi-arbitrary criterion points were chosen: ≥ 2.00 and ≥ 4.00. The prevalence data for these points for both groups across visits in given in Table 16.

A score of 2.00 corresponds to either a single episode of a moderate level or to two episodes of a mild level of nausea, vomiting, or retching during the past 12 hours. Thus, a criterion score of ≥ 2.00 indicates that during the past 12 hours the woman experienced, as a minimum, at least two episodes of a mild level of nausea, vomiting, or retching. The INV Form 2 uses written statements to describe "no," "mild," "moderate," "great," and "severe" levels of nausea, vomiting, and retching. To take an example, a "moderate" level of nausea or vomiting is defined as an experience of any of the following:

1. "I threw up 3-4 times during the last 12 hours."
2. "During the last 12 hours I have felt moderate distress from retching or dry heaves."
3. "During the last 12 hours I have felt moderate distress form vomiting."
4. "I have felt nauseated or sick at my stomach for 2-3 of the last 12 hours."
5. "During the last 12 hours I have felt moderate distress from nausea or sickness at my stomach."
6. "During the last 12 hours I produced a moderate (1/2 to 2 cups) amount each time I threw up."
7. "I have felt nauseated or sick at my stomach 3-4 different times during the last 12 hours."
8. "During the last 12 hours I have had 3-4 periods of retching or dry heaves without bringing anything up."

Previous research with the INV Form 2 have not used criterion points. This study used such a point to add interpretational meaning to the analysis: Both pregnant and nonpregnant women could be compared to a definable reference point. Because of the defensible but quasi-arbitrary use of ≥ 2.00 as a cut-off, a ≥ 4.00 criterion was also included to broaden the analysis.

Table 16

Criterion-based Prevalence of Distress from Nausea, Vomiting, and Retching for Nonpregnant and Pregnant Women at Each Visit

Group	Criterion	Visit 1	Visit 2	Visit 3	Visit 4
Nonpregnant (n = 18)	≥ 2.00	22% (4)	6% (1)	28% (5)	0%
Pregnant (n = 19)	≥ 2.00	79% (15)	53% (10)	32% (6)	11% (2)
Nonpregnant (n = 18)	≥ 4.00	0%	0%	0%	0%
Pregnant (n = 19)	≥ 4.00	47% (9)	26% (5)	5% (1)	0%

CHAPTER NINE

DISCUSSION

9.0. General Discussion

This thesis was motivated by two objectives. The first objective concerned a basic research need: to provide controlled, longitudinal, methodologically sound data on olfactory function during pregnancy. This objective was accomplished by using an olfactory sensitivity test (the PEA odor detection threshold test), and an olfactory identification test (the University of Pennsylvania Smell Identification Test), two widely used tests with good psychometric properties (see Chapter 7: Method). The second objective concerned a theoretical prediction: does olfactory sensitivity increase during first trimester relative to nonpregnant controls? This prediction was derived from Profet's theory (1988; 1992) that pregnancy sickness is an evolved physiological/psychological mechanism that enables women during early pregnancy to avoid exposure to potential embryotoxins naturally found in their diets.

The purpose of this chapter is to interpret, criticize, and integrate the study's data and previously published data in relation to these two objectives. The chapter begins by interpreting the results of the analyses on olfactory sensitivity, olfactory identification, correlations between PEA thresholds and UPSIT scores, food aversions and cravings, and nausea and vomiting. These discussions are followed by sections on levels of olfactory processing, dissociation of olfactory function, genetic and estrogenic influences on olfaction, and an integration of findings. Profet's theory is examined against alternative theories and criticisms: (a) Brown, Kahn, and Hartman's (1997) criticisms of Profet's

theory, specifically, that no relationship exists between intake of a range of foods proscribed by Profet as potentially harmful and the presence of nausea and vomiting in early pregnancy; (b) Deutsch's (1994) evolutionary theory that pregnancy sickness functions to reduce coital frequency; (c) Huxley's (2000) evolutionary theory that pregnancy sickness is a mechanism for reducing maternal energy intake during early pregnancy so that resources can be diverted towards placental development; (d) the view that pregnancy sickness has no adaptive value—it is merely an epiphenomenon reflecting pregnancy-related physiological changes; and (e) the view that pregnancy sickness is a maladaptation. Next, the present study's data, analyses, and methods are discussed in light of limitations related to the following: the nonpregnant control group, the pregnant group, parity, cross-cultural generalizability, tests and questionnaires, study design, sample size, and representativeness. Nine principles of data collection, developed by clinicians performing neuropsychological assessments, were utilized in the data collection of this thesis. Those principles and examples of how they were adapted to the data collection methods of this study are discussed. Next comes a discussion of pregnancy-related gustatory changes, and the often overlooked area of trigeminal chemoreception. Treisman's (1977) adaptive theory of motion sickness is examined as an interesting parallel to the adaptive view of pregnancy sickness, and as an example of how research in one domain can have relevance to research in another. The chapter's penultimate section proposes ideas for future research that will help overcome the limitations of the present study as well as suggestions for new kinds of studies. The chapter closes with a summary and conclusions.

9.1. Olfactory Sensitivity

Results from the PEA olfactory sensitivity test revealed that first trimester women had lower odor detection thresholds (-log concentrations (vol/vol)), that is, greater olfactory sensitivity, than first visit nonpregnant women. This result supports the key prediction derived from Profet's (1988; 1992) pregnancy sickness theory, namely, that increased olfactory sensitivity should be a feature of first trimester. Compared to nonpregnant controls, the heightened olfactory sensitivity persisted through the second and third trimesters and disappeared by the postpartum period—postpartum women were no different than controls. The olfactory sensitivity at first trimester was greater than that at second and third trimester and postpartum. Second and third trimesters women did not differ from each other but women in both trimesters had higher olfactory sensitivity than postpartum women. The odor threshold scores of the nonpregnant women remained stable across the four visits.

Profet's theory focussed on increased olfactory sensitivity during first trimester, thus, the persistence of increased olfactory sensitivity across pregnancy requires explanation. One explanation is that the physiological and hormonal changes underlying the first trimester sensitivity increase persist throughout pregnancy so the second and third trimester sensitivity increases merely reflect this underlying change. The fact that estrogen levels rise throughout pregnancy and that estrogen is associated with increased olfactory sensitivity support this explanation. If this model were correct then olfactory sensitivity should continue increasing across pregnancy since estrogen levels continue to increase—but second and third trimester women have lower olfactory sensitivity than first trimester women. However, the estrogen-antagonizing effects of progesterone, which

also rise as the pregnancy proceeds, may explain the second and third trimester drops. The fluctuating olfactory sensitivity may thus track fluctuating levels of the ratio of estrogens to progesterone, rather than the level of either hormone alone. Reproductive fitness cost/benefit analysis would then say that the costs of the increased olfactory sensitivity in second and third trimesters can be maintained if they are outweighed by the fitness benefits of the first trimester increase.

Alternatively, the increased second and third trimester olfactory sensitivity may have an adaptive value but one with a different goal than the first trimester change. One speculative possibility is that the increased olfactory sensitivity extends into the neonatal period where it supports mother-infant olfactory-based bonding. For example, recently parturient women can identify the scent of their infant from that of other same-aged infants (Porter, Cernoch, & McLaughlin, 1983; Schaal & Porter, 1991). The lack of increased olfactory sensitivity among the postpartum women is not a fair test of this hypothesis because their olfactory sensitivity was measured months after parturition while this hypothesis needs to be tested as soon as possible after parturition. An even more intriguing possibility involves olfactory communication *in utero.* All individuals have "odortypes"—unique body odors that distinguish individuals on the basis of genetic polymorphism at the major histocompatibility complex (MHC) and other loci (Brown, 1979; Brown, Singh, & Roser, 1987; Halpin, 1986). During gestation, part of a pregnant woman's urinary odortype comes from her primarily MHC-derived odortype and partly from the paternal genotype inherited by the fetus (Beauchamp et al., 1995). The paternal odortype would be excreted as fetal urine, which is metabolized by the mother and excreted in her urine. Thus, the pregnant woman's odortype is a hybrid composed of her

own odors of individuality and those of the paternal male. The significance of this finding is still unclear but points to the possibility that olfactory information about the gestating infant may be available to the mother during gestation—a process that increased olfactory sensitivity across pregnancy may support. One test of this hypothesis—best evaluated using experimental animal models—would be to see to what degree can pregnant females detect and discriminate urinary odors that are identical except for variations in the paternally derived odortype component.

A few inconclusive reports (e.g., Henssge, 1930; Le Magnen, 1952; Zwaardemaker, 1895) have suggested increased olfactory sensitivity in first trimester women. This is the first controlled study using validated and objective psychophysical testing methods to document this finding. In contrast, Laska et al. (1996), using the *n*-butanol threshold test, found decreased first trimester olfactory sensitivity compared to controls and no difference among second trimester women. Similar to our findings, they found increased third trimester olfactory sensitivity compared to controls, no difference among postpartum women and controls, and that controls remained stable across all four test sessions.

Laska et al.'s first trimester finding is opposite to Profet's theoretical prediction and our empirical finding. An explanation for this discrepancy may lie in the several methodological differences between the two studies. The *n*-butanol odor detection threshold test used has lower test-retest reliability compared to the phenyl ethyl alcohol test used in this study ($\underline{r} = .88$, $\underline{p} < .001$, $\underline{n} = 57$ versus $\underline{r} = .49$, $\underline{p} < .001$, $\underline{n} = 57$) (Doty et al., 1995). Also, *n*-butanol stimulates trigeminal chemoreception (Silver & Mounton, 1982) and so does not provide as pure an assessment of olfactory nerve function as PEA.

Laska et al.'s use of a psychophysical procedure called triangular testing using an ascending staircase is less reliable than the "up, down" single staircase procedure used in this study (Doty et al., 1995). Other methodological differences may also have contributed to the contradictory findings. All of the nonpregnant women in our study were tested during the menses phase of their cycle and were not taking hormone-based contraceptives. Laska et al. did not report at which phase their nonpregnant women were tested or whether phase was controlled at all. Nor did they report whether hormone-based contraceptive use was controlled. None of the women in our study were previously chronic smokers; Laska et al. did not report if they made a similar exclusion. Failure to exclude previous smokers has been identified as a shortcoming in the literature on the effects of smoking and olfactory function because olfactory deficits persist even after cessation of smoking (Frye et al., 1990). Ultimately, resolution of the discrepancy between Laska et al.'s finding and ours awaits further testing by independent researchers to see which result more reliably replicates.

To date, PEA thresholds for pregnant women have not been reported by any researcher. However, PEA thresholds have been reported for nonpregnant women and for men. In the present study the mean PEA thresholds (-log concentrations) for nonpregnant women collapsed across the four visits was 6.84 with a range of 4.37-10.71. This mean value is within the range of means reported from other studies. One would not expect identical PEA threshold scores between studies because of the differences in participant make-up (e.g., differences in gender, age, smoking history) and variations in testing procedures and conditions. Table 17 compares the present PEA thresholds with those obtained from several published studies.

Table 17

A Comparison of PEA Thresholds (-log concentration) Across Five Studies

PEA threshold (-log concentration)	n[a]	Gender	Reference
6.8 (nonpregnant)	18	F	Present study
8.6 (pregnant)	19	F	Present study
6.3	17	Mixed	Lewitt, Laing, Panhuber, Corbett, & Carter, 1989
6.1	68	Mixed	Smith, Doty, Burlingame, & McKeown, 1993
9.0	30	F	Kopala, Clark, and Hurwitz, 1992
4.5	12	F	Doty, Daniel, Deems, Frye, Pelberg, & Shapiro, 1988

[a]The reported n refers to the group being tested, not the overall sample size of the study.

One virtue of the PEA test is that it is objective. However, future studies ought to examine olfactory self-perception in addition to objective measurement because a divergence between the two may suggest other processes at work. For example, a match-controlled study ($\underline{n}$ = 36) on 18 mixed-gender, American patients reporting multiple chemical sensitivities found greater-than-normal self-reported olfactory sensitivity but no evidence of lower-than-expected threshold values to PEA or methyl ethyl ketone (Doty, Deems, Frye, Pelberg, & Shapiro, 1988). The researchers noted the possibility that threshold sensitivity may not be altered, but that suprathreshold sensitivity or the degree to which sensation increases across higher odorant concentrations may be altered.

The possibility that repeated PEA testing induced changed sensitivity to PEA is an intriguing notion. Theoretically, the direction of the changed sensitivity could either be increased odor thresholds (i.e., desensitization or tolerance) or decreased odor thresholds (i.e., sensitization). Studies examining PEA-induced sensitivity changes from repeated exposure were not found. However, induced sensitivity via simple exposure to the odor of 5α-androst-16-en-3-one (androstenone) was found (Wysocki, Dorries, & Beauchamp, 1989). Up to fifty percent of the general population is anosmic to androstenone which has been described as having a sweaty, musky odor somewhat like sandalwood (Amoore, Pelosi, & Forrester, 1977). Exposure to androstenone can induce sensitivity to it in about 50% of the adults who initially show insensitivity to it (Wysocki et al., 1989). One hypothesis is that initially insensitive individuals actually possess androstenone-sensitive receptors but not in numbers that would allow for conscious perception of the odor Repeated exposure, it is thought, may induce clonal expansion or selection for androstenone receptors in a way parallel to the antigenic response of the immune system.

The resulting change in receptor type or number would allow for the conscious perception of the odor. Studies from a genetically inbred mouse strain has supported this hypothesis (Wang, Wysocki, & Gold, 1993). However, if this mechanism were operating in the present study, then olfactory sensitivity should have increased with repeated testing, not decreased as observed. Some studies have noted modest increases in olfactory sensitivity with repeated threshold testing (Rabin & Cain, 1986), however, the increases were attributed to cognitive factors rather than induced alterations in absolute sensitivity. The strength of the hypotheses of induced sensitization or desensitization to PEA are further mitigated by the data from nonpregnant women in which olfactory sensitivity remained essentially stable over time.

The results of the olfactory sensitivity test demonstrate the existence of measurable changes in olfactory function during pregnancy. In the neuropsychological literature a distinction is drawn between statistically significant changes and clinically meaningful changes (Cimino, 1994). Statistically significant changes occur when an appropriate statistical test, like the ANOVA, detects a difference between measurements sufficiently large that attributing the difference to chance factors can be ruled out with reasonably high statistical probability. A clinically significant finding occurs when the magnitude of that difference is sufficiently large that it noticeably and meaningfully affects individual functioning. Results of an alternative eta effect size calculation ($\eta^2_{alt} = 0.60$)—generally accepted as a moderate effect size (Tabachnick & Fidell, 1989)—indicate that the increase in first trimester olfactory sensitivity was both statistically and clinically meaningful.

One may argue that the difference in olfactory sensitivity between first trimester and first visit nonpregnant women is an artifact related to the phase of menstrual cycle testing for the nonpregnant women. The argument rests on the finding that olfactory sensitivity has been reported to be most acute during the ovulatory phase of the menstrual cycle with a secondary peak during the mid-luteal phase (Doty, 1986). Doty notes, however, that the absolute magnitude of the difference between olfactory sensitivity during the ovulatory phase and olfactory sensitivity at other points of the menstrual cycle is not very great—it is a statistically but probably not clinically meaningful effect. Notwithstanding that qualification, one would still expect the least difference between nonpregnant and pregnant women to occur at these two phases. Symmetrically, one might expect that it would be easier to find a difference between women tested at menses (the present study) when their olfactory sensitivity is presumably very low relative to other phases.

Arguing against this "artifact" argument is that Doty's (1986) finding has not been replicated by a more recent study (Hummel, Gollisch, Wildt, & Kobal, 1991). These researchers tested three odorants—PEA, androstenone, and nicotine—on 14 young, healthy German volunteers with normal menstrual cycles and not on oral contraceptives. Participants were tested at five phases: two pre-ovulatory phases, one ovulatory phase, and two post-ovulatory phases. Olfactory sensitivity was not significantly influenced by the menstrual cycle.

9.1.1. Four Justifications for Using the PEA Test of Olfactory Sensitivity

PEA has no trigeminal activity (Silver & Mounton, 1982) and so is thought to assess the functional integrity of the first cranial nerve. Other chemicals like butanol activate

both the first and fifth (trigeminal) cranial nerves (Silver & Mounton, 1982), and therefore, assess both olfactory and trigeminal sensitivities in a confounded manner.

The pleasant odor of PEA was also chosen out of concern for the pregnant women. If unpleasant, aversive odors do trigger nausea and vomiting, the use of such odors might also have increased the participants' distress levels and reduced their motivation to continue in the study.

