
UNIVERSITY OF NORTH TEXAS
HEALTH SCIENCE CENTER AT FORT WORTH
1970

Herron, Kathryn M., Stress and Social Support as Risk Factors for the Occurrence of Neural Tube Defect-Affected Pregnancies in Women Living Along the Texas-Mexico Border. Master of Public Health, June, 1999, 59 pp., 8 tables, 1 figure, references, 78 titles.

Data were derived from the case-control study of the Texas Department of Health's Neural Tube Defect Project, involving women living along the Texas-Mexico border, June 1995 to October 1998. Social support and stress information was obtained from a questionnaire, and a residual stress scale was created to determine an aggregate measure for each subject. Interviews were conducted with 261 women, with 1.2 controls to each case. Having high residual stress was found to be a significant risk factor for NTDs. Other significant risk factors included periconceptional injury, residential mobility, having no relatives to talk to about private matters, and discontent with relationships.

STRESS AND SOCIAL SUPPORT AS RISK FACTORS FOR THE OCCURRENCE OF NEURAL TUBE DEFECT-AFFECTED PREGNANCIES IN WOMEN LIVING ALONG THE TEXAS-MEXICO BORDER

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THESIS

Presented to the Graduate Council of the

Graduate School of Biomedical Sciences

University of North Texas Health Science Center at Fort Worth

In Partial Fulfillment of the Requirements

For the Degree of

MASTER OF PUBLIC HEALTH

By

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Fort Worth, Texas

June 1999

ACKNOWLEDGEMENTS

I am grateful to a number of persons for their invaluable assistance in this rewarding project. The finished product was made possible with expertise and leadership from Kate Hendricks, M.D. I would like to express my heartfelt thanks to Antonio Rene, Ph.D., John Licciardone, D.O., and Gilbert Ramirez, Dr.P.H., for their patience, guidance, and support throughout this endeavor. I thank Lucina Suarez, Ph.D., Jean Brender, Ph.D., and the Texas Department of Health for providing the data and important suggestions along the way. Finally, none of this would have been possible without the motivation and support of my best friend, Roberto Cardarelli, who inspires me to excel in all that I do.

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CHAPTER I

INTRODUCTION

Background

Birth defects are the leading cause of infant mortality in the United States (Centers for Disease Control and Prevention, 1989). Neural tube defects (NTDs), which comprise a group of birth defects affecting the brain and spinal cord, are the most common type of congenital malformation (Wybrandt & Ludman, 1991), and result from failure of the neural tube to close completely (Elwood, Little, & Elwood, 1992). When the neural tube fails to close properly, an event usually taking place in the fourth week of pregnancy, tissue associated with the brain or spinal cord remains exposed or unprotected, resulting in potentially severe developmental disabilities or death (Wybrandt & Ludman, 1991). The form and severity of an NTD depends on its location and extent and include: spina bifida, failure of the spinal cord to close; anencephaly, failure of the cranium and brain to form completely; and encephalocele, protrusion of the brain through the skull, usually in the back of the head (Wybrandt & Ludman, 1991). NTDs occur in whites more often than in other ethnic groups, in first born more often than other children, and in females more often than males (Wybrandt & Ludman, 1991). A woman who has had an NTD-affected pregnancy has a risk of recurrence estimated to be between 1% and 5%, a risk that increases to 4% to 9% with two NTD-affected pregnancies (Wybrandt & Ludman, 1991). Poverty is an established risk factor for NTDs (Elwood, Little, & Elwood, 1992).

Also, several studies have demonstrated an association with a number of environmental and demographic variables, including calendar year, season, geographic location, ethnicity, and maternal age (Elwood, Little, & Elwood, 1992; Carter, 1969). Maternal periconceptional supplementation with folic acid has repeatedly been shown to significantly reduce the risk of NTDs (Medical Research Council Vitamin Study Research Group, 1991; Czeizel & Dudas, 1992; Daly, Kirke, Molloy, et al, 1992).

In 1992, the Texas Department of Health (TDH) documented a high incidence of NTDs (more than 2.5 times the national rate) among women who conceived during 1990 or 1991 in Cameron County, the southernmost county in Texas (Texas Department of Health, 1992). Later that year, TDH was awarded a cooperative agreement by the Centers for Disease Control and Prevention (CDC) for expanded NTD surveillance, a folic acid intervention, and a case-control study to identify risk factors for NTD occurrence in the 14 counties along the Texas-Mexico border. The study was named the Texas Neural Tube Defect Project. A majority of the population (75.6 %) along the border is Hispanic, and more than one-third fall below the poverty line (Hall & Gaquin, 1997). Thousands live in colonias-- unincorporated areas characterized by substandard housing, roads, and drainage-- and are exposed to unsafe and unsanitary environmental conditions. To expand the currently limited knowledge base concerning the multifactorial etiology of NTDs, the case-control study that was implemented compares various biologic, historical, environmental, and social variables between women with NTD-affected pregnancies and women with normal births (Texas Department of Health, 1998).

Hypothesis

Low socioeconomic status has been identified as a risk factor for NTDs (Nevin, Johnston, & Merrett, 1981; Kock & Furman, 1984; Stone, 1987). Poverty may be accompanied by psychological stress, and stress has shown to increase all-cause mortality as well as adverse birth outcomes (Nuckolls, Cassel, & Kaplan, 1972; Brown, 1981). On a mechanistic level, stress causes the body to release glucocorticoids (Guyre & Munck, 1998), and glucocorticoids have been shown to produce birth defects (Yamada, Nogariya, Ichikawa, et al., 1981; Yamada, Suzuki, Matsumo, et al., 1981). The social context of the individual and her perceived social support network are contributing factors in the relationship between stress and illness, as this network may exacerbate or moderate the effects of stress (Cohen & Wills, 1985). To describe this relationship, the model in Figure 1 is suggested.

The present research used data on life events and social support variables from the TNTDP to determine whether social support appears protective of NTDs. It represents the first reported investigation to focus on social support and NTDs.

Objectives

The objectives of this study were:

(1) To examine the relationship between components of stress and components of social support and the occurrence of NTD-affected pregnancies;

(2) To examine the relationship between residual stress and the occurrence of NTD-affected pregnancies.

CHAPTER II

REVIEW OF THE LITERATURE

This literature review has several components. Initially, the link between social support and NTDs was explored. Next, the measurement of social support and stress was studied. The relationship between social support and morbidity and mortality was then examined, including social support and adverse pregnancy outcomes. Next, studies examining socioeconomic status and NTDs were identified. The relationship between stress and illness was then explored, as well as the effect of social support on stress. Finally, studies investigating the body's response to stress and its relationship to a developing fetus were identified.

Stress and Illness

Stress was first described as a biological syndrome by Selye (1936, p.32):

> Experiments on rats show that if the organism is severely damaged by acute nonspecific nocuous agents such as exposure to cold, surgical injury, production of spinal shock...a typical syndrome appears, the symptoms of which are independent of the nature of the damaging agent... and represent rather a response to damage as such.

The idea behind Selye's observation was that stress manifests itself as a measurable bodily reaction although it may be "unspecifically induced"; that is, it is a general

reaction that occurs in response to any number of different stimuli (Selye, 1956). The biological reaction to which Selye referred was characterized by a general increase in the production of certain hormones from the pituitary and adrenal glands that augmented or ameliorated the mobilization of bodily defenses against different stressors (Selye, 1971). A stressor is defined as a demand made by the internal or external environment that upsets an individual's homeostasis, thus affecting her physical and psychological well-being and requiring action to restore that balance (Lazarus & Cohen, 1977). Selye saw the stress reaction as an adaptive syndrome of the organism in response to external stressors. The form this syndrome takes is known as the General Adaptation Syndrome (GAS). The GAS consists of three phases. Upon confrontation with a stressor, the organism enters the first phase, the alarm reaction, in which overall resistance to a stressor initially decreases, although bodily defenses are mobilized. If the stressor is very intense at this point or if many additional stressors are present, resistance diminishes to zero and the organism ceases to function. During the second phase, the stage of resistance, the organism adapts to the presence of the stressor and maintains itself. The stressor can even increase in magnitude during this stage without causing obvious harm. Bodily defenses are effective, and the organism either maintains these defenses or tolerates the presence of the stressor without extended use of direct defenses. Whether the organism resists a stressor actively or passively, its capacity to do so is finite; the presence of a stressor over an extended period will deplete the organism's resistance capacity and eventually lead to breakdown or death during the third phase, the stage of exhaustion (Selye, 1946).

While the GAS is intended to sustain an organism's resistance to a particular stressor, it also necessarily alters the physiological balance that prevailed before the stressor appeared. This bodily change may have direct deleterious consequences for the organism if the GAS is maintained for extended periods. Selye described these negative consequences as "diseases of adaptation," although he admits the term is less than precise (Selye, 1956). In addition, the GAS may either increase or decrease potential resistance to another stressor, depending on the circumstances (Selye, 1946).

The social context of the individual and her perceived social support network are major contributing factors to the relationship between stress and illness (Bieliauskas, 1982). For example, although bereavement has been linked to an increased risk of mortality, the method by which one deals with bereavement may significantly modify this risk. One study, using widows' subjective reports of physical and mental health, found that those who had increased morbidity perceived their social networks as failing to meet their needs and being actively unhelpful (Maddison & Walker, 1967). The geriatric literature consistently demonstrate a negative association between social support and all-cause mortality (Seeman, Kaplan, Knusden, Cohen, & Guralnik, 1987; Blazer, 1982; Kang & Bloom, 1993). Prospective studies have consistently found a relationship between lack of social support and all-cause mortality (Berkman, 1987; House, Umberson, & Landis, 1988; Israel & Rounds, 1987). The weight of the evidence suggests a clear relationship between social support and illness. House (1987) concluded that, "Although the results of individual studies are usually open to alternative interpretations, the pattern of results across the full range of studies strongly suggests that

what are variously termed social relationships, social networks, and social support have important causal effects on health, exposure to stress, and the relationship between stress and health."