Profet's theory does not predict that olfactory sensitivity will selectively increase to unpleasant odors; it predicts that olfactory sensitivity will increase as part of a general recalibration of the system so that odors that were tolerated before now become unpleasant. Profet's theory underestimates the selectivity of the olfactory system's sensitivity to specific odors. Many genes code for olfactory receptors, probably one gene per receptor (Axel, 1995; Buck & Axel, 1991), therefore, it may be argued that one test cannot provide a comprehensive assessment of olfactory sensitivity. Furthermore, there is an extensive literature on specific anosmias and selective odor deficits (Amoore, 1971; 1977). It is possible that pregnancy-related olfactory sensitivity changes are selective to certain aversive odorants like smoke but not to pleasant odorants like mint, or perhaps selectivity shifts occur to broad hedonic odor categories like all citrus-like odors. This study did not directly test the odor specificity of the changes in olfactory sensitivity. Indirect evidence that the olfactory sensitivity changes were general, at least to a range of chemical odorants, come from the fact that PEA detection thresholds correlate with the detection thresholds of several other chemicals including acetic acid, diallyl sulfide, camphor, phenol, skatole, cyclopentadecanolide, and isovaleric acid (Yoshida, 1984).

One may argue that a second test of olfactory sensitivity, such as the commonly used *n*-butanol test, might give greater generalizability to the results. While this may be true, it should be noted that in a comparison of the 10 most common olfactory tests, the PEA test had the second best test-retest reliability ($\underline{r} = .88$, $\underline{p} < .001$, $\underline{n} = 57$ (Doty et al., 1995))—the UPSIT was first—while the *n*-butanol test had the second worst test-retest reliability ($\underline{r} = .49$, $\underline{p} < .001$, $\underline{n} = 57$ (Doty et al., 1995)).

In summary there are four justifications for the use of the PEA test of olfactory sensitivity: (a) no measurable trigeminal activity thus providing a purer assessment of cranial nerve I function, (b) ethical concerns about the real possibility of inducing nausea and vomiting in the pregnant participants, (c) positive correlation with detection thresholds from other chemicals, and (d) established psychometric superiority.

9.2. Olfactory Identification

There were no differences in olfactory identification abilities between pregnant and nonpregnant women. This finding was not unexpected because Profet's theory made no predictions about olfactory identification. Previous studies offer little guidance here because none have investigated olfactory identification in pregnant women using quantitative and validated procedures. The present study used the University of Pennsylvania Smell Identification Test (UPSIT), the most widely used and best validated quantitative assessment of olfactory identification ability in the world (Doty, 1995; Doty et al., 1995). Indeed, the UPSIT has even been used as a validation criterion for other clinical olfactory tests (Wright, 1987).

Age- and gender-specific normative data are available for the UPSIT (Doty et al., 1984). Among nonpregnant women, the average ability to identify odors peaks between

20 and 40 years, and begins to decline monotonically after this time, with a slight decrease during the sixth decade and a marked decrease after the seventh decade (Doty et al., 1984). Normative data for pregnant women are not currently available for the UPSIT, however, both groups of women in this study were within the age range of optimal olfactory identification performance based on the normative data for nonpregnant women. As stated in the Results, the UPSIT defines microsmia for normal nonpregnant women within the present sample's age range as a total score between 20 and 34. Using this definition, a few of the women in both groups scored in the high range of microsmia (i.e., slightly below normal). Mild microsmia was detected in 9.3% (7 out of 75) of trials for the pregnant women and 9.7% (7 out of 72) of trials for the nonpregnant women. This result may represent an olfactory adaptation effect or reduced attention given that UPSIT testing occurred after PEA threshold testing, two tasks that require focussed attention. The fact that both pregnant and nonpregnant groups showed near ceiling effects with the UPSIT suggests that olfactory fatigue was not a powerful factor, except perhaps for the individual cases of women that did show lower than expected UPSIT performance. Two procedures were used to minimize potential fatigue effects and the sustained attentional demands of these tests. First, standard rest breaks were placed between tasks and, if requested, within tasks. Second, a non-olfactory test, the food aversions and cravings questionnaire, was placed between the olfactory sensitivity test and the olfactory identification test to further reduce the effects of olfactory fatigue.

9.2.1. Ceiling Effects and the UPSIT

The UPSIT, like most tests of olfactory identification, was designed to test decreases in olfactory identification ability compared to normal performance. Because normal

female performance on the UPSIT is defined as a total identification score of 35 or above out of 40, the UPSIT possesses a ceiling effect with respect to increased olfactory identification ability. In this sense, the test was not a challenging test for individuals with normal or superior olfactory identification ability. In its defense, the test was used because of its excellent psychometric properties and because increased olfactory identification ability was not a direct prediction of Profet's theory, or an anticipated finding based on previous research. In the event that olfactory identification was decreased at any of the trimesters or postpartum, the UPSIT would have detected that decrease. The present evidence that olfactory identification ability is not impaired during pregnancy, justifies the use of a more challenging olfactory identification test for future studies.

In summary, we can conclude that olfactory identification among pregnant women, at least to a modest range of 40 synthetic food and nonfood odors, remains stable across pregnancy and does not differ from that of healthy nonpregnant women. While the UPSIT is a good test of olfactory identification, it may have underestimated the abilities of pregnant women because of ceiling effects and the use of simple, synthetic odors.

9.2.2. Correlations Between PEA Thresholds and UPSIT Scores

In samples of healthy women and men, olfactory sensitivity and identification are highly and negatively correlated with each other, as measured by the Pearson correlation coefficient between the PEA detection threshold values and UPSIT scores ($r = -.79$, $p < .001$, $n = 43$) (Doty et al., 1984). Thus, as olfactory sensitivity increases so too does olfactory identification ability. Note that the correlation coefficient is negative because

the powers of the PEA log concentration values are negative, that is, smaller powers indicate greater olfactory sensitivity.

In the present study the Pearson product moment correlation between PEA thresholds and UPSIT scores for both nonpregnant and pregnant women collapsed over all sessions was $r = -.16$, $p < .05$, $n = 37$ (see Section 8.2.1 of the Results). This correlation is in the same direction as that observed by Doty et al. (1984), however it is not as high. This may have to do with the lower sample size and the more heterogenous sample used in the present study, and with the fact that olfactory sensitivity increased in pregnant women but not controls. More refined correlational analyses of PEA scores versus UPSIT scores session by session yielded negative correlations as expected (with the exception of the postpartum group), however, none of these were significant (see Table 9 in the Results). The lack of statistical significance is attributable to the low sample sizes of the more focussed correlations. A theoretical power calculation was computed to see what power would be needed to obtain a correlation coefficient equal to the one (i.e., $r = -.79$) obtained by Doty et al. (1984) using 18 observations and an alpha set at .05. The required power of .986 is much higher than the range (.054-.610) of actual power values obtained. Thus, future studies will need larger sample sizes if they are to investigate the nature of the correlations between sensitivity and identification.

9.2.3. Olfactory Identification, Memory, and Pregnancy

Memory functioning was not directly investigated in this study. Anecdotally, a number of pregnant women complained of memory disturbances, however, no data was collected on this phenomenon. Olfactory identification ability depends to some extent on intact recognition and verbal recall memory, so the finding of normal olfactory

identification ability among the pregnant women suggests that explicit memory is not decreased during pregnancy. Nevertheless, pregnancy-associated changes in memory are physiologically plausible given the dramatic endocrinological alterations of pregnancy (Yu, 1994), and the findings that vasopressin, oxytocin, corticosteroids, and opioids may influence memory in nonpregnant subjects (Martinez, Jensen, Messing, Rigter, & McGaugh, 1981; Sahgal, 1984; McGaugh, 1989).

Brindle, Brown, Brown, Griffith, and Turner (1991) investigated memory functioning in 32 pregnant women and nine nonpregnant controls, all of whom were healthy, British volunteers. Explicit memory, tested by both recognition and recall tasks, was preserved, while implicit memory showed signs of impairment. Explicit memory involves conscious recognition of previous experiences and facts, and is also referred to as autobiographical, representational, episodic, or working memory. Implicit memory is a nonconscious, nonintentional form of memory also referred to as perceptual, dispositional, semantic, or reference memory (Kolb & Whishaw, 1995; Squire, 1987). Brindle et al.'s finding of spared explicit memory functioning is consistent with our findings of intact olfactory identification; however, the finding of impaired implicit memory is remarkable in the context of the neuropsychological literature on memory impairment. That literature has shown that when injury causes a dissociation in explicit and implicit memory, that explicit memory is typically deteriorated while implicit memory is preserved (Kolb & Whishaw, 1995; Lezak, 1995). Further research is needed to determine the reliability of this finding and its implications.

9.3. Food Aversions and Cravings

The food aversions and cravings questionnaire assessed whether women experienced a food aversion or craving anytime within the past two weeks, with recall being prompted by a standardized list of 142 food items representing major food categories (see Method for description). This procedure is similar to the one used in a number of studies including the well-designed Yale Pregnancy Study (Rodin & Radke-Sharpe, 1991). Analyses were performed on the total number of food aversions and cravings as well as to the following subcategories: vegetable aversions, meat/seafood aversions, fruit cravings, and dessert cravings. Note that caution is warranted in the interpretation and generalization of these findings given the unknown psychometric properties of this questionnaire.

Contrary to Profet's prediction, more food aversions were not experienced by first trimester women compared to first visit nonpregnant women, though a trend existed in this direction. Nor were differences seen between the two groups at any other time. First trimester women did experience more food aversions than second trimester, third trimester, and postpartum women—which could be seen as partial support for Profet's prediction. The number of food aversions experienced by nonpregnant women remained stable across the four test sessions.

It is interesting to note that the between-subjects analysis of aversions was not significant while the within-subjects analysis of pregnant women revealed the predicted difference. This divergence of findings between the two levels of analysis was also seen in the study on pregnancy-related cravings and aversions by Rodin and Radke-Sharpe (1991). They noted that while fruit cravings among pregnant women at each trimester

were not statistically greater than pre-pregnancy, though the trend was in this direction for each trimester, second trimester women displayed more fruit cravings than nonpregnant controls.

More refined analyses of the food aversions data were conducted by segmenting the total number of aversions into food subcategories. Twenty-four of the 142 food labels were vegetables (see Results) and 21 of the 142 labels were meats & seafoods. Profet's theory predicts that first trimester food aversions are not randomly distributed across foods but tend to cluster around vegetables, meats, and seafoods. Clustering of food aversions has also been noted among other studies (Dickens & Trethowan, 1971; Hook, 1978; Loewen, 1988; Pope et al., 1992; Rodin & Radke-Sharpe, 1991; Walker et al., 1985). According to Profet these foods contain a high level of endogenous toxins and are more susceptible to bacteria, molds, and fungi than other foods; therefore, first trimester women should find these foods, and the odors that emanate from them, particularly aversive.

Contrary to theory, the focussed analyses did not find evidence of a greater number of aversions to vegetables among first trimester women compared to first visit nonpregnant women, although again there was a trend in this direction. This finding is inconsistent with several other studies that noted a high incidence of aversions to vegetables (Dickens & Trethowan, 1971; Finley et al., 1985; Hook, 1978; Loewen, 1988; Walker et al., 1985). Rodin and Radke-Sharpe (1991), for example, found a greater number of vegetable aversions at first, second, and third trimester compared to nonpregnant controls, and first trimester vegetable aversions were also higher than the pre-pregnant group.

In this study, evidence of a greater number of meat and seafood aversions among first trimester women versus first visit nonpregnant women was found. Aversions to meats and seafoods are the most frequently reported aversions of pregnancy (Hook, 1978; Pope et al., 1992; Worthington-Roberts et al., 1989). Rodin and Radke-Sharpe (1991) noted that aversions to red meats was higher among first and second trimester women than controls, and was higher among first trimester women than pre-pregnant women.

The fact that the data on vegetable aversions did not confirm Profet's prediction weakens the theory as a whole, while the data on meats and seafoods are consistent with theoretical predictions—within the limits of this assessment tool—and previous findings.

Contrary to theory, more food cravings were not experienced by first trimester women compared to controls, nor were differences seen between the two groups at any other time. The number of cravings by both groups remained relatively stable across all sessions, and both groups had a relatively high number of cravings which is consistent with past findings that revealed food cravings to be a feature of both pregnant and nonpregnant women (Loewen, 1988; Rodin & Radke-Sharpe, 1991).

Profet predicted that first trimester food cravings are not randomly distributed but should cluster around (ripe) fruits given their very low levels of endogenous toxins. Evidence of an increased number of fruit cravings among first trimester women compared to controls was found—consistent with theoretical predictions. Fruits, evolutionarily speaking, are "meant" to be eaten—they represent a reproductive strategy plants have evolved to promote seed distribution by the exploitation of animal vectors. It is in plants' genetic interests to promote fruit consumption and seed distribution by animals. This is very likely the reason that fruits are typically accessible, brightly colored,

sweet, nutritious, and not protected by physical or toxic plant defenses—except for the fruit's seeds which are invariably bitter. Many studies report that fruits are the most prevalent (or among the top three) food craving experienced by pregnant women (Dickens & Trethowan, 1971; Edwards et al., 1954; Harries & Hughes, 1958; Hook, 1978; Loewen, 1988; Pope et al., 1992; Posner et al., 1957; Selby, Calhoun, Vogel, & King, 1980; Taggart, 1961; Worthington-Roberts et al., 1989). The precise sensory dimensions and interactions—odor, taste, texture, appearance, juiciness—that make fruit so appetizing to pregnant women have yet to be rigorously investigated.

Numerous studies have shown that pregnant women specifically develop cravings for desserts and sweet things (Dickens & Trethowan, 1971; Hook, 1978; Pope et al., 1992; Loewen, 1988; Walker et al., 1985; Worthington-Roberts et al., 1989)—although Rodin and Radke-Sharpe (1991) found the opposite to be true. There was no evidence of a difference in cravings to desserts between first trimester women and controls, a surprising finding given that cravings to desserts and other sweet things are often one of the top two (after fruit) cravings during pregnancy. For example, the top three cravings in Hook's (1978) study were ice cream, chocolate, and citrus fruits; the top two cravings in Pope et al.'s (1992) study were sweets and fruits; and the top three cravings in Loewen's (1988) study were ice cream, non-chocolate desserts, and fruit. The absence of a difference in cravings to desserts between pregnant and nonpregnant women may also be an artifact of the assessment procedure. Both pregnant and nonpregnant groups were queried to recall food cravings within the last two weeks, but because the nonpregnant women were queried during the time of menses, the two-week recall period would have included the premenstrual period—precisely the time during the menstrual cycle when

cravings to sweet things are most prevalent (Dalvit-McPhillips, 1983; Smith & Sauder, 1969; Wurtman, Brzezinski, Wurtman, & Laferrere, 1989), although some researchers have disputed this phase specificity to food categories (Rodin & Radke-Sharpe, 1991; Weingarten & Elston, 1990).

The most salient feature of the food aversions and cravings among both groups was the high degree of individual variability in the number and nature of aversions and cravings. Experimental studies and market research have documented how human dietary habits are influenced by geographical, social, cultural, economic, religious, psychological, experiential, sensory, maturational, climatic, physiological, and genetic factors (Blank & Mattes, 1990; Booth, 1990; DeSilva & Rachman, 1987; Khan, 1981; Logue et al., 1981; Worsley, 1980). These factors can cause differences to exist within individuals over time, between individuals, and between groups. Any changes to dietary habits that occur as a consequence of pregnancy are, therefore, superimposed upon these complex, pre-existing influences.

One method of controlling these pre-existing factors would be to expand the longitudinal assessment period to include a pre-conception phase for the pregnant women. The number and nature of food aversions and cravings (and olfactory function) could then be assessed before the dramatic changes of pregnancy—with each woman serving as her own control. One longitudinal study of 129 pregnant American women found that their was a significant association between experiencing food aversions and cravings before pregnancy and experiencing food aversions and cravings during pregnancy (Crystal, Bowen, & Bernstein, 1999). Rodin and Radke-Sharpe (1991) also

assessed aversions and cravings before conception and found that pre-pregnancy cravings were almost as high as pregnancy cravings.

9.4. Nausea and Vomiting

Data collected using the Rhodes Index of Nausea and Vomiting Form 2 revealed that first trimester women experienced more total symptom distress from nausea, vomiting, and retching than did first visit nonpregnant controls. This finding is consistent with Profet's prediction and with the majority of studies published on nausea and vomiting in pregnancy (Biggs, 1975; Brandes, 1967; Brown et al., 1997; DiIorio, 1985; Jarnfelt-Samsioe et al., 1983; Klebanoff et al., 1985; Tierson et al., 1986).

In this study, prevalence estimates of distress from nausea, vomiting, and/or retching in the pregnant group were calculated using an INV Form 2 average total distress score of ≥ 2.00 as a criterion. A score of 2.00 corresponds to either a single episode of a moderate level or two episodes of a mild level of nausea, vomiting, or retching during the past 12 hours. Thus, a criterion score of ≥ 2.00 indicates that during the past 12 hours the woman experienced, as a minimum, at least two episodes of a mild level of nausea, vomiting, or retching. The INV Form 2 uses written statements to describe "no," "mild," "moderate," "great," and "severe" levels of nausea, vomiting, and retching (see section 8.5. of the Results). Prevalence rates in this study were 79% (first trimester), 53% (second trimester), 32% (third trimester), and 11% (postpartum). These prevalence estimates are within the range reported in the literature (50-80%) and indicate that our sample was not different from previous samples of pregnant women in this regard.