Social Support and Pregnancy Outcome

In the area of social support and pregnancy complications (including adverse birth outcomes, but excluding NTDs), data are inconclusive, and authors consistently stress a need for further research (Wasserman, Shaw, Selvin, Gould, & Syme, 1998; Canfield, Annegers, Brender, Cooper, & Greenberg, 1996; Wasserman & Shaw, 1995). One study measured psychosocial assets and stressing life events in relation to prognosis for a normal pregnancy. Assets were first measured early in pregnancy, and then life stressors were measured for the two years preceding pregnancy and at 32 weeks into the pregnancy in order to see what changes had occurred. Alone, neither social assets nor life changes could determine a tendency toward complications in pregnancy. Together, however, if life changes were high before or during pregnancy, women with high social assets had only one-third the rate of complications found in women with lower social assets (Nuckolls, Cassel, & Kaplan, 1972). It has been suggested that deficiencies in support systems do not contribute to illness in and of themselves unless stress is present. When strong support systems are available, stressors have only a minor impact (Cassel, 1975).

Fetal Stress

Fetal stress is commonly equated with stress in the adult, which is associated with increased cortisol secretion (Casey & MacDonald, 1998). Cortisol is a glucocorticoid released by the body in response to stress (Guyre & Munck, 1998). Corticoids play an invaluable role in the acute response of a human to stress, by increasing energy substrates and stimulating cardiovascular tone. However, the prolonged effects are deleterious to the developing brain because of the their catabolic action and the inhibition of cell division (Balazs, 1972; Benesova & Pawlik, 1989). Glucocorticoids also increase the susceptibility to hypoxic ischemic injury in rats (Sapolsky & Pulinelli, 1985) and in cultural hippocampal neurons (Tombaugh, Yang, Swanson, & Sapolsky, 1992).

Normally the fetus is partially protected against maternal glucocorticoids by placental 11-β-hydroxysteroid dehydrogenase, but excessive or exogenous corticotropin causes inhibition of this enzyme (Benediktsson, Lindsay, Noble, Seckl, & Edwards, 1993). Also known as hydrocortisone, cortisol is metabolized (80-90%) during passage through the placenta (Gitau, Cameron, Fisk, & Glover, 1998). Previous research has demonstrated a linear relationship ($r = .60$, $p<.001$) between maternal and fetal cortisol concentrations (Gitau, Cameron, Fisk, & Glover, 1998). Gitau et al. (1998) suggested that this correlation between maternal and fetal cortisol levels may explain how maternal stress affects the fetus, resulting in impaired neural tube development. Since fetal concentrations of cortisol are much lower than the maternal concentrations, a contribution of 10-20% from the mother could still double fetal concentrations (Gitau, Cameron, Fisk, & Glover, 1998).

Important effects of severe prenatal stress on neural development have been demonstrated in experimental conditions (Weinstock, Fride, & Hertzberg, 1988; Fride & Weinstock, 1989; Peters, 1989; Insel, Kinsley, Mann, & Bridges, 1990). Low birth weight and preterm birth have been shown to be associated with low social support (Newton & Hunt, 1984; Rothberg & Lits, 1991). One study that examined whether an effect of psychosocial factors on fetal brain growth could be identified found that the effect of stress on head circumference was still significant after corrected for birthweight ($p = .01$), indicating a specific effect of stress on brain growth (Lou, Hansen, Nordentoft, et al., 1994). Impaired head growth indicates cerebral maldevelopment (Chase, Welch, Dabiere, Vasan, & Butterfield, 1972). Glucocorticoids inhibit cell division in the brain (Howard, 1965; Balazs, 1971). Animal studies show that elevated cortisol levels during pregnancy can cause cleft palate and NTDs (Yamada, Nogariya, Ichikawa, et al., 1981; Yamada, Suzuki, Matsumo, et al., 1981). However, whether or not this same mechanism exists in humans remains controversial (Fraser & Sajoo, 1995).

Social Support and NTDs

A literature review was conducted to identify existing research addressing the association between social support and NTDs. No investigation of this sort was encountered. One published study did include social support as a variable in a table of results, revealing a mixed association, but this association was not discussed in the text (Shaw, Velie, & Wasserman, 1997). However, after speaking with the primary author of the study, it was disclosed that little consideration was paid to the association between

social support and NTDs (G.M. Shaw, personal communication, January 7, 1999). The value of this encountered study is that two of the primary variables, perceived number of close friends and family supporters, are identical to two used in the present study. Contact was made with the CDC's Birth Defects Branch (D. Erickson, personal communication, November 20, 1998) and the California Birth Defects Monitoring Program (G.M. Shaw, personal communication, January 7, 1999) to inquire about the existence of unpublished studies in this area; experts at these agencies were unaware of any such research, published or not.

Stress and Social Support

The measurement of stress was investigated next to obtain a firm understanding of the issue. Stress research often focuses on the quantification of stressful life events (Brown, 1981). For example, Holmes and Rahe (1967) developed the Social Readjustment Rating Scale (SRRS). Studies showed that individuals who scored high on the SRRS experienced more illness than those with low scores. Later research examined life experiences using ratings of the subjective impact of the events (Sarason, Johnson, & Siegel, 1978; Horowitz, Wilner, & Alvarez, 1979).

Social support has been conceptualized in many ways (Israel & Schurman, 1990). Some definitions focus on quantifying the social support network, that is, focusing on the number of friendships and close relatives; others focus on measuring the quality of the network (Heitzmann & Kaplan, 1988). Therefore, no "gold standard" instrument exists for the measurement of social support.

Socioeconomic Status and NTDs

Data are inconclusive in exploring the relationship between low (SES) and NTDs. In Great Britain, a twofold to fourfold increased prevalence of NTD-affected pregnancies was found among women of middle and lower class compared with those of upper social classes (Nevin, Johnston, & Merrett, 1981). Similar results have been found in the United States (Kock & Furman, 1984; Stone, 1987), Canada (Hunter, 1984; Greenberg, James, & Oakley, 1983), and Australia (Sever & Emanuel, 1981). Authors of the most recent article addressing the issue concluded that "both lower SES and residence in a lower SES neighborhood increase the risk of having a neural tube defect-affected pregnancy, with elevated adjusted odds ratios ranging from 1.5 to 2.4," but they were unable to explain this risk (Wasserman, Shaw, Selvin, Gould, & Syme, 1998). Some suggestions for this increased risk include diet, housing conditions, and exposure to environmental toxins.

CHAPTER III

METHODS

The Texas Neural Tube Defect Project (TNTDP)

TDH was awarded a cooperative agreement in 1992 by CDC to conduct NTD surveillance, risk reduction activities, and a case-control study for NTD risk factors in the 14 counties along the Texas-Mexico border: Cameron, Hidalgo, Starr, Webb, Zapata, Maverick, Kinney, Val Verde, Terrell, Brewster, Presidio, Jeff Davis, Hudspeth, and El Paso. The surveillance component of the TNTDP involved prospective case-finding through the following data sources: hospitals; birthing centers; ultrasound centers; abortion centers; prenatal clinics; genetics clinics; and birth attendants which include lay midwives, certified nurse midwives, and nonhospital physicians. All women identified through the surveillance protocol were contacted by telephone, letter, and/or in person. Women who lived outside the study area and women with NTD-affected pregnancies before 1993 were provided education but not given folic acid. Women whose index pregnancy was delivered or terminated in 1993 or later and who resided in the study area at that time were enrolled in the intervention program. The women enrolled were interviewed and provided preconception, pregnancy, and NTD risk reduction education and counseling. If they were contracepting, they were given a multivitamin with 0.4 mg folic acid; if they were not, they were given daily dosepacs consisting of 4.0 mg folic

acid- one multivitamin with 1.0 mg folic acid and three 1.0 mg tablets of folic acid. A Geographic Information System (GIS) component was added to the project in 1997 to evaluate the role of environmental exposures in the development of NTDs (Texas Department of Health, 1998).

The case-control study of the TNTDP began in June 1995. A case was defined as a woman identified through surveillance that resided in one of the 14 counties along the Texas-Mexico border at the time of delivery or termination of an NTD-affected pregnancy and that continued to live in the area at the time of the case-control study. A control was a woman with a non-NTD-affected pregnancy that resided in the study area at the time of delivery. For each case, 1.2 population-based, nonmatched controls were enrolled. The case-control protocol included a general questionnaire (hereafter referred to as the "mother questionnaire"); laboratory tests of blood, urine, stool, and tissue; and a food-frequency questionnaire. Most of these were completed one month after delivery or termination. Environmental and occupational exposures that may be seasonal in nature were assessed by collecting blood and urine biomarkers and by administering a short questionnaire 11 to 13 months after conception. Women were offered $20 for participation in the postpartum biologic sampling portion of the study and another $20 for participation in the questionnaire portion. One year after conception, women were offered $15 to participate in the follow-up biomarker portion of the study (Texas Department of Health, 1998).

The study depended upon cooperation with the labor and delivery units (L&D) within the 21 hospitals along the border. These units were asked to notify one of three NTD

teams (located in El Paso, Laredo, and Harlingen) of an impending case or control delivery. The teams knew of many cases due to prenatal diagnosis, but some cases presented to hospital emergency departments and neonatal units without prior notice. Cord blood, placenta, and other tissue samples were collected at delivery. The L&D units played a key role in team notification of cases that were drawn from their logs according to preassigned delivery numbers. The L&D units also assisted in obtaining informed consent from the cases and controls (Texas Department of Health, 1998).

The Mother Questionnaire

The mother questionnaire was based primarily on the CDC's Birth Defects Mother Questionnaire, an instrument developed by the Birth Defects Branch of the CDC and Survey Research Associates. TDH tailored this questionnaire to make it more specific to NTDs, the proposed hypotheses, and the Texas-Mexico border population. The instrument was made available to women in both English and Spanish. The mother questionnaire was divided into 11 sections: maternal health; reproductive history; family demographics and medical history; nutritional supplements; tobacco; alcohol; street drugs and inhalants; environment; occupation; stress and social support; closing remarks; and interviewer assessment (Texas Department of Health, 1998).

The social support section of the questionnaire was derived from several existing instruments and new questions developed by the TNTDP investigators. A number of questions were taken from a National Cancer Institute questionnaire and from the 23-item Abbreviated Duke Social Support Index (Koenig et al., 1993). Due to the multiple

derivations of questions, an index was created to categorize women according to their levels of social support-- high, moderate, and low-- based on answers to these questions.

A member of one of the three NTD teams administered the questionnaire after consulting with the team physician to estimate the date of conception of the index pregnancy. This was important because the questionnaire was primarily concerned with the period of time from three months prior to conception to three months after conception. The instrument was designed to be administered in person in approximately three hours and in one setting. After completion, the interviewer edited the questionnaire and sent it to the central office in Austin. Responses were entered into a database and were then checked for accuracy by re-entering by another individual.