The corresponding prevalence estimates for the nonpregnant controls were 22% (first visit), 6% (second visit), 28% (third visit), and 0% (fourth visit). These data tell us that

the prevalence of nausea and vomiting is low but not absent among nonpregnant women and shows variability over time even when women are tested at the same phase of their menstrual cycle (menses in this case). Although the nonpregnant women also experienced distress from nausea, vomiting, and/or retching, it should be noted that the intensity of their experiences was less than those of the pregnant women. This becomes apparent when a more rigorous INV Form 2 criterion of ≥ 4.00 was used to estimate prevalences. At this higher intensity criterion, prevalence rates among the pregnant group were 47% (first trimester), 26% (second trimester), 5% (third trimester), and 0% (postpartum), while the corresponding rates among the nonpregnant group fell to 0% across all four visits.

The prevalence data for pregnant women revealed that distress from nausea, vomiting, and retching is highest during first trimester and decreases, but does not disappear, as pregnancy proceeds. This finding is consistent with recent research into the frequency, intensity, and patterns of change of pregnancy-related nausea and vomiting. A prospective study of 160 pregnant Canadian women revealed that 74% of women reported nausea lasting a mean of 34.6 days, 50% reported relief by 14 weeks gestation, and 90% reported relief by 22 weeks gestation (Lacroix et al., 2000). Another Canadian study ($\underline{n}$ = 103) reported that the mean duration of symptoms of nausea with or without vomiting was 3.8 months ($\underline{SD}$ = 2.1), and that 73.2% of women reported that symptoms had stopped by 6 months gestation (Zhou et al., 1999). Both these studies confirm the idea that nausea and vomiting are principally features of first trimester but can persist beyond that time.

An examination of the actual nausea and vomiting distress scores reveals that the present sample of pregnant women experienced less total symptomatic distress than seen in other samples. The INV Form 2 has a basement score of 0 (no distress) and a ceiling score of 32 (maximum distress). These scores reflect two dimensions: the number of episodes of distress within a 12 hour period and the intensity of those episodes. The mean (±SEM) distress for first trimester women was 5.39 (±1.03), whereas Belluomini et al. (1994) reported total INV distress scores of 11.47 (±0.91) in their pretreatment pregnant control group and 12.64 (±1.06) in their pretreatment pregnant intervention group. This discrepancy can be explained by the fact that Belluomini et al.'s sample had an inclusionary criteria which selected women with complaints of nausea with or without emesis, while our study did not specifically recruit pregnant women with symptoms of nausea and/or vomiting. Our study may be more representative than Belluomini et al.'s in terms of distress from nausea and vomiting because we included pregnant women who experienced little or no distress. Because our study did not advertise itself as an intervention to reduce nausea and vomiting, we may have inadvertently created a "healthy-patient" self-selection bias in the sense that pregnant women experiencing little or no distress from nausea and vomiting would more likely participate precisely because they feel well.

The data on nausea and vomiting during pregnancy collected in this study complements data collected by the Rhodes INV Form 2 in other studies of pregnant women (Belluomini et al., 1994; O'Brien et al., 1996; O'Brien & Zhou, 1995; Stainton & Neff, 1994; Zhou et al., 1999). This study also expands that data set by being the first to longitudinally assess nausea and vomiting in pregnant women. Although other

instruments for assessing nausea and vomiting exist (see Lacroix et al., 2000; Melzack, Rosberger, Hollingsworth, & Thirwell, 1985), the Rhodes INV Form 2 is a good choice in terms of its established validity, reliability, and ease-of-use. Wider use of this instrument and instruments like it will facilitate comparative and meta-analytic studies of nausea and vomiting during pregnancy.

Currently, published studies on pregnancy-related nausea and vomiting suffer from widely different methodologies including: different definitions of nausea and vomiting, inconsistent time sampling techniques (e.g., one-time versus multiple-day assessments), and weak designs. Some studies have evaluated nausea and vomiting using a symptomatic vs. aysmptomatic dichotomous measure (e.g., Depue, Bernstein, Ross, Judd, & Henderson, 1987; Jarnfelt-Samsioe et al., 1983). Such a dichotomous evaluation would inappropriately place a woman with mild, short duration nausea in the same "symptomatic" group as a woman with frequent and severe vomiting.

Most of the studies of nausea, vomiting, and retching have been retrospective in the sense that data is collected after, sometimes months after, the actual experience of symptoms (e.g., Jarnfelt-Samsioe et al., 1983; Vellacott et al., 1988). Retrospective data is vulnerable to memory biases such as a tendency to recall more severe symptoms (Gadsby et al., 1993). Other studies on nausea and vomiting in pregnancy have relied on health diaries, non-psychometrically validated self-reports, or chart reviews based on the caregiver's impressions of the women's symptoms. Nausea is associated with such prodromal signs as pallor, tachycardia, and salivation, but the essence of nausea is a subjective experience that is best evaluated by the individual experiencing it using subjective scales (Melzack et al., 1985; O'Brien & Zhou, 1995).

Pennebaker (1982) has noted that the individual experiencing symptoms may erroneously assume that the person recording those symptoms will organize and interpret bodily sensations the way they do. Bias arises when a discrepancy exists between the pregnant woman's subjective perception and the observer's impressions or empirical observations. Health diary data tends to be more accurate than either recall or self-report data (Morrell & Wale, 1976), but it still falls short of an instrument with good psychometric properties.

Even the use of an instrument as good as the Rhodes INV Form 2 has potential problems. In the present study, one issue that may obscure the data in both groups is that the INV Form 2 was completed at home over a three day period. No objective verification check was made to see if the women complied with completing the form in the days immediately after their visit or at the appropriate time of day. Such challenges to compliance mean that the data in the nonpregnant women could have been collected at any phase of their menstrual cycle, while the data in the pregnant women could have been collected some time after their most recent visit. One solution to this problem would have been to have the women fill out only one form during their visit and sacrifice the broader data collecting period for increased precision in the timing of data collection. Alternatively, data could have been obtained by telephoning the women at home over the appropriate three day period.

9.5. Levels of Olfactory Information Processing

Odorants (volatilized chemicals) first come into contact, via diffusion or attached to binding proteins, with olfactory receptors located on the cilia of bipolar olfactory neurons. The olfactory neurons, supporting cells, basal cells, mucus film, and microvilli

comprise the olfactory epithelium, a 5 cm^2 structure sequestered high in the dorsal posterior recess of the nasal cavity (Dodd & Castellucci, 1991). Olfactory information, coded as neural impulses, is transmitted down the small unmyelinated axons of the olfactory neurons which synapse with the descending dendrites of mitral cells in areas called glomeruli in the olfactory bulb. The axons of mitral and tufted cells within the glomeruli project to secondary olfactory areas: the anterior olfactory nucleus, the olfactory tubercle, the pyriform cortex, the cortical nucleus of the amygdala, and the entorhinal cortex. Figure 8 illustrates in sagittal section these olfactory sites and pathways. Other neural sites that contribute to olfactory information processing include the medial dorsal nucleus of the thalamus, the hippocampus, locus coeruleus, raphe nucleus, zona incerta, medial septum, insula, temporal pole, nucleus of the diagonal band, and the orbitofrontal cortex (Dodd & Castellucci, 1991; Farbman, 1992; Haberly & Price, 1977; Halasz, 1990; Shipley, 1985).

The transmission of olfactory information is not a simple process of forward information processing. Electroencephalogram field potential studies, autoradiography, immunohistochemical imaging methods, lesion studies, positron emission tomography, and functional magnetic resonance imaging have revealed the complexity of information processing architectures within the olfactory system (Dodd & Castellucci, 1991; Halasz, 1990; Kauer, 1991). This complexity is achieved, in part, via reciprocal feedback mechanisms, stochastic neural dynamics, and centrifugal afferents from cortical sites to the olfactory bulb (Farbman, 1992; Kay, 1995). Some investigators have characterized the various olfactory functions in terms of the level of nervous system information processing involved, using distinctions such as peripherally mediated processes (e.g.,

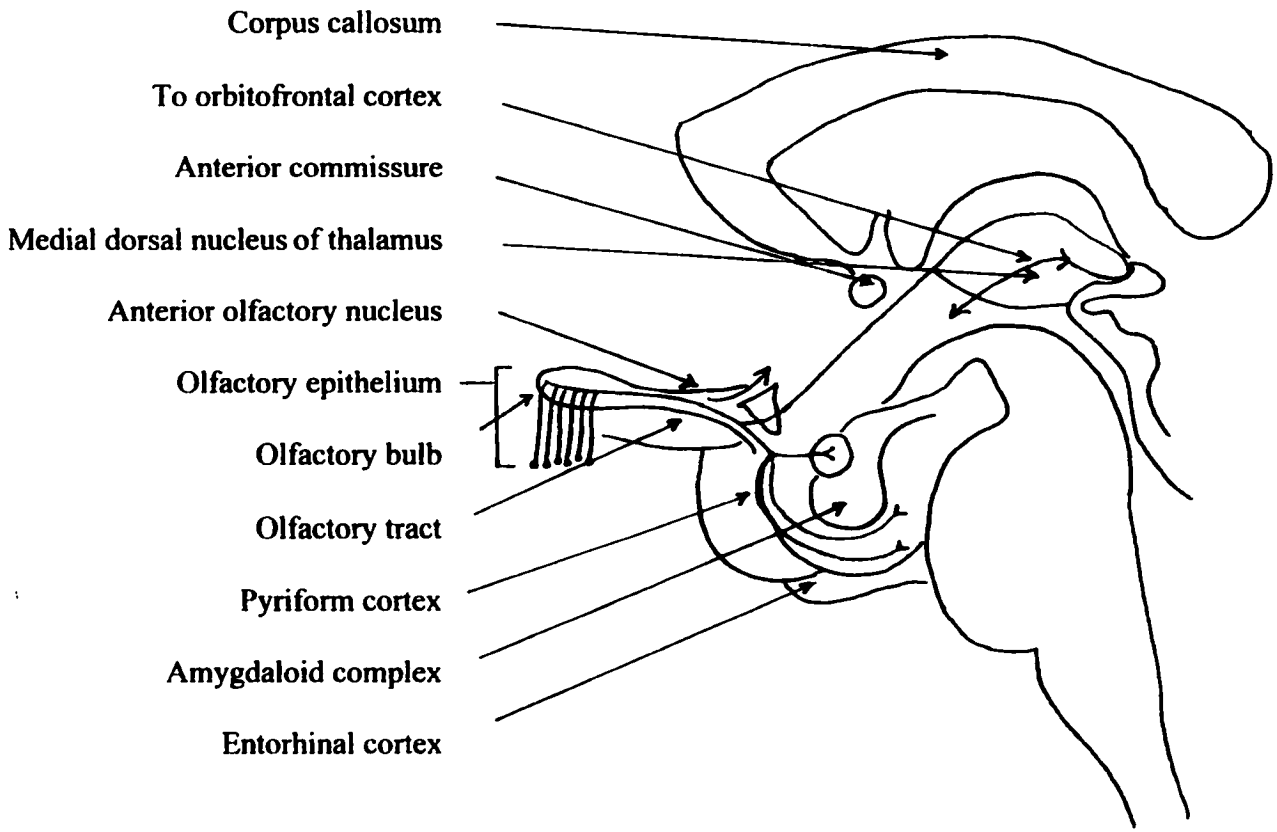

Figure 8. Sagittal section view of the main neural sites and pathways of the human olfactory system.

Note. Adapted from Dodd & Castellucci, 1991.

odor detection) versus centrally mediated processes (e.g., odor identification). However, even such "peripheral" processes as odor detection are influenced by centrally mediated events from relatively higher—more synaptically distant—cortical systems. A more useful information processing distinction may be to discuss odor detection as "primary" and all the other olfactory functions as "secondary" (Martzke, Kopala, & Good, 1997). This distinction acknowledges the dependence of the secondary measures upon odor detection while not limiting the range or direction of cortical system influences. Even given these refined distinctions, a complete description of hierarchical organization in the olfactory system is still unresolved, as Churchland and Sejnowski (1992) have alluded to in their general discussion on nervous system design, "The organization typical of earlier sensory areas is only approximately, roughly, and incompletely hierarchical" (p. 23).

9.5.1. Dissociation of Olfactory Functions: Sensitivity vs. Identification

The relevance of these points for the present thesis becomes apparent in the search for causal mechanisms explaining the changes in olfactory function observed. Thus, if olfactory sensitivity is conceptualized as a purely peripheral process, one may not actively seek or may overlook pregnancy-induced cortical changes that might exert a "top-down" influence on olfactory sensitivity.

In clinical olfactory testing, a dissociation between olfactory sensitivity and olfactory identification can suggest "primary" versus "secondary" deficits. Thus, clinicians view decreased olfactory sensitivity as suggestive of receptor cell dysfunction, nasal passageway obstructions, or alterations in the nasal epithelium, while decreased identification ability suggests cortical dysfunction. Dissociations between olfactory sensitivity and identification have been reported for male schizophrenics (Hurwitz,

Kopala, Clark, & Jones, 1988; Kopala, Clark, & Hurwitz, 1992), individuals with dorsal medial nucleus of the thalamus lesions (Mair et al., 1986), and orbital frontal cortex lesions (Jones-Gotman & Zatorre, 1988).

It may be argued that the present study revealed a dissociation, in the strict sense of the term, between olfactory sensitivity and identification among first, second, and third trimester women. However, because functional dissociations typically involve normal function in one domain with a deterioration in function in the other domain, the typical pattern of dissociation was not seen here. The fact that the olfactory identification test showed a ceiling effect also hints at the possibility that the observed dissociation was a test artifact of the UPSIT—not a true functional dissociation.

9.6. Genetic Contributions to Olfaction

Studies into the genetic basis of olfaction have revealed the large genetic variation, both intra- and interindividual, that exists within the olfactory system (Axel, 1995; Bartoshuk & Beauchamp, 1994; Stevens, Cain, & Burke, 1988; Wysocki & Beauchamp, 1984; 1991). In contrast to these studies, one twin study found little evidence of heritability in olfactory sensitivity to the odors acetic acid, isobutyric acid, and 2-sec-butyl-cyclohexanone (Hubert, Fabsitz, & Feinleib, 1980). However, heritability estimates are limited by the reliability of the psychophysical test, and the procedures utilized by these investigators were not refined. Also, large intra-individual variance may have obscured the detection of genetic effects.

It is possible, and likely, that the olfactory sensitivity changes observed in the present study have a genetic basis. Indeed, if the changes in olfactory sensitivity are to serve any kind of adaptive function, then those changes must necessarily have a genetic basis

because genes are required for the passage of adaptations from parents to offspring (Dawkins, 1976/1989).

Several convergent genetic methodologies can be applied to addressing this question. The methodologies include classic monozygotic/dizygotic twin studies (olfactory sensitivity should be more highly correlated for monozygotic twin pairs), heritability studies, within-family mother-daughter comparisons, studies on specific anosmias, and molecular biological techniques (e.g., monoclonal antibodies, genetic cloning, and retroviruses) for uncovering receptor protein regulation (Axel, 1995; Bartoshuk & Beauchamp, 1994; Kandel, 1983). To the extent that the olfactory changes observed here are also seen in animals (an area not yet researched), then transgenic and mutant gene studies in animal models will also yield insights into the regulatory mechanisms underlying the observed psychophysical changes.

One of the useful aspects of understanding the genetic basis of olfaction is that impaired olfactory function may be an early warning sign of neuropsychiatric disease progression. First-degree relatives of Alzheimer's patients show impairments on the UPSIT relative to matched controls (Serby, Mohan, Aryan, Williams, Mohs, & Davis, 1996), suggesting that olfactory identification deficits may be an early indicator of Alzheimer's. It is possible that a certain olfactory profile in the pre-pregnant state or a history of symptoms in close relatives may be early indicators of a susceptibility to pregnancy sickness or even hyperemesis gravidarum.

9.7. Estrogenic Influences on Olfaction

The symptoms of pregnancy sickness reported here—increased olfactory sensitivity, increased food aversions and cravings to certain foods, and increased nausea and

vomiting—have been discussed in the light of evolutionary theory. Parallel research into the proximate mechanisms—molecular, cellular, hormonal, neural, anatomical, and physiological—underlying these changes are needed. It is important to note that these parallel investigations are completely compatible with functional/adaptive investigations; the two levels of inquiry deal with different kinds of questions and, as such, can coexist and even inform each other.

Perhaps the most dramatic physiological change of pregnancy is the increase in certain hormonal levels that support pregnancy. The most important of these hormones are human chorionic gonadotropin, estrogens (estriol, estradiol, estrone), progesterone, prolactin, insulin, pregnanediol, corticosteroids, and cholecystokinin (CCK) (Frick et al., 1990; Ganong, 1987; Leavitt, 1995). Several lines of experimental animal evidence and quasi-experimental human evidence indicate that the olfactory system is sensitive to hormonal changes, in particular the estrogens (Briepohl, Mackay-Sim, Grandt, Rehn, & Darrelmann, 1986; Doty, 1986) which are secreted in quantities orders of magnitude greater than during the menstrual cycle (Seeley et al., 1992).

Data from mice show that the olfactory epithelial tissues contain estradiol receptors (Vannelli & Balboni, 1982), and further, pregnancy has been shown to stimulate the proliferation of olfactory neurons within the olfactory epithelium (Kaba, Rosser, & Keverne, 1988). A recent rat study ($\underline{n} = 22$) showed that estrogen protects against 3-methylindole-induced olfactory loss (Dhong, Chung, & Doty, 1999). Female rats pre-treated with 17β-estradiol dissolved in corn oil and then exposed to the olfactotoxicant 3-methylindole were found to have superior olfactory discrimination performance between the odors ethyl acetate and butanol than control rats pre-treated with just corn oil. In an

earlier study, olfactory sensitivity in the female rat was found to fluctuate according to the estrous cycle (Pietras & Moulton, 1974). It was further found that estrogen facilitated olfactory sensitivity while progesterone depressed it. Injections of the androgen testosterone (which increases across pregnancy) dose-dependently improved the olfactory sensitivity performance of female rats. In nonpregnant animals, estrogen and progesterone administration produce an increased appetite for salt (Denton, 1982), leading to the postulate that pregnancy-related taste changes are likely to be of maternal hormonal origin. This finding was extended by data showing depressed preference for sweet taste is related to a decreased availability or efficacy of estradiol in the activation of taste mechanisms (Richter & Barelare, 1938; Wade, 1972; Wade & Zucker, 1969). The blocked estradiol activity may be related to progesterone, which typically antagonizes estradiol's effects, and has been shown to reduce the number of estradiol receptors while increasing the activity of the breakdown enzyme estradiol dehydrogenase (Gurpide & Tseng, 1976).

Quasi-experimental human data on the role of estrogens in olfaction corroborate the experimental animal evidence. Thus, postmenopausal women placed on conjugated estrogen replacement therapy obtained statistically significant higher UPSIT scores than normal control women not receiving estrogen (32.7 ±10.5 vs. 22.4 ±11.2, respective means and standard deviations, n not reported) (Deems et al., 1991). Neuroanatomical studies have shown that neural regions high in estrogen receptor concentrations such as the amygdala, orbital frontal cortex, and hippocampus are also involved in olfactory information processing (MacLuskey, Naftolin, & Goldman-Rakic, 1986; Pelletier, Liao, Follea, & Govindan, 1988).

A pioneering Canadian study by Kopala et al. (1995) examined olfactory identification ability (UPSIT) and estradiol levels (radioimmunoassay) in 15 premenopausal women with DSM-III-R diagnosed schizophrenia (APA, 1987), 17 premenopausal normal controls, 12 postmenopausal women with schizophrenia, and 8 premenopausal normal controls. Women ranged in age from 20 to 64 years. The data revealed olfactory identification deficits in women with schizophrenia, and that deficits were worse among the postmenopausal women with schizophrenia. Also, all of the schizophrenic women had reduced estradiol levels compared to normal controls, perhaps due to neuroleptic medication, thus revealing that estrogen depletion worsens the olfactory identification deficits of schizophrenia since neuroleptics do not themselves cause olfactory deficits (Hurwitz et al., 1988; Kopala, Clark, & Hurwitz, 1992).

The finding that smokers experience less pregnancy-related nausea than nonsmoking women has been linked to estrogens. Women who smoked during pregnancy had lower serum estriol and prolactin levels during the final 20 weeks of pregnancy than did nonsmokers (Bremme, Lagerstrom, Andersson, Johansson, & Eneroth, 1990). The lowered estriol levels may lead to lowered olfactory performance in addition to the direct blunting effect cigarette smoking has on the olfactory system (Doty et al., 1984; Frye et al., 1990).

In summary, pre- and postmenopausal data, estrogen replacement and depletion data, psychiatric patient data, experimental animal data, and neuroanatomical data all point to an activational, and perhaps even an organizational, role of estrogens in both olfactory sensitivity and identification. Together, these data suggest the fruitfulness of assessing

estradiol's role (and other hormones such as progesterone) in the olfactory changes of pregnancy.

9.8. Integration of Findings

Profet's theory of pregnancy sickness uses modern evolutionary theory and insights from embryology, obstetrics, sensory psychology, nutrition, toxicology, and teratology to provide an integrated explanation of several curious temporal correlations during the first trimester: period of organogenesis, highest prevalence of miscarriages and birth defects, most intense nausea and vomiting, peak in food aversions, and, more equivocally, altered olfactory perception (see Figure 1). The data from this thesis do not "prove" Profet's pregnancy sickness theory; however, the weight of the data reported here are consistent with the theory and lend support to certain key predictions. Table 18 lists outcomes from this research in relation to specific *a priori* predictions derived from Profet's theory.

Many studies in normal populations and in populations with disorders have now documented the influential role of olfaction on the sensory and hedonic experience of foods and beverages and on subsequent nutritional outcomes. Studies of age-related olfactory declines have revealed higher odor detection thresholds (Deems & Doty, 1987; Murphy, 1986; Schiffman, 1979; Stevens & Cain, 1987), lower suprathreshold intensities (Stevens, Bartoshuk, & Cain, 1984; Stevens & Cain, 1985; 1987), lower olfactory identification ability (Ship, Pearson, Cruise, Brant, & Metter, 1996), and lower odor discrimination performance (Doty et al., 1984; Schiffman & Leffingwell, 1981) amongthe elderly. These olfactory alterations underlie complaints about food palatability and are associated with nutritional problems such as lowered food intake (Murphy, 1985; 1993; Schiffman, 1977; 1993; Stevens & Lawless, 1981). Similar studies linking

Table 18

Outcomes of the *A Priori* Predictions Comparing First Trimester Pregnant Women to First Visit Nonpregnant Women

Test	Prediction (P vs. NP)[a]	Outcome (Yes = Supported)
1. Phenyl Ethyl Alcohol Olfactory Sensitivity Test	↑ olfactory sensitivity (i.e., lower odor thresholds)	Yes
2. University of Pennsylvania Smell Identification Test	No explicit prediction	Not applicable
3. Food Aversions Questionnaire	↑ total food aversions	No[b]
4. Food Aversions Questionnaire	↑ vegetable aversions	No
5. Food Aversions Questionnaire	↑ meats & seafoods aversions	Yes
6. Food Cravings Questionnaire	↑ fruit cravings	Yes
7. Food Cravings Questionnaire	no explicit prediction	Not applicable
8. Distress from Nausea, Vomiting and Retching (INV Form 2)[c]	↑ total symptomatic distress	Yes

Note. Predictions derived from Profet's theory of pregnancy sickness (1988; 1992).

[a]P = first trimester pregnant women. NP = first visit nonpregnant women.

[b]First trimester women had more aversions than second trimester, third trimester, and postpartum women.

[c]Rhodes Index of Nausea and Vomiting Form 2.

olfactory variables to nutritional variables have not been conducted in pregnant women, a surprising oversight given the critical and well-researched role of nutrition during pregnancy for both the mother, the developing embryo/fetus, and birth outcomes (Committee on Nutritional Status during Pregnancy and Lactation, 1990; National Academy of Sciences, 1990; Ravelli, Stein, & Susser, 1976; Stein, Susser, & Rush, 1978).

The physiological connections between changes in olfactory perception, food aversions and cravings, and nausea/vomiting were not examined in this study but deserve further inquiry. It has been widely accepted that nausea/vomiting mediate the acquisition of learned food aversions in nonpregnant human populations (Garb & Stunkard, 1974; Mattes, 1991; Logue, 1985; Pelchat & Rozin, 1982) and among animals (Brower & Brower, 1964; Garcia & Koelling, 1967; Garcia, Lasiter, Bermudez-Rattoni, & Deems, 1985; Gustavson, Garcia, Hankins, & Rusiniak, 1974; Lett, 1985), although some animal and human data contradict this finding. Thus, antiemetics have not been found to protect against food aversion formation in rats (Rabin & Hunt, 1983), and do not appear to be necessary stimuli in human chemotherapy populations (Mattes, Arnold, & Boraas, 1987).

Presently, there are no studies on whether nausea/vomiting or olfactory changes mediate food aversions in pregnant women. The role of mediator variables can be evaluated using multiple regression techniques (not used in the present two-factory study because evaluating the contribution of mediator variables benefits from sample sizes larger than the one used here). Such studies would help determine the underlying mechanisms of food aversion acquisition in pregnant women, and in doing so, can also illuminate the nature of food aversion acquisition in other populations.

9.9. Alternative Theories and Criticisms

In the book based on her theory, Protecting Your Baby-to-Be (1995), Profet suggested that first trimester women avoid consuming the following: (a) particularly pungent or bitter vegetables such as broccoli, Brussels sprouts, peppers, onions, garlic; (b) vegetables known to have high levels of toxins such as mushrooms and potatoes; (c) barbecued or burned foods because burning produces mutagens (Overik et al., 1987); (d) all spices and herbs; and (e) beverages derived from bitter plant parts, including coffee, tea, herbal teas, and colas. Profet did not claim that these foods are embryotoxic; indeed, she repeatedly states that information is lacking on which toxins and in what quantities are harmful: "We know that all vegetables contain many natural toxins, but we don't know just which of these toxins—or which vegetables—can harm embryos" (Profet, 1992, p. 137). However, because she advised that pregnant women avoid certain foods before waiting for empirical evidence proving the accuracy of that advice, she has been berated by many nutritionists and obstetricians. Her critics feel that—apart from the correctness or incorrectness of her theory—that her advice is premature at best, and counterproductive at worst. One critic commented, "It is suggested 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" (Brown et al., 1997, p . 179).

9.9.1. Criticisms by Brown et al. (1997)

Brown et al. (1997) claimed to have refuted Profet's theory by testing the prediction that nausea and vomiting deters women from ingesting certain vegetables and other foods that contain potential embryotoxins. Data was obtained from the "Diana Project," a 1989-1994 population-based study of women members of a health maintenance organization in

the Minneapolis-St. Paul area. Women participating in the Diana Project were attempting to become pregnant when they enrolled in the project. The demographics of the study were as follows: women had a mean age of 29.0 years; 97% were white, 63% completed college, and 7% reported smoking during pregnancy. Data on dietary intake, illnesses, and pregnancy outcomes were obtained for 546 participants for whom dietary intake and illness data were available during the first 2 months after conception. The 546 pregnancies resulted in 94 (17%) miscarriages, fetal deaths, and infants diagnosed with one or more minor or major congenital anomalies, and 452 (83%) live-born infants with no evidence of congenital anomalies by 6 to 8 weeks after birth. The relevant finding of this study was that no relationship between intake of a range of foods proscribed by Profet as potentially harmful and the presence of nausea and vomiting in early pregnancy was identified. This conclusion was based on a comparison of food intake (servings per week) between women who reported nausea or nausea and vomiting (79%) and women who reported neither nausea or vomiting (21%). No statistically significant difference in mean food intake was found between these two groups.

This conclusion is problematic for several reasons. First, the composition of the two groups is questionable because placement in the "nausea or nausea and vomiting" group versus the "no nausea or vomiting" group was based on self-identification of the dichotomous presence or absence of these symptoms. An objective measure of nausea and vomiting such as the Index of Nausea and Vomiting Form 2 was not used, nor was quantitative information collected on the frequency, intensity, or duration of these symptoms. In short, there was no objectively obtained evidence that the two groups statistically differed from each other on the basis of nausea and/or vomiting. The second

criticism relates to the low intakes of the foods sampled in the study. The mean number of servings per week for all 12 vegetables examined in this study was 0.80 (± 1.0 SD) (range = 0.1 ± 0.3 SD to 3.6 ± 2.6 SD) for the symptom group and 0.83 (± 1.1 SD) (range = 0.0 ± 0.1 SD to 4.0 ± 3.7 SD) for the nonsymptom group. These intake sizes are considerably lower than the 3 to 5 servings of vegetables per day recommended by the Daily Food Guide of the United States Department of Agriculture (reported in Whitney & Rolfes, 1996). This suggests that women in both the symptom and the nonsymptom groups were largely avoiding these vegetables, creating a basement effect that actually supports Profet's prediction rather than refuting it. A third criticism is that the authors reported an 80% power for detecting a mean difference as small as 0.30 servings per week. However, the actual mean difference in 11 of the 12 vegetables analyzed was 0.30 or less, suggesting insufficient power for the detection of subtle differences.

9.9.2. Deutsch's Pregnancy Sickness Theory: Reduction in Coital Frequency

Deutsch (1994) offered theoretical criticisms of Profet's theory and proposed an entirely different adaptive theory of pregnancy sickness. Deutsch's first criticism was that it is difficult to explain why nausea and vomiting often occur in the morning when the stomach is empty. A full stomach, however, is not a necessary condition for experiencing nausea. Furthermore, researchers (e.g., DiIorio, 1985; Gadsby, 1993; Lacroix et al., 2000) have argued that the "morning" aspect of "morning sickness" ignores the fact that symptoms occur throughout the day. Gadsby et al.'s (1983) study of 363 British women found that 53% of vomiting episodes occurred between 6:00 am and 12:00 noon. Thus, vomiting can often occur after breakfast (when the stomach is full), and in 47% of cases occurs after 12:00 noon. They further suggest that the term morning sickness be replaced

by the term "episodic daytime pregnancy sickness." Lacroix et al. (2000) reinforced this view with their finding that 80% of women (128 of 160 participants) reported nausea lasting all day.

Deutsch's next criticism was that toxin ingestion should lead primarily to diarrhea and not vomiting because diarrhea is the preferred adaptive mechanism for getting rid of toxins produced by enterobacteria (Carpenter, 1987). However, Profet's theory primarily concerns toxins ingested from food and not toxins produced by enterobacteria. Moreover, the basis of learned food aversions—whether in animals, anoretic/bulimic women, hospitalized alcoholics, chemotherapy/radiotherapy patients, or pregnant women—is that neural mechanisms associate vomiting, not diarrhea, with the odor and taste of the most recent food consumed (Garcia & Koelling, 1967; Logue, 1985; Mattes, 1994; Mattes, Curran, & Whittington, 1991).

Deutsch's theory about the function of pregnancy sickness postulates that pregnancy sickness and mastalgia (breast pain) evolved to reduce coital frequency in early pregnancy. Reducing coital frequency is important, he argues, because coitus stimulates uterine motility—via endogenous oxytocin release and prostaglandins in the seminal fluid—which could induce abortion (Fox & Knaggs, 1969; Fox, Wolff, & Baker, 1970). This theory may have some merit in that it leads to a testable prediction: is coital frequency during first trimester associated with an increased risk of miscarriage? To date, this central prediction of Deutsch's theory has not been tested. Also, Deutsch's theory fails to adequately explain why nausea, vomiting, food aversions, and olfactory changes coincide with organogenesis. How these symptoms would reduce coital frequency, other than by general malaise, is unclear.

9.9.3. Huxley's Pregnancy Sickness Theory: Promotion of Placental Development

A more recent functional explanation for pregnancy sickness—specifically nausea and vomiting—suggests that pregnancy sickness functions to promote the development of the placenta (Huxley, 2000). Huxley begins by acknowledging that pregnancy sickness has been associated with positive pregnancy outcomes: decreased risk of miscarriage, pre-term birth, low birthweight, and perinatal death. Huxley argues that pregnancy sickness—via hCG and thyroxine secretion—reduces maternal energy intake, which results in lowered levels of insulin and insulin growth factor-1, thus suppressing maternal tissue synthesis in early pregnancy and favoring nutrient partitioning toward the developing placenta. Like Profet's theory, this interesting functional theory of pregnancy sickness, requires further empirical testing before its merits can be evaluated. At a general level, Huxley's theory is not incompatible with either Deutsch's (1994) or Profet's (1992) theory. Reduced maternal energy intake in early pregnancy is consistent with Deutsch's hypothesis of reduced coital frequency in early pregnancy but is also consistent with Profet's hypothesis of reduced food intake in early pregnancy via increased food aversions. Mutually exclusive predictions between the three functional theories will need to be identified and tested in future studies.

9.9.4. Pregnancy Sickness as an Epiphenomenon

Some scientists and physicians have conceptualized pregnancy sickness as an epiphenomenon: the incidental by-product of pregnancy-related hormonal changes. This hypothesis proposes that pregnancy sickness simply reflects the magnitude of a mediating factor such as hormone level. Thus, if pregnancy sickness is caused by high levels of a hormone that contributes to successful reproductive outcome, then low levels of the

hormone will both worsen reproductive outcome and diminish pregnancy sickness symptoms. In this view, pregnancy sickness is an epiphenomena—it merely serves as an indicator of hormone levels.

While epiphenomena do exist—the red colour of blood cells are epiphenomenal consequences of the molecular structure of hemoglobin's interactions with light—the "explanation" that something is epiphenomenal is often an admission that the phenomenon is not well-understood. In some senses, "epiphenomenal" theories are not theories at all: they make no predictions and they require little evidence. An epiphenomenal explanation for pregnancy sickness cannot account for why a condition that appears to be maladaptive—it leads to a waste of nutrients, reduced dietary intake, distress, and constrained mobility—has not been selected out of the human population, but instead persists with high prevalence. Ironically, the explanation that pregnancy sickness represents a by-product of hormone levels that do ensure a healthy pregnancy, in fact, relies on an implicit evolutionary argument of its own: that high levels of some reproductive hormone are adaptive for successful pregnancy. While it is possible that pregnancy sickness is an epiphenomenon, considerable convergent evidence points to a function for pregnancy sickness.