Data collection

Data for this study were obtained from the central TNTDP office in Austin. Demographic information, known risk factors, and variables related to social support and stress were collected from mother questionnaire data. Women who had taken valproic acid, tegison, or any chemotherapeutic drugs any time within 3 months prior to conception until 3 months after conception were excluded from analysis; these substances are known teratogens.

Statistical Analyses

Data were managed and analyzed using SPSS software. Descriptive statistics were compiled of prevalence and incidence of NTDs in the study area. Demographic characteristics of cases and controls were compiled for comparison purposes.

Logistic regression was employed to calculate odds ratios and 95% confidence intervals for a number of known and suspected NTD risk factors, including country of origin, use of folic acid-containing multivitamins, diabetes, use of insulin, street drug or inhalant use, and cigarette smoking. For each analysis, the outcome was regressed on the independent variable, which was whether or not the woman had an NTD-affected pregnancy. The continuous variables of age, number of close friends, number of close relatives, number of people in the household, total number of occupations for the subject and father, and number of residences in the year prior to conception were recoded as categorical variables. Marital status was coded as either married or single, which included never married, divorced, and widowed. Logistic regression was also used to examine the relationship of each independent stress and social support variable with the outcome. Multiple logistic regression was then used to compute odds ratios and 95% confidence intervals for each of these variables to adjust for age, country of origin, education, and periconceptional vitamin use. These variables were determined to be potential confounding variables according to recent research (L. Suarez, personal communication, March 23,1999). Referent groups for each analysis were chosen as the least likely to be a risk factor for NTDs.

An aggregate scale was then created to divide women into one of three categories: low, moderate, or high social support. The scale was derived from the social support section of the Mother Questionnaire and other variables not in the section, but relevant to the determination of social support and stress. These additional variables included a woman's marital status, income, number of persons living in her household, number of residences lived in for more than a month in the year prior to conception, number of jobs she and the baby's father had during the period from 12 months prior to conception to 3 months after conception, and whether she had been involved in an accident or injured during the period from within 3 months prior to conception to 3 months after conception. Points were assigned positive values for social support questions and negative values for questions relating to stress. These points were then summed to give a woman a cumulative score, considered her social support index score, which then placed her in one of the three categories. A breakdown of points given to responses for each question is given in Table 1. Logistic regression was then used to investigate the relationship between a woman's social support level and case/control status. Finally, multiple logistic regression was performed to further investigate this relationship, while adjusting for education, age, multivitamin use, and country of origin. All hypotheses were tested at the 0.05 level of significance.

CHAPTER IV

RESULTS

Demographics

The overall NTD rate for the entire study period (1993 to 1998, including surveillance predating the case-control study) was 13.7 per 10,000 live births (6.2 for anencephaly and 6.5 for spina bifida). There were 352 resident NTD-affected births/terminations. Of these, 319 (91%) occurred in the 4 most populated border counties- Cameron, Hidalgo, El Paso, and Webb. The remaining 10 border counties accounted for 9% of the births in the study area and 33 (9.4%) of the NTD-affected pregnancies in the study area. A gestational age was known for 348 NTD-affected pregnancies; 64 (18%) were induced or spontaneously aborted at <20 weeks of gestation; 85 (25%) were delivered or induced from 20 through 33 weeks of gestation; and 199 (57%) were delivered at $\geq$ 34 weeks. A prenatal diagnosis (any time prior to delivery or termination) was reported for 77% of the resident cases.

Table 2 shows the demographic characteristics for the 125 cases and 136 controls in the current study. These characteristics were similar for cases and controls. The majority of cases and controls were 25 years old or younger (67.2% and 56.6%, respectively), married (72.0% and 77.2%), Hispanic (96.8% and 96.3%), and in the lowest income bracket of $\leq$ $10,000 (48.0% and 43.4%). The mean number of previous

pregnancies was 2.5 ± 1.8 and 2.5 ± 1.6, respectively, for cases and controls, and most subjects had not completed high school (mean education completed, 10.2 ± 3.5 and 10.9 ± 3.4 years).

No women had taken valproic acid or tegison, known teratogenic agents, during pregnancy. One control woman did take a chemotherapeutic agent, methotrexate, during pregnancy. Although chemotherapeutic agents have been known to be teratogenic, she was not excluded because she was a control.

Suspected risk factors

A logistic regression analysis of risk factors that have been explored in previous studies was undertaken (Table 3). Odds ratios were mildly elevated and nonsignificant for country of origin (odds ratio [OR] 1.08, 95% confidence interval [CI] 0.66 – 1.76 for Mexico-born; OR 1.13, CI 0.15 – 8.26 for other country-born), use of multivitamins (OR 1.28), and smoking cigarettes (OR 1.23). Having an income of $10,000 to $25,000 was a very slightly elevated but nonsignificant risk (OR 1.02, CI 0.51 – 2.06), and an income of less than $10,000, a category into which over 50% of the study population fell, demonstrated an even greater risk, although still not significant (OR 1.25, CI 0.64 – 2.43). Having diabetes (OR 2.10), using insulin (OR 1.88), and using street drugs or inhalants (OR 2.10) also demonstrated elevated odds ratios, but all confidence intervals contained the null value.