9.9.5. Pregnancy Sickness as a Maladaptation

As a qualification of the adaptive argument, it should be noted that pregnancy sickness is not being conceptualized here as an unmitigated good. Adaptations that have one end goal can, nonetheless, create maladaptive situations for other systems. Because mother and embryo share an average of 50% of their genes, it is equivalent to say that the embryo alters the mother's physiology to protect itself, or that the mother alters her own

physiology to protect the embryo, a situation that is an interesting example of what Trivers (1974) has termed "parent-offspring conflict" and what Haig (1993) has called "maternal-fetal conflict." In this case, parent and offspring have mutual genetic interests (i.e., offspring protection and viability) but the mechanism (i.e., pregnancy sickness) for achieving those interests comes at a maternal cost. Thus, at least two antagonistic selection forces are at work in the mother: selection for increased pregnancy sickness (to promote offspring health) and selection for decreased pregnancy sickness (to promote maternal health). This analysis also reveals how an adaptive view of pregnancy sickness has positive heuristic value: it leads to theorizing with rich conceptual possibilities, while epiphenomenal explanations as a research strategy typically shut the door on further inquiry.

It is the position of this thesis that pregnancy sickness is very likely an adaptation and that hyperemesis gravidarum represents a maladaptive extreme of that adaptive mechanism. In general, the *prima facie* existence of a maladaptation is neither a necessary nor a sufficient condition for the logical invalidation of a putatively adaptive mechanism. Maladaptive extremes of otherwise adaptive mechanisms are commonplace. It is often mistakenly thought that maladaptations prove that a trait, structure, process, or behavior cannot be an adaptation; in fact, maladaptations typically prove the opposite because maladaptations often presume adaptations.

It is important to be clear that the terms "adaptation" and "maladaptation" are being used in their evolutionary sense and expressly not in their psychological sense. In their colloquial or psychological senses, these terms refer to notions of personal well-being, social appropriateness, and the ability to adjust to shifting conditions (Buss et al., 1998;

Nesse, 1990). The evolutionary definition of adaptation is an inherited and reliably developing characteristic that came into existence as a feature of a species through natural selection because it helped to directly or indirectly facilitate reproduction (Tooby & Cosmides, 1992).

There are several possibilities that shed light on hyperemesis gravidarum in the context of an adaptive view of pregnancy sickness. First, because natural selection is a slow process, there will often be a lag between a new adaptive problem and the evolution of a mechanism designed to solve it (Williams, 1992). An example of this is the evolved human preference for sugar. In our evolutionary past, the high calories provided by sugar were a valuable and limited resource. The evolution of a preference for sweet taste increased the likelihood of sugar consumption. In modern times, cheap sugar refining has made sugar widely accessible. Disorders associated with sugar over-consumption (i.e., obesity and tooth decay) represent maladaptations to the evolved adaptation of sugar preference. Allman (1994) expresses this theme by arguing that humans live in a modern world but are burdened with brains designed to deal with ancient adaptive problems.

An extension of this novel environment perspective argues that maladaptations are produced when adaptations are challenged by extreme conditions. For example, moderate levels of anxiety improve performance and are adaptive for the fight or flight response, while high levels of anxiety lead to "performance anxiety" which can prove psychologically incapacitating and can exert depressive effects on the immune system. Clearly, the existence of debilitating anxiety due to extreme conditions does not thereby invalidate the notion that anxiety may have adaptive functions as a psychological process under a wide range of prevailing conditions.

Similarly, it may be the case that hyperemesis gravidarum is now a problem, or a more widespread problem than it ever used to be, because modern and artificial conditions somehow trigger this reaction or exacerbate this susceptibility. The tightly choreographed systems of hormone-receptor interactions that underlie the activation of the typical pregnancy-related nausea and vomiting response may become over-reactive in some individuals, causing HG. The system works in the majority of cases, but in some individual's the system's calibration is off and "sickness" results.

Any adaptation requires a sophisticated orchestration of developmental, and micro and macro environmental factors for proper operation. It is reasonable then that disturbances to these factors can lead to suboptimal performance in that adaptation, that is to say, in a maladaptation. In this sense, maladaptations are necessary evils that one would expect to exist as a consequence of complex systems, constraints on optimal design, the existence of novel or extreme environments, and the speed of evolutionary change. In any population, maladaptive extremes of adaptations can coexist if the survival and reproductive benefits of the adaptation under normal conditions outweigh the costs.

9.10. Limitations and Criticisms

The present study attempted to examine olfactory function during pregnancy in a while avoiding many of the criticisms directed at previous studies. Examples of these improvements include the use of a control group, prospective assessments made at each trimester and postpartum, use of objective, psychometrically sound olfactory function tests and nausea and vomiting instruments, and comprehensive exclusionary criteria.

Despite these improvements, a number of limitations and criticisms can be leveled at the present study. This section discusses these problems and suggests potential solutions.

9.10.1. Limitations Related to the Nonpregnant Control Group

This study compared pregnant women to nonpregnant women at a particular phase of their cycle. However, the condition of "nonpregnancy" can be subdivided into 4 relatively distinct hormonal states across the menstrual cycle: (a) menses, (b) the follicular phase (or preovulatory or proliferative phase), (c) ovulation, and (d) the luteal phase (or postovulatory or secretory phase) (Berne & Levy, 1988; Pinel, 1990; Yu, 1994). Nonpregnant women in this study were tested during the menses phase of their cycle—two to five days after menstruation onset. This period was selected because the onset of menstrual flow is a relatively clear indicator of the menses phase, whereas markers for the other phases tend to be more subjective or require disruptive efforts on behalf of the nonpregnant women. For example, obtaining data on menstrual cyclicity by use of retrospective questionnaires has been considered unreliable because of the inaccuracy of recall (Scialli & Lemasters, 1995). Participants in a Minnesota cohort study of 2500 women reported age at onset and cessation of menses with 75% accuracy but become highly inaccurate when recalling cycle length and variability (Bean, Leeper, Wallace, Sherman, & Jagger, 1970; Treolar et al., 1967).

Objective methods for more precisely determining the other phases of the menstrual cycle involve morning oral temperature monitoring, luteinizing hormone (LH) assays to detect the LH surge of ovulation, or assessments of mucosal viscosity (Prior, Vigna, Schulzer, Hall, & Bonen, 1990). These methods were not employed because they require training and high compliance by the participants or because they are expensive,

disruptive, and/or invasive. Future studies that compare pregnant women against women at different phases of their cycles, they will also have to contend with various statistical and conceptual problems for normalizing and averaging what is essentially heterogenous intra- and intersubject menstrual cycle data (Doty, 1979a; Doty & Silverthorne, 1975).

Another reason for choosing menses as the reference point is that this period avoids the estradiol surge of the follicular phase, the luteinizing hormone and follicle-stimulating hormone surges of ovulation, and the progesterone and secondary estradiol surges of the luteal phase (Stephens, & Tate, 1992). This relatively "quiet" hormonal state presumably lowers some of the group variability due to individual differences in hormone production. While this methodology is defensible, it remains an open question whether similar results would have been obtained had the nonpregnant women been in other phases of the cycle. One could make the case that there are at least five control groups possible—one group corresponding to each menstrual cycle phase, and one group randomized for menstrual cycle phase.

Presumptive evidence that the results would not have been the same had the controls been segmented into specific menstrual cycle phases are suggested by studies on psychological, cognitive, motor, and perceptual changes that correlate with specific menstrual phases (Doty, 1986; Hampson, 1990; Hampson & Kimura, 1988; Kimura, 1998; McGee, 1979). Thus, olfactory sensitivity has been reported to peak during ovulation with a secondary peak at the mid-luteal phase (Doty, 1976; Doty, Snyder, Huggins, & Lowry, 1981), although other researchers have not replicated this finding (Hummel et al., 1991). Enhanced performance on tests of articulatory and fine motor skills and poorer performance on spatial ability tests have been reported during the late

follicular phase compared to menses (Hampson, 1990). It should be noted that the magnitude of these performance variations over the menstrual cycle tend to be small, especially when compared to inter-individual differences, and would likely go unnoticed for most women in everyday situations. Notwithstanding these qualifications, these results suggest that a more complete understanding of pregnancy-related olfactory changes awaits studies comparing pregnant women to nonpregnant women tested at the other phases of their menstrual cycles.

Other physiological and psychological processes also show menstrual periodicity. Women with late-luteal phase premenstrual dysphoric disorder (PMS) report negative mood and increased food cravings and food intake during the late luteal phase (Dye, Warner, & Bancroft, 1995; Evans, Foltin, & Fischman, 1999; Ivey & Bardwick, 1968; May, 1976). The association between preference for a specific food type and menstrual phase are still inconclusive (Rodin & Radke-Sharpe, 1991; Weingarten & Elston, 1990). It has been suggested that carbohydrate consumption and a craving for sweets increases in the luteal (premenstrual) phase (Dalvit-McPhillips, 1983; Smith & Sauder, 1969; Wurtman et al., 1989). Some of these findings may be unreliable because many of the studies determined menstrual cycle phase retrospectively, and assessed food cravings using a single-item question. In the face of this uncertainty, it is still possible that the present study may have created a confound when assessing the number of food cravings experienced by the nonpregnant women since it queried the women to recall their food cravings during the past two weeks—a time that would include both the menstrual phase and the late luteal phase of their cycles. A narrower window of recall for food aversions

and cravings such as the past 4 days may help align data to specific menstrual phases better.

9.10.2. Limitations Related to the Pregnant Group

Women experiencing different levels of pregnancy sickness should be explicitly included in the study design. This would mitigate the "healthy patient effect" which may have biased the present sample toward women with low levels of nausea and vomiting since women with high levels of nausea and vomiting were not explicitly targeted or offered specific incentives to participate. Testing a group of hyperemesis gravidarum patients may also yield insights; however, the ethical and practical issues of testing such a group require careful consideration.

Another factor shown to influence data on the symptomatic experience of pregnancy sickness is whether the pregnancy was wanted or unwanted. A study of 99 pregnant women drawn from an urban, medical school-based family practice residency showed that the women with wanted pregnancies (n = 48) were more likely to report amenorrhea, breast tenderness, and pregnancy sickness than the women with unwanted pregnancies (n = 51) (Bluestein & Levin, 1991).

9.10.3. Limitations Related to Parity

Both the nonpregnant controls and the pregnant group consisted of women with nulli-, primi-, or multiparous histories. It is possible that prior history of pregnancy in either group may have a lasting influence on the pregnancy sickness variables examined here. Currently, the evidence for this hypothesis is equivocal. The presence of nausea and vomiting symptoms has been associated with nulliparity by some researchers (Depue et al., 1987; Klebanoff et al., 1985; O'Brien & Zhou, 1995) and with multiparity by others

(Jarnfelt-Samsioe et al., 1985; Petitti, 1986). A study 126 American women found that nulliparous women were more likely to experience vomiting than multiparous women (O'Brien & Zhou, 1995). The researchers attributed this result to the lower levels of estrogens among multiparous women (Depue et al., 1987), and the finding that estrogen metabolism is altered during first pregnancies so that the amount of free estradiol drops in subsequent pregnancies (Bernstein et al., 1986). Contradicting the O'Brien and Zhou (1995) study, an older Swedish study of 152 women found no association between parity and the presence and degree of nausea during pregnancy (Uddenberg, Nilsson, & Almgren, 1971). The Swedish findings should be interpreted cautiously given their methodologically weak assessments of nausea and because most of the women were tested during second trimester when nausea and vomiting begin to decline for many women.

In the present study, more homogenous between-group controls would consist of nonpregnant women whom had never been pregnant before, while more homogenous within-group controls would be pre-pregnant women with no prior history of pregnancy. One virtue of the heterogeneity in the present control groups is that the study findings have greater generalizability.

9.10.4. Limitations to Cross-Cultural Generalizations

Different cultures, including cultural subgroups within a nation, can differ along a vast number of dimensions, with language, educational experiences, and values being especially important variables (Anastasi, 1988). The majority of pregnant (89%) and nonpregnant (78%) women identified their ethnic backgrounds as being "white," with ethnicity being used here as a socially-relevant construct not a biologically meaningful

one (Diamond, 1994; Shreeve, 1994). The lack of diverse cultural/ethnic representation in this study's sample limits cross-cultural generalizations. The point is not a minor one given the possible mediation of cultural differences on olfactory perception, diet, and pregnancy sickness symptomatology.

Culturally based differences in olfactory identification have been found: Korean Americans scored significantly higher on the UPSIT than African and white American groups, and all three groups scored higher than a native Japanese group (Doty, Applebaum, Zushos, & Settle, 1985). Cross-cultural differences have been noted in simple taste preferences (Moskowitz, Kumaraiah, Sharma, Jacobs, & Sharma, 1975), and Rainville (1998) has noted that pica is more common among pregnant African American women than white American women—however, the complexities of accurately assessing the taboo subject of pica demand more and better research before confident conclusions about cultural differences can be made.

The actual tests used may also possess cultural biases in their design and administration (Anastasi, 1988; Triandis & Brislin, 1984). Most of the world's scientific tests have been created in North America or Europe and, therefore, can possess biases related to western values and language. Some tests are becoming available that acknowledge these cultural biases and attempt to correct for them. Doty, Marcus, and Lee (1996), for example, have developed a 12-item cross-cultural olfactory identification test that incorporates odors that are easily recognizable by persons from a variety of cultures. After consulting with researchers from China, Columbia, France, Germany, Italy, Japan, Russia, and Sweden, Doty et al. noted that certain UPSIT odors would not be easily recognized by the following cultural groups: (a) Italy: cheddar cheese, dill pickle, fruit

punch, lilac, lime, pumpkin pie, root beer, and wintergreen; (b) France: cheddar cheese, dill pickle, gingerbread, peanut, root beer, and wintergreen; (c) Germany: cedar, cheddar cheese, cherry, dill pickle, fruit punch, gingerbread, grape, natural gas, root beer, and wintergreen; (d) Russia: bubble gum, cheddar cheese, clove, coconut, dill pickle, fruit punch, gingerbread, licorice, lime, mint, peanuts, pizza, pumpkin pie, root beer, and wintergreen; (e) Columbia: cheddar cheese, dill pickle, gingerbread, licorice, peanut, root beer, and winter green; (f) Sweden: fruit punch, grape, licorice, and wintergreen; and (g) China: cedar, cinnamon, clove, dill pickle, gingerbread, mint, pizza, pumpkin pie, root beer, and wintergreen. The 12 odors chosen for the cross-cultural olfactory identification test were as follows: banana, chocolate, cinnamon, gasoline, lemon, onion, paint thinner, pineapple, rose, soap, smoke, and turpentine. Certain words specific to North America were also substituted in the lists of response alternatives: "dog" for "skunk," "garlic" for "pumpkin pie," "woody" for "pine," and so on.

In this study an interesting pattern was observed—women often spent noticeably more time trying to identify the following UPSIT odors: cheddar cheese, natural gas, grass, cedar, and wintergreen. Quantitative temporal data were not recorded on this phenomenon. It is unclear whether the difficulties in recognizing these odors had to do with variations in odor concentration, specific sensitivity to those synthetic odors, cultural unfamiliarity with those odors, relative inexperience with those odors, or difficulties with assigning a name to those odors. What is clear is that even a superficially simple task such as olfactory identification is actually subject to multiple factors—cultural and otherwise—that complicate data interpretation.

In summary, future studies need to account for potential cultural differences in their design, analysis, and interpretation, and should utilize tests that minimize cultural biases.

9.10.5. Limitations in the Tests and Questionnaires

This study used two objective, quantitative tests of olfactory function, one psychometrically validated self-report instrument of nausea, vomiting, and retching, and an investigator-designed questionnaire of food aversions and cravings. Data from the last of these requires the greatest caution in terms of interpretation and generalization because it was not tested for validity (except face validity) or reliability. A good food aversions and cravings instrument would require the following psychometric properties: good internal and external validity, and good short-term and long-term test-retest reliability. Determining the split-half reliability coefficient and the short-term test-retest reliability coefficient would provide information on the internal consistency and self-correlation of such a test, as well as its stability and dependability over time. The instrument would also need to contain subscales that could discriminate between food categories (e.g., fruits from vegetables). These subscales would also require high test-retest reliability.

A number of researchers have attempted to measure food aversions; however, a widely accepted test with the above detailed properties has not yet emerged (Mattes & Cowart, 1994). This is due to the difficulty researchers have faced with developing a consensus definition of the terms "food aversion," and "food craving," (M. Pelchat, personal communication, 1994) difficulties in evaluating the psychometric properties of an instrument, and difficulties with overcoming practical issues of actually measuring food aversions (e.g., compliance).