Social support and stress

Univariate logistic regression analysis revealed elevated odds ratios for several stress variables and demonstrated significant inverse relationships between social support and the occurrence of NTDs. As shown in Table 4, if a subject indicated that she felt understood by family and friends (OR 0.17), that she felt useful to family and friends (0.06), that she was listened to by family and friends (OR 0.21), that she had a definite role in her family and among friends (OR 0.17), that she could count on family and friends in times of trouble (OR 0.21), or that she could talk about her deepest problem (OR 0.35), she was at a significant ($p<.05$) reduced risk for an NTD-affected pregnancy. If a subject indicated that she was only somewhat satisfied with her relationships, her odds ratio was elevated (OR 1.69), but this was not statistically significant. However, if a subject stated that she was not at all satisfied with her relationships, the odds ratio was significantly elevated at 4.71 (CI 1.27 – 17.39), $p<.05$. A slight, though not significantly, decreased odds ratio was observed for being married (OR 0.73), participation in group activities or community service groups (OR 0.86), knowing what is happening with family and friends (OR 0.52), attending religious worship services (ORs 0.65, 0.74), and having prenatal care (OR 0.52), but the null value was included in these confidence intervals. Number of close friends did not seem to be a predictor of NTD-affected pregnancy, since having no friends (OR 1.40, CI 0.69 – 2.84) was a nonsignificant risk and having 1-2 friends appeared protective (OR 0.82, CI 0.44 – 1.52). Number of close relatives emerged as a better predictor, since having no close relatives increased the odds

ratio to 3.05 (CI 1.21 – 7.68, p<.05), while having 1-2 close family members decreased this risk to 1.24 (CI 0.73 – 2.09).

Variables hypothesized to be stressful did appear to increase risk for having an NTD-affected pregnancy. If the subject had been involved in an accident or injured during the period from 3 months prior to conception to 3 months after conception, this significantly increased the risk for an NTD-affected pregnancy (OR 5.15, CI 1.43 – 18.51). Additionally, it was hypothesized that if the total number of jobs that the subject and the baby's father had held in the last year was zero or greater than 3, this would present a stressful situation. Analysis revealed that having 0 or more than 3 jobs in the last year was a nonsignificant risk factor (OR 1.26, CI 0.63 – 2.51). Having more than 8 persons in the household revealed an elevated odds ratio of 1.3, but this was not significant (CI 0.57 – 2.96). However, having 5 to 8 people in the household appeared protective (OR 0.88, CI 0.53 – 1.48). A notable finding among the stress variables was that if a woman lived in 2 residences for more than a month each in the year prior to conception, her odds ratio was 2.35 (CI 1.29 – 4.27), p<.01. Furthermore, if she had lived in more than 2 residences in the last year, the odds ratio increased to 4.08 (CI 1.41 – 11.81), p<.01.

After adjusting for education level, age, use of multivitamins, and country of origin, all significant odds ratios lost significance (Table 5). Odds ratios changed very little in magnitude, with a few exceptions. Having no close friends (OR 0.87, CI 0.25 – 6.97) and having 1-2 close relatives (OR 0.79, CI 0.38 – 1.64) became protective. The odds ratio for whether a subject could count on family and friends in times of trouble fell to a value near zero, the risk for a subject who had been involved in an accident or injured increased

to a remarkably high value, and their respective confidence intervals approached infinity. Additionally, the odds ratio for women who were not at all satisfied with their relationships dropped to nearly half (OR 2.25, CI 0.19 – 26.52) of what it was in univariate regression (OR 4.71). The same trend was observed for number of residences in the last year. If a subject had lived in 2 residences, her odds ratio dropped from 2.35 to 1.39 (CI 0.58 – 3.34). If she lived in more than 2 residences, her odds ratio fell from 4.08 to 1.46 (CI 0.37 – 5.83). Other variables that demonstrated a switch from being a protective factor to a risk factor include marriage (OR 1.07, CI 0.42 – 2.7) and having 5 to 8 persons in the household (OR 1.17, CI 0.57 – 2.39)

Residual stress scale

After compiling women's scores for answers to social support- and stress-related questions, 82 subjects fell into the low residual stress category, 70 into the moderate category, and 95 into the high category (see Table 6). Data were unavailable for 7 cases and 7 controls. Scores ranged from –4 to 19. The mean score (± standard deviation) was 12.69 (± 3.53), the median was 13, and the mode was 14.

Univariate logistic regression revealed elevated odds ratios for moderate and high residual stress categories, compared to the high category (Table 7). Women in the moderate residual stress category had an odds ratio of 1.11 (CI 0.58 – 2.13). Women in the high residual stress category had an odds ratio of 2.04 (CI 1.12 – 3.72), $p = .02$.

After adjusting for education, age, multivitamin use, and country of origin, odds ratios lost significance (Table 8). The moderate category increased in magnitude, from 1.11 to

1.38 (CI 0.56 – 3.42). The high residual stress category odds ratio increased in magnitude as well, at 2.53. The odds ratio did contain the null value (CI 0.98 – 6.57), and the p-value demonstrated a trend toward significance (p=.056).