The olfactory tests used here assessed two dimensions of olfaction: sensitivity and identification But olfactory perception is a global construct that can be assessed in multiple ways. These tests include olfactory sensitivity (e.g., odor detection and recognition thresholds), olfactory identification (e.g., forced-choice, yes-no), olfactory memory, olfactory discrimination, and suprathreshold amyl acetate scaling of hedonic qualities such as intensity and pleasantness (Cain, Cometto-Muniz, & De Wijk, 1992; Doty & Kobal, 1995; Doty et al., 1995).

The forty UPSIT odors represent a broad range of common odors; however, the environment is filled with thousands of different odors, odor mixtures, and subtle variations on odor themes (e.g., lemon scent versus lime scent). All of the UPSIT odors were chemically simple, synthetic compounds; it is unknown whether complex and biologically-relevant "real-world" odors would reveal different olfactory identification abilities. The real scent of gingerbread, for example, is more complex than the artificial scent of gingerbread used in the UPSIT. It is known that complex odors are not perceived in the same way as simple odors. Perceptual ratings of intensity are suppressed when odors are mixed, that is, the intensity of the mixture is less than the sum of the intensities of the components when tested alone (Cain, 1975). To make matters more complex, odor and taste mixtures appear to be additive: the perceived intensity of the mixture is equal to the sum of the intensities of the components when tested apart (Gillan, 1983; Murphy, Cain, & Bartoshuk, 1977; Murphy & Cain, 1980). Similar to the arguments around the UPSIT's synthetic odors, an olfactory sensitivity test that uses a biologically relevant odor (not a synthetic or chemical odor) would extend the real-world validity of the study.

However, currently there are no psychometrically sound olfactory sensitivity tests that employ "real" odors.

The testing of real world odors is important because many substances, stimulate both the olfactory and trigeminal systems, and a mutual sensory inhibition has been demonstrated during concurrent stimulation: trigeminal stimulation suppresses odor perception and vice-versa (Cain & Murphy, 1980; Doty et al., 1978). It would be interesting to see if this mutual suppression exists in pregnant women and if the strength of the interaction is the same.

More realistic and naturalistic paradigms using "real world" foods need to be utilized (Meiselman, 1992). The development of food aversions and cravings questionnaires with good psychometrics will provide valuable data. Other measures of eating behavior such as food intake, beliefs about foods, and pica will also contribute to our understanding of pregnancy sickness.

9.10.6. Limitations in Study Design, Sample Size, and Representation

The present design was a quasi-experimental design in the sense that it employed a control group similar to the experimental group on many relevant variables except the one being investigated. It was not a true experimental design because there was no randomization of initially nonpregnant women to each of the two groups: pregnant and nonpregnant. Such randomization is essential to experimental designs but is unethical in the present context. As in other research domains that do not permit true experimental designs, the solution lies in a convergent operations approach that combines experimental studies in non-human animals with quasi-experimental, ethoexperimental, qualitative, and field studies in humans.

The olfactory function tests and food aversions and cravings questionnaire were all administered in a reasonably controlled testing environment. However, a general problem always arises in the attempt to exert control over potential confounding factors, namely, that laboratory investigations are often accompanied by seriously diminished pertinence to real world situations (Halpern, 1997; Meiselman, 1992). This problem can be addressed by undertaking field studies, qualitative studies, and studies employing more naturalistic methods like the ethoexperimental approach (Blanchard, Brain, Blanchard, & Parmigiani, 1989). Such parallel studies need to identify critical boundary conditions that should be incorporated in controlled investigations. By doing so, such studies can capture some of the situational complexity that exists as pregnant women negotiate through the sensory richness of the real world. As an example, it would be informative to explore the behavior of first trimester women encountering real foods in real situations.

The present study utilized four test sessions—one corresponding to each trimester in the pregnancy group and the postpartum. Although longitudinal and cross-sectional studies allow for the detection of patterns over time, the issue remains of what temporal interval to use. Possibly, four sessions do not represent a sufficiently fine-grain level of analysis for the detection of interesting alterations in olfactory perception. Future studies might consider including more test sessions, although any such considerations would have to be outweighed by increases in cost, effort, and participant time.

These very issues of cost, effort, and time constrained the sample size of the present study. Larger sample sizes increase the statistical power (i.e., the probability of correctly rejecting the null hypothesis (Keppel & Zedeck, 1989)) of a study, thereby enabling the detection of relevant but subtle effects.

The present sample was primarily a convenience sample. Women self-selected to participate in this study; techniques such as random sampling or stratified random sampling were not used. The present sample of women were representative of certain demographics. The majority were young, white, educated women. All were city dwellers, therefore caution is needed when generalizing the results to a rural population. The sample did not include teenage women, women with hyperemesis gravidarum, or women taking any intervention for pregnancy sickness.

9.11. Principles of Data Collection During Testing

Standardization of test administration is a hallmark of good psychological testing protocol because it allows test results to be compared across administrations and examiners, and it allows for comparisons with normative databases. However, the rigid adherence to standardization procedures does not protect the test results from subtle influences. Anastasi (1988) highlighted factors that exert such influences: (a) testing environment, (b) examiner-participant rapport, (c) oral presentation style and rate, (d) similarity or familiarity between the personal characteristics of examiner and participant, (e) supportive or encouraging gestures and comments, and (f) test-taking anxiety. In the ideal testing situation, standard conditions are identical with those conditions that result in optimal test performance for the particular participant (Lezak, 1995); however, in real-world testing situations there is often a discrepancy between the two. This raises a natural question regarding the nature of standardization and how to achieve it: is standardization the actual physical conditions, instructional set, and mechanical procedures or is it the flexible testing conditions employed to ensure good understanding of what is expected from the participant and the efficient, ethical execution

of tasks? Williams (1965) echoed this point: "The same words do not necessarily mean the same thing to different people and it is the meaning of the instructions that should be the same for all people rather than the wording" (p. 17).

With respect to neuropsychological test administration, Vanderploeg (1994) has argued that the needs of the overall assessment are what are important; testing *per se* is only a tool in the assessment process. Vanderploeg identified nine principles to help guide researchers and clinicians regarding questions about testing procedure. These principles and examples of how they were implemented in this study follow:

Principle 1. Follow standardized procedures as outlined in the test manual as carefully as possible. If participants have limitations preventing them from following the specific conditions apply Principle 2. **Example:** The published guidelines for administration of the PEA test, the UPSIT, and the INV-Form 2 were carefully followed.

Principle 2. What is important are the testing conditions that allow each individual participant to meet the standardized testing conditions, rather than the actual wording or procedures. Examiners may have to amplify or repeat instructions or use pauses or slow the rate of instructional presentation to make sure that comprehension is achieved. **Example:** During UPSIT testing, a participant would sometimes request to sniff an odor stimulus twice, because they forgot that odor's sensation while trying to recognize it among the response alternatives. This procedural variation was permitted.

Principle 3. Minimize environmental factors extraneous to the brain-behavior relationship under study. **Example:** The testing room environment was chosen to be a quiet, comfortable space free of clutter and distractions. This testing condition reduced competition for the participant's attentional resources.

Principle 4. Ensure the participant is sufficiently alert to engage the brain-behavior under study. **Example:** Maintaining participant arousal was achieved by building in rest breaks during testing, by confirming the participant's comfort levels during testing, and by alternating olfactory tasks with non-olfactory tasks.

Principle 5. Present all perceptual and visuospatial tasks at the participants' midline to ensure a consistent presentation orientation across participants and conditions. It is particularly important for participants with neglect or visual field cuts. **Example:** This principle was not critical in the present study because the participants did not have neuropsychological conditions sensitive to presentation orientation. However, in the interests of consistency, tests were presented in the same visual orientation.

Principle 6. For timed tasks, carefully time each response with a stopwatch and record the time of the participant's answer. **Example:** Timed tasks were not a central concern in this study, so this procedure was not adopted.

Principle 7. Provide only enough help and encouragement to maintain the participant's behavioral performance in the task under investigation. Balance providing enough help to make sure the task is being completed correctly with so much help that performance may become artificially enhanced. **Example:** The investigator used judgement, context, verbal and non-verbal feedback, and experience with the tests to make considered, real-time decisions about how much assistance to provide any given participant.

Principle 8. Periodically review the test manuals to minimize "examiner drift," the slow and unwitting modification of aspects of test administration and scoring over time.

Example: The published instructions on test administration for the tests used in this study were reviewed regularly to ensure compliance.

Principle 9. Remember that neuropsychological evaluations are an assessment process, guided by clinical questions, not just testing. In conflicts between assessment and test administration requirements, assessment needs should take precedence.

Example: A balance was sought between the consistent application of testing procedures and the flexible modification of those procedures to deal with issues of comprehension, task completion, fatigue, and participant comfort.

9.12. Pregnancy-Related Gustatory Changes

Olfaction, gustation, and trigeminal stimulation are integrated chemosensory systems which all contribute toward food selection and flavor perception (Halpern, 1997). For practical reasons involving expense, participant fatigue, and the complexity of testing procedures this thesis did not focus on pregnancy-related gustatory changes. Future studies ought to examine gustatory changes in the light of Profet's predictions that increased gustatory sensitivity to the tastes of bitter and sour should accompany first trimester. Two early studies noted increased taste thresholds for salt, sour, bitter, and sweet solution among pregnant women (Hansen & Langer, 1935; Schmidt, 1925). These results are obscured by the fact that trimester phase was not reported and because they relied on what would now be considered questionable psychophysical testing methods.

Similar to the literature on pregnancy-related olfactory changes, the literature on pregnancy-related gustatory changes presents a heterogeneous profile based on only few studies (Bowen, 1992; Brown & Toma, 1986; Pike & Yao, 1971). Animal studies show that, given free access, pregnant rats and rabbits will voluntarily consume more salt than

nonpregnant rats and rabbits, and that these increased salt intakes exceed their calculated need for sodium (Pike & Yao, 1971; Richter & Barelare, 1938). In a human study, Brown and Toma (1986) studied taste perception in relation to salt and sucrose in 23 pregnant and 23 nonpregnant healthy American women. All of the women were white, 23-34 years old, and were recruited from the University of Minnesota School of Public Health. Pregnant women were significantly less able to correctly identify differences in the concentration of salt solutions and preferred significantly stronger salt solutions than nonpregnant women, thus, suggesting an increased threshold for salt. The results for the sucrose solutions were not significant. Data on trimester phase were collected—13% first trimester, 22% second trimester, and 65% third trimester—however, the data were collapsed to create the global category "pregnant women," thus precluding the testing of trimester-specific predictions. In contrast to these findings, Dippel and Elias (1980) found that pregnant women at each trimester preferred weaker sucrose solutions than did nonpregnant women (regardless of oral contraceptive use), suggesting increased taste sensitivity to "sweet" that persists across pregnancy.

Taste intensity and preference were investigated in 46 pregnant and 41 healthy American female controls as part of the larger Yale Pregnancy Study (discussed earlier; Duffy, Bartoshuk, Striegel-Moore, & Rodin, 1998). Pregnant women were studied pre-pregnancy and at each trimester; nonpregnant controls were tested in parallel. Participants rated the intensity and preference for NaCl (salty), sucrose (sweet), citric acid (sour), and quinine hydrochloride (bitter). Results indicated that intensity ratings for bitter were greatest during the first trimester compared to pre-pregnancy or second and third trimesters, a finding consistent with Profet's prediction.

Future studies ought to examine gustation in addition to olfaction. Data on thresholds for the tastes bitter, sour, sweet, salty, and umami would be interesting in light of the present results. It would also be interesting to examine if there is a relationship between so-called "supertasters" and symptoms of pregnancy sickness. Approximately 25% of the U.S. population are supertasters: people with an inherited dislike for bitter compounds (Fackelmann, 1997).

9.13. Trigeminal Chemoreception

Olfaction is only one of the chemical senses, which are now conceptualized as multiple independent and interacting chemoreceptive systems comprised of olfaction, gustation, trigeminal chemoreception, vomeronasal chemoreception, and nervus terminalis chemoreception (Keverne, Murphy, Silver, Wysocki, & Meredith, 1986; Tucker, 1971). In addition to its sensitivity to mechanical and thermal stimuli, the trigeminal system also possesses chemoreceptive sensitivity, specifically toward irritating chemical vapors. In the olfactory system, perceived intensity grows slowly as a function of concentration, with typical exponents ranging from 0.2 to 0.7 when intensity and concentration are plotted as a power function on log-log coordinates. Trigeminal stimulation, however, produces steeper slopes—exponents like 1.2 for CO_2 exposure—consistent with the system's primary function as a warning system (Cain & Murphy, 1980; Jones, 1954).

Trigeminal perception involves hedonic evaluations variously described as "irritating," "pungent," "tickling," "warm," "cool," "burning," "stinging," "painful," and "sharp." Trigeminal receptors are the free nerve endings of the posterior nasal, nasopalatine, and anterior ethmoidal branches of the ophthalmic and maxillary divisions

of the trigeminal nerve (Keverne et al., 1986). The three general somatic afferent branches of the trigeminal nerve—the ophthalmic V_1, maxillary V_2, and mandibular V_3 divisions (Doty et al., 1978; Farbman, 1992; Nolte, 1993; Seeley et al., 1992)—follow the ascending somatosensory pathway, probably ipsilaterally, to the thalamus and parietal cortex, though some projections reach the thalamus indirectly via the reticular formation (Nolte, 1993).

The trigeminal stimulation by noxious and potentially harmful chemical stimuli elicit a suite of physiological responses that include apnea, bronchodilation or broncho-constriction, bradycardia, reduction in cardiac output, vasoconstriction (except for the capillary beds in the head), increased epinephrine secretion, variable effects on blood pressure, and withdrawal reflexes (Allen, 1929; Angell-James & Daly, 1975; Keverne et al., 1986).

Many volatile compounds (e.g., propionic acid, heptanol, amyl acetate, butanol, menthol) (Silver and Mounton, 1982) elicit trigeminal activity, and this activity plays an important role in food palatability. Trigeminal activation is responsible for the perception of "spiciness" in hot foods, the "fizz" from alcoholic and carbonated beverages, and the "sting," "burn," or "pungency" from volatilized toxins such as those emitted from cut onions (Cain & Murphy, 1980; Cometto-Muniz & Hernandez, 1990; Doty et al., 1978; Schwimmer, 1968).

This study did not directly assess trigeminal perception, however, future studies ought to examine this sense given its interactions with olfaction and gustation and its importance in mediating food palatability. Many substances, especially "real-world" stimuli stimulate both the olfactory and trigeminal systems, and a mutual sensory

inhibition has been demonstrated during concurrent stimulation: trigeminal stimulation suppresses odor perception and vice-versa (Cain & Murphy, 1980; Doty et al., 1978).

Profet (1992) does not make any explicit predictions about altered trigeminal perception during early pregnancy; however, increased sensitivity to chemical irritants—which typically signal danger—is consistent with an adaptive view of pregnancy sickness. A reasonable prediction based on her arguments would be that early pregnancy should be associated with a lowered threshold (i.e., higher sensitivity) for trigeminal stimulation. The two olfactory tests used in the present study could not test this prediction. Phenyl ethyl alcohol has little trigeminal activity (Silver and Mounton, 1982) and so is thought to assess the functional integrity of the first cranial nerve. A few of the UPSIT odors are aversive, minor trigeminal irritants (e.g., the natural gas, menthol, and smoke stimuli). These trigeminal stimuli were included in the UPSIT because they allow for the detection of some types of malingerers because the majority of anosmics have intact trigeminal chemoreception (Doty et al., 1978). The majority of the 40 UPSIT odors evidenced no or minimal ability to stimulate non-cranial nerve I intranasal or pharyngeal trigeminal activity (Doty, 1995). The prediction of increased first trimester trigeminal sensitivity—within the constraints of ethical experimentation—awaits testing.

9.14. Parallels Between Pregnancy Sickness and Motion Sickness

At a more theoretical level, an ingenious proposal by Treisman (1977) postulated an evolutionary explanation for motion sickness similar in conceptual form to Profet's pregnancy sickness theory. Treisman noted that the pallor, nausea and emetic response that accompanies motion sickness has a high prevalence, is disadvantageous for the individual experiencing it, is transhistorical (early writers of Greek mythology noted it),

and is seen in many species including dogs, horses, monkeys, chimpanzees, cows, seals, some birds, sheep, cats, and fish (Chinn & Smith, 1955; Desnoes, 1926; McEachern, Morton, & Lehman, 1942; Treisman, 1977; Tyler & Bard, 1949). Like pregnancy sickness, a phenomenon that is widespread, transhistorical, and poses survival costs yet still persists presents a problem for evolutionary theory. Also disturbing was the question of why nausea and emesis should be the end-point of motion sickness, as opposed to some more directly adaptive behavioral response that might reduce the disruptive motion.

Until Treisman proposed his Darwinian perspective, researchers had asked only the proximate question, "what causes motion sickness?" or had attempted to ask the ultimate question, "why does motion sickness exist?" but came up frustrated. In his comprehensive review of the subject, Money (1970) sensed the need for a new approach. "The essential nature of motion sickness remains a mystery... it is an anomaly the elucidation of which could cause (or follow) a truly major advance in biological knowledge" (p. 30).