CHAPTER V

DISCUSSION

Known and Suspected Risk Factors

Several published studies have demonstrated an association between maternal lack of folic acid and ethnicity and NTDs (Elwood, Little, & Elwood, 1992). These variables were not confirmed as significant risk factors in this study. In fact, maternal use of multivitamins during the period from 3 months prior to conception to 3 months after conception conferred a slightly elevated risk of 1.28. However, use of a folic acid-containing vitamin at some time during this period does not ensure that the woman was taking a multivitamin at the critical time of neural tube development, estimated to be 2-4 weeks post-conception (Wybrandt & Ludman, 1991). That is, women who begin prenatal care at 2 or 3 months post-conception and are instructed to take multivitamins would answer "yes" to this question. Furthermore, the relationship between vitamin use and NTDs may have been obscured due to the fact that very few women in both the case and control group used the vitamins. Country of origin was found to be a very weak, nonsignificant predictor of an NTD-affected pregnancy in this study. The present study population resided on the Texas-Mexico border, thus increasing the likelihood of a control or case originating from Mexico. Therefore, a relationship between country of origin was not likely to be demonstrated in this relatively homogeneous population. Due

to the inconsistency of these findings with past studies, it is questionable whether these two variables should be adjusted for in multivariate analyses. Nevertheless, they were included in the multivariate model due to the association demonstrated in previous studies. Adjustment for vitamin use and country of origin will not overestimate risk estimates.

The relationship between congenital malformations and maternal smoking during pregnancy is uncertain, with previous studies resulting in both positive (Evans, Newcombe, & Campbell, 1979) and negative (Shaw, Velie, & Morland, 1996) findings. This study showed an elevated risk associated with smoking, but this was not statistically significant. Although periconceptional use of street drugs or inhalants was determined to be risk factor for NTDs in the present study (despite the nonsignificance of this odds ratio), other studies have found no association between drug use and NTDs (Shaw, Velie, & Morland, 1996). Finally, the risk of diabetes and insulin use for the occurrence of NTD-affected pregnancy has been well-demonstrated (Elwood, Little, & Elwood, 1992). This risk was substantiated in the present study, although it was not statistically significant.

Social Support

If a subject indicated that she felt understood by or useful to family and friends, that she felt listened to by family and friends, that she had a definite role in family and among friends, that she could count on family and friends in times of trouble, or that she could talk about her deepest problem, each of these variables protected against having an NTD-

affected pregnancy. However, multivitamin use, education level, age, and country of origin confounded these risks. Furthermore, if a woman indicated that she was not at all satisfied with her relationships, she was at a significantly increased risk for an NTD-affected pregnancy. This finding was no longer significant after adjusting for the four potential confounding variables. Marriage appeared to be protective for an NTD-affected pregnancy, but became a risk factor after adjusting for the confounding variables. Neither participation in community or group activities nor attendance at religious worship activities appeared predictive for NTDs. Women with multiple close friends did not exhibit a consistent pattern for risk. Women with fewer than 3 close relatives did exhibit an inverse relationship between number of close relatives and risk for an NTD-affected pregnancy. These results obscure whether quality or quantity of social support may predict an NTD-affected pregnancy.

After adjustment for vitamin use, educational level, age, and country of origin, the odds ratio for whether the subject felt that she could count on family and friends in times of trouble fell to a value near zero. Furthermore, the confidence interval reached a value approaching infinity. This occurred due to the small number of cases/controls contained in cells. Also after adjustment, the only category of number of close friends or relatives that continued to have an elevated risk, although nonsignificant, was having no close relatives. This risk fell from 3.05 to 1.32.

These results may not be expected since being Hispanic is a risk factor for NTDs, and Hispanic women traditionally tend to have extensive social support networks (Balcazar, Peterson, & Krull, 1997). Perhaps the quality of these relationships as related to the

ability of the woman to express her feelings, count on her family and friends, etc., may be poor. The cultural context of social support should be given consideration as well (Jacobson, 1987). People's concepts, beliefs, and values regarding themselves and others, including the criteria by which they classify and count supporters, the meanings they attribute to their relationships, and their ideas about who should give and get support define the cultural context in which individuals perceive social support (Mitchell, 1969).

Stress

Having been involved in an accident or injured within 3 months prior to or after conception was a significant risk factor for the occurrence of an NTD-affected pregnancy. These findings support the results of a previous study, in which Richards (1969) noted a higher frequency of accidents during pregnancies resulting in NTDs. An accident or injury was not defined in clear terms for the subject during the interview and therefore was open to individual interpretation, obscuring this relationship. Few studies have addressed this relation.

If a woman had moved residences once in the last year, she was at a statistically significant elevated risk for an NTD-affected pregnancy. Furthermore, if she moved more than once, this risk nearly doubled. Although these odds ratios lost significance after adjusting for possible confounding variables, they represent possible stressful circumstances which cannot be fully explained. These residence moves may not have been elective and may reflect an unstable family life, unstable economic situation, or other circumstances. A study of poor pregnant women in inner-city areas of Washington,

D.C. (Boone, 1988), found that women with low social support over the course of repeat pregnancies tended to have moved frequently and to have more low birth weight babies and abortions. This finding should be addressed in future research. It is important that future investigations use residence at the time of conception, as this study did, to measure possible environmental teratogens, due to the misclassification that may result from using the residence at the time of birth as a proxy. Ordinarily, such misclassification should be inconsequential if very few individuals changed residence during the course of a pregnancy. However, because of the high residential mobility of the U.S. population in general and especially among young individuals around the time of marriage and family formation, such a problem should be addressed (Khoury et al., 1988).