The new approach came when Treisman redefined the question in evolutionary terms and used reverse engineering (see Pinker, 1997) as a conceptual booster rocket: what survival problem does nausea and emesis solve? Treisman's proposal prefigured Profet's own adaptive view of pregnancy sickness by a decade: motion sickness is the accidental by-product of a neural system originally designed to detect and expel ingested neurotoxins. Treisman theorized that the neural mechanism to detect neurotoxins would have to be exquisitely sensitive in order to detect the minute but potentially dangerous levels of neurotoxins that might be digested along with common foodstuffs. In his newly focussed search for a proximate mechanism he relied once again on evolutionary insight:

evolution rarely designs a solution to a specific problem *de novo*; rather, it exploits existing structures and processes within existing genetic, developmental, and ecological constraints (Buss et al., 1998; Dawkins, 1982; Dennett, 1995; Williams, 1992). In this case, evolution's exploitation strategy took the highly sensitive neural system that coordinated information concerning awareness of the body's spatial location as defined by visual, vestibular, and proprioceptive inputs, and connected that system to the neural systems controlling the nausea/emetic response.

The sensitivity of this spatial location system arises from the fact that most animals must organize their movements in relation to a spatial framework. To do this they rely on information from three spatial reference systems: proprioceptive information from the trunk and limbs, vestibular information from the semicircular canals and otolith organs, and visual information from the eyes. Normally these three systems work in close coordination with each other to provide the organism with accurate information about balance, orientation, and the body's location in space. To take an example, catching a ball involves visually guided eye movements synchronized with vestibularly controlled head movements and coordinated with proprioceptively controlled adjustments in body movement and posture. In the case of air sickness, the visual system indicates a smooth trajectory of the body through space while the vestibular system indicates small but constant shifts (i.e., rolling, pitching, and yawing) in body position that are inconsistent with the visual information. Thus, motion *per se* does not cause motion sickness; desynchronous coordination between the three spatial information systems does.

Because the spatial location coordination system is highly sensitive to conflictual neural information and is in almost constant use, it provides an ideal warning system for

the detection of early disruptive effects of neurotoxins. Neurotoxin-induced disruptions in the coordination of these information streams would then trigger the nausea/emetic response in an effort to rid the body of the ingested toxins. Motion information mismatches produced by cars, ships, air and space travel, and even films (all recent phenomena by evolutionary time scales) represent inappropriate stimuli evoking an otherwise adaptive response designed for a specific biological function.

Treisman's theory of motion sickness and Profet's theory of pregnancy sickness both posit that the "sickness" response is an adaptive outcome of a mechanism designed to protect the individual from ingesting or ingested toxins. This parallel suggests an obvious and simultaneous test of both theories: is motion sickness susceptibility positively correlated with pregnancy sickness susceptibility? One can also ask whether treatments developed for motion sickness might have cross-efficacy for pregnancy sickness. Both of these questions are intriguing and highlight how the evolutionary approach can complement more traditional etiological approaches to the study of sickness and health.

9.15. Future Research Directions

The above discussions, particularly those related to limitations and criticisms suggest future research directions. Future studies will benefit from longitudinal studies using

(a) A pre-pregnant group with no prior history of pregnancy and intending to become pregnant within a specified time frame (i.e. wanted pregnancies).

(b) At least three pregnant groups corresponding to each trimester. More refined temporal resolutions can be achieved by subdividing the first trimester group.

(c) A postpartum group tested shortly after delivery and a post-partum group tested long after delivery (e.g., one year later).

(d) A nonpregnant control group subdivided into distinct menstrual cycle phases or randomized across phases.

The present study did not screen women for symptoms of pregnancy sickness. Lack of such screening may have biased the study towards "healthy participants:" women with low levels of pregnancy sickness may have been more motivated to participate. A future study might examine the relationship between olfactory perception and food aversions and cravings in pregnant women who all possess a certain criterion threshold of nausea and/or vomiting. Investigation of this more homogenous group symptomatic group may help increase the power of detecting actual effects.

Parallel studies need to be done on the molecular and physiological mechanisms that occur in the olfactory system to produce increased olfactory sensitivity. Various hormones have been implicated in the etiology of pregnancy-related nausea and vomiting (Masson, Anthony, & Chau, 1985; Soules et al., 1980)—similar studies examining the hormonal profile underlying pregnancy-related olfactory changes will be informative.

An olfactory identification test that does not possess a ceiling effect for normosmics or hyperosmics will be useful. Since the UPSIT is currently the world's best olfactory identification test, finding a test that is more challenging than the UPSIT and possesses good psychometrics may prove challenging. A test of trigeminal sensitivity is warranted given that this chemoreceptive system is specifically designed to detect irritating chemical vapors. Gustatory tests of gustatory sensitivity, in particular to bitter will be informative.

In light of the perceptual complexity of real-world stimuli, the present findings should be seen as a first step in the elucidation of the olfactory profile of pregnant

women. Future studies should investigate real-world food odors—and interactions with the gustatory and trigeminal systems—and should include broader assessments of olfactory function including hedonic perception (e.g., intensity, pleasantness, pungency).

Animal studies need to be done to see whether pregnancy sickness is a phylogenetically conserved phenomenon, or restricted to humans and perhaps a few other animals. One would predict that pregnancy sickness should be most prevalent in experimental omnivores like humans, and less common or absent in carnivores or animals that rely on a narrow dietary diversity. Anecdotal evidence from primate researchers, indicates that pregnancy sickness had not been seen among chimpanzees (S. Wasser, personal communication, July, 1994), although food rejection during early pregnancy has been observed in rhesus monkeys (Czaja, 1975). Primate observations require cautious interpretation. First, fruits comprise a large percentage of a primate's diet, and since fruits are typically not found to be aversive to pregnant women, one may expect the same to be true for pregnant non-human primates. Also, if a researcher is not looking for symptoms of pregnancy sickness, then subtle changes—like shifts in food selection—may go unnoticed. Further, while vomiting can be objectively measured, the largely subjective experience of nausea is far more difficult to validly assess in animals. To date, no studies have been conducted on olfactory performance during pregnancy in animals, so the prediction of increased olfactory sensitivity in early pregnancy awaits confirmation. Measuring olfactory function in animals poses unique challenges, however, creative solutions have been offered to overcome these difficulties and could shed light on this question (e.g., Alberts & May, 1980; Brown et al., 1987; Davis, 1973; Hastings,

1990; Pierson, 1974; Schellinck, Brown, & Slotnick, 1991; Slotnick & Schoonover, 1984).

In addition to olfactory and other sensory influences on pregnancy-related eating behavior, future studies will need to map how cognitive, behavioral, social, and physiological factors influence pregnancy-related eating behavior. Eating behavior itself is a global term subsuming such things as dietary selection, food habits, consumption frequency, cravings, dieting, etc. Some of the pregnancy-related changes in eating behavior may be due to physiological changes such as the increased metabolic demands of third trimester, while others may be more psychological such as the renewed interest in proper eating—both what to eat and what to avoid—motivated by concerns for a healthy pregnancy. There is also a food "folklore" surrounding eating in general, and during pregnancy in particular, which a woman may encounter from family members, friends, and media sources (Gulick, Franklin, & Elinson, 1986; Snow & Johnson, 1978). Cognitive and behavioral factors such as anxiety, depression, locus of control, restricted food intake, selective information processing of food words, and preoccupation with foods influence eating behavior in nonpregnant women and may also influence eating behavior in pregnant women (Fairburn, Cooper, Cooper, McKenna, & Anastasiades, 1991; Francis, Stewart, & Hounsell, 1997; Frost, Goolkasian, Ely, & Blanchard, 1982; Hill, Weaver, & Blundell, 1991; Stewart & Samoluk, 1997; Worsley, 1980).

Among nonpregnant women Herman and Polivy (1975) have theorized that emotionality or highly palatable foods can disinhibit the controlled eating behavior of restrained eaters. They showed that unrestrained eaters consumed more ice cream than

restrained eaters during times of low stress but that restrained eaters consumed more ice cream than unrestrained eaters during times of high stress.

At a more extreme level, some pregnant women may experience eating disorders (e.g., anorexia nervosa, bulimia nervosa) during pregnancy, although the prevalence and symptoms of such pregnancy-related eating disorders has not been systematically explored. One of the few studies to do so compared eating disorder symptomatology in pre-pregnant (retrospectively) and pregnant women (prospectively) (Turton, Hughes, Bolton, & Sedgwick, 1999) using the 26-item Eating Attitudes Test (EAT) (Garner & Garfinkel, 1979). A sample of 421 British women (mean age = 29.9 years) attending antenatal follow-up clinics at hospitals in an inner London borough participated in the study. Results of the EAT showed that 4.9% of pregnant women scored above the test's recommended threshold. It was predicted that between 2.4-3.3% of women may have suffered from some form of clinical eating disorder in the two years preceding pregnancy. Because one third of these women also reported eating disorder symptoms during pregnancy it was estimated that as many as 1% of pregnant women may suffer from some form of eating disorder during pregnancy. Eating disorder symptomatology was also found to be associated with younger age, previous symptomatology, lower educational attainment, poorer housing, employment status, and previous miscarriage.

A more recent study—the first of its kind—used prospectively collected data to examine the outcome and impact of pregnancy on the eating disorder symptomatology of a cohort of pregnant women (Blais et al., 2000). Fifty-four American women identified from a sample of 246 women participating in a longitudinal study on anorexia nervosa and bulimia nervosa participated in the study. Out of the 82 self-reported pregnancies

56% resulted in live birth, 30% in therapeutic abortion, and 13% in spontaneous abortion. The live birth rate was lower than the expected 66% in the general population and the therapeutic abortion rate was 11% higher than the expected 19% general population rate (comparative data generated from the U.S. Department of Health and Human Services, 1995). Women with anorexia nervosa and bulimia nervosa also showed a significant decrease in the severity of their eating disorder symptoms during pregnancy. This decrease returned to pre-pregnancy levels for the anorexics by six months postpartum and remained decreased for the bulimics even at nine months postpartum. This thesis did not attempt to investigate the psychological and social factors influencing eating behavior in the pregnant women, however, it acknowledges the importance of studying these variables as part of a more comprehensive understanding of the etiology of food aversions and cravings.

Nausea and vomiting are not unique to pregnancy but also occur in other conditions such as motion sickness (on land, sea, air, and space), as a side-effect of many drugs (e.g., chemotherapy), poisoning, pain, myocardial infarctions, and post-surgical recovery (Rhodes, 1990). Research into pregnancy-related nausea and vomiting will benefit from integrating the findings from research into the causes and treatments of other forms of nausea and vomiting. An example of the potential fruitfulness of this approach is the "autogenic-feedback training exercise" (AFTE), a combined application of biofeedback and autogenic therapy (a learned self-regulation technique), developed by the Ames Research Center of the National Aeronautics and Space Administration to prevent motion sickness in astronauts. In the course of 24 years of research at Ames, more than 350 individuals have been trained in autogenic feedback, with significant improvement in

motion sickness tolerance observed in 85 percent of participants (Ames Research Center, 1997). To date there have been no studies investigating the effectiveness of AFTE on symptomatic relief from pregnancy sickness.

Finally, any follow-up theory should be conducted using a theoretical framework. Predictions can only be derived and tested from a theoretical foundation; in this way, the state of the field can be advanced. These studies will begin the process of moving the field in a data *and* theory rich direction.

9.16. Summary & Conclusions

The findings reported in this study should be accepted with the same tentativeness and skepticism that is the hallmark of all good science. The history of the biobehavioral and psychological sciences reveals that single experiments rarely yield firm and abiding conclusions. More often it is the convergent evidence supplied by multiple, theory-driven studies using similar (literal replication) and different (constructive replication) methodologies, that allow for the crystallization of reasonably clear conclusions.

It is relevant to note, quite apart from the eventual correctness or incorrectness of Profet's theory, that no other theory currently exists that explains the temporal correlations and several other empirical findings about pregnancy sickness with the same level of coherence, parsimony, and predictive power.

What we "know" now—in the provisionally scientific sense of the term—that we didn't know before is that olfactory identification ability, when tested with the UPSIT, is no different in pregnant women across trimesters and postpartum than in nonpregnant women. We also "know" that olfactory sensitivity as measured by the PEA test increases among first trimester women relative to the other trimesters, postpartum, and

nonpregnant women. Also, olfactory sensitivity remains higher across pregnancy but shows no difference by the postpartum period. The study's other findings, that first trimester women experience increased aversions to meats and seafoods, increased cravings to fruits, and increased distress from nausea and vomiting are consonant with previous findings. The findings that aversions to vegetables and cravings to sweets were not higher among pregnant women do not align with previous studies.

A basic distinction in Darwinian medicine is that a difference exists between a defense and a disease. Profet's (1988; 1992) theory of pregnancy sickness, like Treisman's (1977) theory of motion sickness, both cast their respective problems in the light of defensive strategies which, nevertheless, pose stresses on the individual affected. Because a defensive strategy is not a disease, does not mean that treatments should not be brought to bear on lessening the physical and psychological discomforts associated with that defense. However, this crucial distinction does have implications about the form such treatments might take, the circumstances in which they should be taken, and the reasons justifying their administration.

The reinterpretation of pregnancy sickness as a physiological/psychological adaptation rather than a pathology or incidental hormonal by-product suggests that efforts be put into symptomatic relief rather than "turning-off" or "curing" what could prove to be a potentially beneficial mechanism. This view is supported by research linking pregnancy sickness with positive birth outcomes (Weigel & Weigel, 1989a,b). Presently, few evidenced-based strategies exist for the effective management of pregnancy sickness. Health professionals and pregnant women are reluctant to use antiemetic drugs during the first trimester because of the possibility, real or perceived, of teratogenic effects. The

scepter of the Thalidomide-induced birth defects of the 1950s casts a long shadow still. Nonpharmacological therapies include hypnotherapy, vitamin therapy, herbal therapy, PC-6 point acupressure, and self-care measures such as resting, eating small meals, avoiding bright lights and noises, and avoiding foods and food odors known to trigger nausea and vomiting (DiIorio, 1985; Jenkins & Shelton, 1989; O'Brien & Naber, 1992; O'Brien & Reylea, 1999; Stainton & Neff, 1994).

The present study was not an intervention study; it was conducted in the spirit of basic research with the hope that its findings would lead to a clearer understanding of the nature of pregnancy-related olfactory changes. To the extent that that goal has been accomplished, this study may stimulate future researchers to consider changes in olfactory perception as part of the symptomatology of pregnancy sickness, and, simultaneously, as a potential window into new treatments, perhaps olfactory-based, for the relief of pregnancy sickness.

Appendix A

Raw Data of the Phenyl Ethyl Alcohol (PEA) Odor Thresholds (-log concentration (vol/vol))

Participant	Status[a]	PEA threshold -log concentration (vol/vol)			
		Visit 1	Visit 2	Visit 3	Visit 4
1	n	4.37	4.83	5.87	4.62
2	n	6.10	5.50	6.68	6.40
3	n	8.08	7.60	6.40	6.50
4	n	10.71	6.36	5.00	6.68
5	n	9.87	8.50	4.87	6.25
6	n	8.25	4.62	8.00	8.00
7	n	5.57	6.68	6.59	5.00
8	n	8.37	5.75	8.12	7.50
9	n	4.37	5.00	4.88	5.12
10	n	7.81	7.37	6.79	7.50
11	n	7.24	8.62	7.37	7.00
12	n	6.99	6.73	6.98	8.37
13	n	6.75	5.62	7.50	7.50
14	n	7.62	6.75	6.62	6.62
15	n	5.37	6.54	5.12	5.12
16	n	7.49	8.24	7.25	7.50
17	n	7.00	8.12	6.75	8.37
18	n	8.50	7.32	7.60	8.54

table continues

Appendix A (continued)

Raw Data of the Phenyl Ethyl Alcohol (PEA) Odor Thresholds (-log concentration (vol/vol))

Participant	Status[a]	PEA threshold -log concentration (vol/vol) Visit 1	Visit 2	Visit 3	Visit 4
19	p	8.12	5.24	6.72	8.00
20	p	8.00	9.60	10.37	10.70
21	p	12.23	9.50	10.70	9.91
22	p	11.24	9.72	11.87	10.00
23	p	9.87	6.50	8.50	8.50
24	p	11.23	9.91	8.00	8.73
25	p	10.00	8.50	8.73	10.65
26	p	9.50	8.57	6.50	8.45
27	p	10.62	9.62	8.37	9.50
28	p	11.00	7.86	8.54	7.49
29	p	12.34	11.00	10.65	9.72
30	p	9.75	8.25	8.45	8.50
31	p	6.75	8.37	7.49	6.00
32	p	10.75	8.87	8.00	8.00
33	p	11.25	8.80	9.30	9.30
34	p	10.87	7.45	9.23	9.23
35	p	6.25	6.65	7.43	7.43
36	p	8.50	9.00	9.00	--
37	p	10.12	7.89	8.65	6.68

Note. Higher scores indicate lower thresholds and greater olfactory sensitivity.

[a]Pregnancy status: n = nonpregnant, p = pregnant.

In the pregnant group, Visit 4 is the postpartum phase.

Appendix B

Raw Data of Total University of Pennsylvania Smell Identification Test Scores

Participant	Status[a]	Total UPSIT Score (Max = 40)			
		Visit 1	Visit 2	Visit 3	Visit 4
1	n	38	34	35	36
2	n	37	36	35	36
3	n	38	39	38	38
4	n	39	38	39	37
5	n	39	37	35	37
6	n	37	35	37	35
7	n	39	37	38	37
8	n	37	40	37	38
9	n	39	40	39	38
10	n	35	37	38	37
11	n	40	40	40	40
12	n	37	37	38	38
13	n	35	36	35	36
14	n	36	34	31	35
15	n	34	34	33	34
16	n	39	38	38	39
17	n	37	36	39	37
18	n	37	36	37	38

table continues

Appendix B (continued)

Raw Data of Total University of Pennsylvania Smell Identification Test Scores

Participant	Status[a]	Total UPSIT Score (Max = 40)			
		Visit 1	Visit 2	Visit 3	Visit 4
19	p	35	34	34	35
20	p	38	34	39	38
21	p	35	36	37	37
22	p	39	40	38	39
23	p	36	38	37	39
24	p	39	35	36	36
25	p	37	35	33	36
26	p	35	35	37	36
27	p	39	36	36	37
28	p	37	38	35	37
29	p	38	37	36	37
30	p	37	36	37	36
31	p	38	38	38	37
32	p	40	39	39	40
33	p	36	37	38	38
34	p	38	33	37	35
35	p	33	34	35	35
36	p	38	39	38	--
37	p	39	40	40	39

Note. Higher scores indicate more accurate odor identification performance.

[a]Pregnancy status: n = nonpregnant, p = pregnant.

In the pregnant group, Visit 4 is the postpartum phase.

Appendix C

Raw Data of the Number of Food Aversions Recalled Over a Two Week Period

Participant	Status[a]	Number of Food Aversions Recalled			
		Visit 1	Visit 2	Visit 3	Visit 4
1	n	0	2	0	1
2	n	8	3	3	10
3	n	7	9	7	11
4	n	5	4	9	7
5	n	11	5	3	5
6	n	2	1	1	0
7	n	21	23	17	25
8	n	17	12	10	15
9	n	2	0	0	2
10	n	4	8	6	7
11	n	4	5	5	8
12	n	6	8	5	4
13	n	3	3	2	5
14	n	12	11	14	17
15	n	8	1	5	6
16	n	3	4	3	6
17	n	23	9	7	13
18	n	9	5	6	4

table continues

Appendix C (continued)

Raw Data of the Number of Food Aversions Recalled Over a Two Week Period

Participant	Status[a]	Number of Food Aversions Recalled			
		Visit 1	Visit 2	Visit 3	Visit 4
19	p	6	3	5	6
20	p	19	3	1	4
21	p	14	5	7	8
22	p	35	2	1	3
23	p	10	7	8	5
24	p	15	11	14	11
25	p	41	44	5	7
26	p	3	3	2	4
27	p	26	9	4	5
28	p	5	6	13	10
29	p	3	0	3	2
30	p	9	8	8	7
31	p	1	0	0	2
32	p	8	14	6	8
33	p	12	9	3	4
34	p	15	8	11	12
35	p	11	13	9	8
36	p	21	12	10	--
37	p	18	29	18	16

Note. The number of food aversions reported were based on verbal prompting from a list of 142 common food items.

[a]Pregnancy status: n = nonpregnant, p = pregnant.

In the pregnant group, Visit 4 is the postpartum phase.

Appendix D

Raw Data of the Number of Food Cravings Experienced Over a Two Week Period

Participant	Status[a]	Number of Food Cravings Recalled			
		Visit 1	Visit 2	Visit 3	Visit 4
1	n	4	6	4	5
2	n	10	8	6	7
3	n	12	14	11	13
4	n	23	18	25	21
5	n	15	11	3	14
6	n	10	4	6	7
7	n	4	8	9	6
8	n	21	23	17	18
9	n	18	12	14	21
10	n	5	2	4	4
11	n	21	20	26	22
12	n	31	24	24	30
13	n	34	26	22	20
14	n	19	5	20	10
15	n	30	24	28	23
16	n	17	11	8	14
17	n	28	30	27	25
18	n	15	18	19	16

table continues

Appendix D (continued)

Raw Data of the Number of Food Cravings Experienced Over a Two Week Period

Participant	Status[a]	Number of Food Cravings Recalled			
		Visit 1	Visit 2	Visit 3	Visit 4
19	p	11	17	15	14
20	p	6	10	0	4
21	p	12	11	8	10
22	p	28	28	22	30
23	p	21	14	22	23
24	p	3	2	5	6
25	p	11	1	8	10
26	p	9	5	4	13
27	p	23	33	23	18
28	p	23	20	17	18
29	p	5	21	13	20
30	p	28	26	21	22
31	p	10	13	2	11
32	p	4	7	6	8
33	p	14	20	10	11
34	p	24	13	14	20
35	p	9	14	19	21
36	p	16	9	7	--
37	p	27	28	35	32

Note. The number of food cravings reported were based on verbal prompting from a list of 142 common food items.

[a]Pregancy status: n = nonpregnant, p = pregnant.

In the pregnant group, Visit 4 is the postpartum phase.

Appendix E

Raw Data of the Total Distress Experienced from Nausea, Vomiting, and Retching During a 12-Hour Period (Average of Six Consecutive 12-Hour Periods) using the Rhodes INV Form 2

		Total Distress from Nausea, Vomiting, & Retching			
Participant	Status[a]	Visit 1	Visit 2	Visit 3	Visit 4
1	n	0.00	0.33	1.00	1.00
2	n	2.33	1.00	1.67	0.50
3	n	0.00	1.67	0.50	1.67
4	n	0.67	1.17	0.83	0.83
5	n	0.00	1.33	0.00	0.00
6	n	1.00	0.50	3.33	1.00
7	n	2.50	1.83	2.17	1.33
8	n	0.67	0.00	0.00	0.00
9	n	1.00	1.67	2.17	1.00
10	n	0.00	0.17	0.83	0.83
11	n	3.00	1.00	2.33	1.00
12	n	0.00	0.00	0.00	0.00
13	n	0.00	0.67	0.33	0.50
14	n	1.67	1.83	1.33	1.67
15	n	2.67	1.83	2.00	1.83
16	n	0.00	0.67	0.00	0.00
17	n	1.00	2.00	1.00	1.33
18	n	0.00	0.00	0.00	0.00

table continues

Appendix E (continued)

Raw Data of the Total Distress Experienced from Nausea, Vomiting, and Retching During a 12-Hour Period (Average of Six Consecutive 12-Hour Periods) using the Rhodes INV Form 2

		Total Distress from Nausea, Vomiting, & Retching			
Participant	Status[a]	Visit 1	Visit 2	Visit 3	Visit 4
19	p	2.00	1.17	0.67	2.00
20	p	2.00	0.00	3.00	1.17
21	p	3.00	2.17	0.00	2.00
22	p	11.67	6.67	3.33	1.00
23	p	8.00	5.83	5.00	0.50
24	p	1.67	0.00	0.50	0.50
25	p	10.33	2.83	0.00	0.00
26	p	13.00	7.83	2.83	1.17
27	p	0.00	0.00	0.00	0.00
28	p	0.00	0.00	0.00	0.00
29	p	10.66	3.83	0.33	0.50
30	p	7.00	1.50	0.17	1.67
31	p	0.00	0.00	0.00	0.00
32	p	6.00	2.50	0.50	0.50
33	p	3.33	4.00	3.50	1.17
34	p	7.83	0.00	0.00	0.00
35	p	2.83	1.00	1.33	1.00
36	p	10.50	3.17	0.83	--
37	p	2.50	4.17	2.17	0.00

Note. Higher scores indicate greater distress. Maximum score = 32.

[a]Pregnancy status: n = nonpregnant, p = pregnant.

In the pregnant group, Visit 4 is the postpartum phase.

Appendix F

CLINICAL INFORMATION FORM

SMELL PERCEPTION AND PREGNANCY SICKNESS

Contact:

Farhad Dastur, MSc.

Tel: **492-8675** or **494-2036**

Dept. of Psychology, Dalhousie University, Halifax, NS B3H 4J1

E-mail: synapse@is2.dal.ca

Place & Time:

The IWK-Grace Health Centre for Children, Women and Families

5980 University Ave., Halifax, NS

Any day of the week, starting from mid-morning to late afternoon

INTRODUCTION

You are being invited to take part in a **voluntary** research study. The purpose of this research is to measure changes in your sense of smell, your diet, and your experiences of nausea and vomiting. Many pregnant women report experiencing changes in their sense of smell, especially during the first three months (1st trimester). The nature of these changes and the reason why they occur are still largely unknown. Many pregnant women (probably over 80%) also report experiencing some form of "morning sickness" ("pregnancy sickness" is a better term since it can occur any time of the day). Pregnancy sickness involves one or all of the following: nausea, vomiting, retching, and aversions

Appendix F (continued)

to certain smells, tastes, and foods. The reasons why women develop pregnancy sickness are unclear and the best way of managing the considerable discomfort it can cause has not yet been found. Understanding the relationships between smell, diet and pregnancy sickness may eventually lead to effective ways of reducing the discomfort of pregnancy sickness.

IMPORTANCE

Your participation in this study is important because it will promote maternal health in three ways. First, we will gain a better understanding of what happens to the sense of smell during pregnancy. So far, only a handful of studies have looked at this question and most have not given clear answers. Second, this research will help us understand why many women develop pregnancy sickness early in their pregnancy. This question also has not been adequately answered. Third, a future application of this research may involve the development of a "pregnancy sickness management plan." This plan will give pregnant women information about those odours and activities that should be avoided in order to minimize triggering pregnancy sickness. Such guidelines will be useful because they will give women a potentially effective way of reducing pregnancy sickness before resorting to drugs.

WHO CAN TAKE PART?

All healthy women older than 20 and who have not yet reached menopause. All women may participate in this study except those whose state of health might affect the results, e.g., women who smoke, women with diabetes, women taking hormone supplements, etc.

Appendix F (continued)

PREGNANT WOMEN:

You will be tested once during each trimester and once postpartum. Whenever possible, your visits can be timed to match those times that you come to the IWK-Grace for such things as ultrasound or blood tests.

NONPREGNANT WOMEN:

You will be tested four times over a 9 month period. Testing will be timed with your period: 2 to 7 days after the beginning of menstrual flow. You should not be taking any hormone-based contraceptives (e.g., birth control pills) during this study.

HOW MUCH TIME WILL THIS STUDY TAKE?

Each test session will take about 2 hours. If it is more convenient for you we can divide a single test session into two shorter sessions done over two days. The pace of each session goes as fast or as slow as you are comfortable with. The total duration of the study is approximately 9 months.

WHAT DO I HAVE TO DO?

On your test day you will come to the IWK-Grace Hospital where a researcher will do the following:

(1) Ask you some questions about your background and health (first visit only).

(2) Measure your smell sensitivity.

(3) Ask you some questions about any food aversions and cravings recently experienced.

(4) Measure your ability to identify certain common smells.

(5) Give you a 3-day take-home questionnaire on nausea and vomiting.

Appendix F (continued)

ETHICS & CONFIDENTIALITY

Participation in this study is entirely voluntary and all results will be kept strictly confidential. You do not have to take part, and you are free to leave the study at any time and for any reason. You are also free to ask any questions at any time. The quality of medical care that you receive at the IWK-Grace Health Centre will not be affected by your decision to participate, or by your decision to leave if you so choose. Information that would reveal your personal identity will not be printed or released. This study has received ethical approval from both the IWK-Grace Health Centre and from Dalhousie University.

DESCRIPTIONS OF THE TESTS & QUESTIONNAIRES

ELIGIBILITY QUESTIONNAIRE

This questionnaire is given to find out if you are eligible to take part in this study. It asks specific questions about your health such as whether you smoke, if you have any nutritional problems, etc.

Duration: 5 minutes.

DEMOGRAPHIC QUESTIONNAIRE

This questionnaire asks background questions such as your age and occupation. The purpose of these questions is to see how representative this study is of the larger community of pregnant and nonpregnant women.

Duration: 2 to 3 minutes.

Appendix F (continued)

SMELL SENSITIVITY TEST

In the smell sensitivity test you will be given two bottles, one containing artificial rose scent (dissolved in a carrier), and one without the scent (carrier only). You will be asked to choose the bottle containing the stronger scent. If you choose the correct bottle, the concentration will be lowered until you can only detect the scent 50% of the time.

Duration: 15-20 minutes.

SMELL IDENTIFICATION AND PERCEPTION TEST

In the smell identification test, you will smell 40 "scratch and sniff" strips, each with a different scent. The scents mimic ones you encounter in daily life, like mint, banana, and lemon. After scratching the strip, you hold the strip near your nose, smell it, and then choose the smell's name from a list of four answers.

Duration: 30 to 35 minutes.

FOOD AVERSIONS AND CRAVINGS

In this questionnaire you will encounter 142 common food items divided into several categories. You will be asked to state whether you have experienced an aversion or craving to each food item anytime during the past two weeks.

Duration: 20 to 25 minutes

3-DAY NAUSEA & VOMITING DIARY

This questionnaire will ask you to rate your experiences of nausea and vomiting. A number of choices are given to you and you select the one that applies to you. You will complete this simple questionnaire at home every 12 hours for three days.

Duration: 5 to 6 minutes per day.

Appendix F (continued)

WHAT ABOUT RISKS?

None of the tests used here involve any known harm or risk to you or your baby. Some of the smells you sample may be unpleasant, and it is possible that they may make you feel a little nauseous. If this happens, we can stop, go outside for fresh air, and continue if and when you desire. In a pilot study of 10 women, none of the women experienced any problems. All of the scents that you will smell are used in very low concentrations, and all of them have been used in previously published studies and were found to be safe.

WHAT ABOUT BENEFITS?

There are no immediate and direct health benefits to you from participating in this study. This study is the first of its kind to examine the relationship between changes in smell perception, changes in diet, and pregnancy sickness. Your participation will improve our knowledge of the relationship between these three important aspects of pregnancy. At the end of the study you can obtain information about your own sense of smell.

WHAT WILL HAPPEN TO THIS INFORMATION?

This study will be submitted for publication in a scientific journal. You may request a copy of any publication or report that results from this study.

For further information feel free to call

Mr. Farhad Dastur at 492-8675 or 494-2036.

Appendix G

INFORMED CONSENT FORM

Project Title: **Changes in Smell Perception & Symptoms of Pregnancy Sickness**

Researchers: **Farhad N. Dastur, MSc, Donald C. Brown, MD, Kathy Harrigan, BSc, Heather Wile, MA, & Richard E. Brown, PhD**

The research procedures to be used in this study, of which I have a copy (**the Clinical Information Form**), have been described and explained to me. Any questions that I have asked have been answered to my satisfaction, and I know that I may ask further questions about this study at any time. I understand that there are no direct benefits to me by participating in this study, nor are there any known risks beyond those explained to me. I have been assured that all records relating to me will be kept strictly confidential and that no information that would reveal my personal identity will be released or printed. I understand that I may ask for a copy of any publication or report derived from this study.

I understand that this study is voluntary, and that I may withdraw from the study at any time and for any reason. I also understand that if I do not participate in this study, or if I withdraw at any time, that the quality of medical care that I receive at the IWK-Grace Health Centre will not be affected.

NAME: I, _____,
hereby consent to participate in this study. (PRINT NAME)

ADDRESS: _____

_____

TELEPHONE: _____(home) _____(work)

DATE (D / M / Y): _____

SIGNATURE: _____

Who to contact about this study: **Mr. Farhad Dastur**

Who may be reached at: **492-8675 or 494-2036**

Appendix H

DEMOGRAPHIC INFORMATION FORM

I would like to ask you some background questions. This information is voluntary so you don't have to answer any question you do not wish to. This information will be kept confidential.

NAME: _____

ADDRESS: _____

TELEPHONE # Home: _____ **Work:** _____

DATE OF BIRTH (Y/M/D): _____

CURRENT EMPLOYMENT STATUS:

A. Working full-time (at home)
B. Working full-time (outside home)
C. Working part-time (at home)
D. Working part-time (outside home)
E. Seeking Employment
F. Student
G. Other: _____

LEVEL (NUMBER OF YEARS)OF FORMAL EDUCATION:

A. Elementary: 1-8
B. High school graduate: 9-12
C. College/University Degree: 13-16 (Diploma/BA/B.Sc.)
D. Advanced Degree (MA, MD, Ph.D.): 17-22
E. Other: _____

ARE YOU ON ANY KIND OF DIET? **Yes:** ____ **No:** ____ **WHAT KIND?** _____

ETHNIC BACKGROUND

A. Indigenous B. North American C. European D. Asian E. South Asian F. Latin American G. Middle Eastern H. African I. Polynesian J. Caribbean K. Mediterranean L. Other____

DO YOU SMOKE? **Yes** _____ **No** _____ **HOW MUCH?** _____

WEIGHT (kg): _____ **HEIGHT (cm):** _____

BODY MASS INDEX: _____**(weight(kg)/height(m^2)**

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