An excessive number of jobs or no jobs for the subject and the baby's father were assumed to represent a stressful situation. Indeed, having no job or more than 3 jobs in the last year was a risk factor for NTDs. Number of people in the household was not a significant predictor either, although having more than 8 persons living in the house was an elevated risk. After adjusting for vitamin use, education level, age, and country of origin, having 5 to 8 persons in the household became protective.

As was the case for one of the social support variables, the injury/accident variable's odds ratio became incalculable. The odds ratio value was exceptionally high, and the confidence interval approached near infinity. This occurred due to the small numbers of cases/controls in the cells.

Residual Stress Categories

When the social support and stress variables were aggregated into an index, a high amount of residual stress was shown to be a significant risk factor for the occurrence of an NTD-affected pregnancy. Women in the high residual stress category were over 2 times more likely to have had an NTD-affected baby than women with a low level of residual stress. The moderate category had a slightly elevated, nonsignificant risk compared to the referent group. However, these results were also confounded by vitamin use, education level, age, and country of origin. After this adjustment, the risks increased, compared with the referent group. It should be noted, though, that despite the adjustment, the relationship between high residual stress and NTDs continued to demonstrate a trend toward significance. These are the strongest data yet to support the current hypothesis that a great amount of residual strss is a risk factor for NTDs.

Limitations

This study focused on the impact of psychosocial characteristics on the occurrence of an NTD-affected pregnancy while accounting for the use of multivitamins, educational level, age, and country of origin. The reported odds ratios suggest a relationship between residual stress and NTDs. However, the strength of the association may have been underestimated in this study for several reasons. Psychosocial factors are difficult to measure and the instrument used relied on self-report, which may have resulted in misclassification. A reluctance to describe stressful conditions in one's life is likely to weaken the associations between social support/stress factors and NTD-affected

pregnancy. Furthermore, the social support being measured may be a consequence of the pregnancy outcome. That is, a woman with a non-NTD-affected pregnancy may not have her social support system tested as much as a woman whose pregnancy ended in termination or delivery of an NTD-affected child. In addition, the fact that risk estimates remained elevated for the high residual stress category after adjustment for confounding variables suggests that the study may have been limited by its size. Perhaps future studies will repeat these measurements with a larger population, thereby increasing power.

As in any case-control study, these results are subject to recall bias. Subjects were asked to recall details of their environment and actions from as long as 12 months prior to conception. The study is also subject to interviewer bias. Interviewers were not blinded to case/control status, but even if they were, it would be virtually impossible to not discover the pregnancy outcome through the course of a three-hour interview with the subject. This may have influenced the manner in which questions were asked.

The social support section of the Mother Questionnaire was compiled from questions of validated instruments and questions composed by the Texas Department of Health. More detailed questions concerning social support and stress were lacking. Therefore, results may not be truly reflective of social support and/or stress for subjects. Additionally, the residual stress scale that was created has not been validated. Responses to certain questions were given more weight than others, and these judgments were made by the author based on consultations with epidemiologists. For example, if a subject attended religious worship services weekly or more than 1 time a week, the response was

given +2 points. If she attended 1 to 2 times a month, the response was given only +1 point. It is recognized that the weights given to responses are debatable.

Measurement of stress and social support in this study was, for the most part, subjective, based upon responses from subjects concerning their perceptions of support from family and friends, their feelings of self-worth, and stressful conditions. Therefore, the reported risk estimates may reflect actual differences in life circumstances, or merely individual differences in perception of one's life. Although such an alternative explanation cannot be completely ruled out in studies based on self-reported rather than independent observational data on psychosocial factors, this explanation is unlikely to be the sole explanation for the findings on life circumstances in this study. Research has demonstrated the negative effects of stress on physical health (Selye, 1936; Selye, 1956). Second, a detailed look at results from the current study shows that psychosocial factors were not uniformly weakly or strongly associated with the occurrence of an NTD-affected pregnancy. Whereas there were strong associations for not being satisfied with relationships and having more than 1 residence in the last year, number of close friends and relatives and number of jobs in the last year seemed unrelated to the occurrence of an NTD. This risk pattern cannot be explained by general individual perception bias.

Results might have been substantiated by measuring the presence of glucocorticoids in the blood. Unfortunately, a lack of funds precluded the ability to test for biomarkers.

Conclusion

The relationship between social support, stress, and incidence of NTDs remains unclear. Results from this study indicated an inverse relationship between residual stress and NTDs, which was confounded by educational level and age. Stressful variables were identified as potential risk factors for NTDs, and satisfying social support was demonstrated to moderate these risks.

The influence of social factors on the etiology of disease is an area of research that has gained increasing prominence recently. Due to the rarity of neural tube defects, it is unlikely that a prospective study will be conducted to investigate the relationship between congenital anomalies and psychosocial variables, although such a study design would allow for the demonstration of a temporal relation. Therefore, the quality of retrospective studies should be refined. Future research in this area should attempt to minimize bias by interviewing subjects as soon as possible, and the survey instrument used in future studies should be a validated one. The literature demonstrates conflicting views of proper measurement of psychosocial assets and stressful events, and, therefore, this may not be an easy task. In order to clarify the relationship between psychosocial risk factors and NTDs in the present Hispanic population, focus groups of women that live along the Texas-Mexico border might be conducted. These groups would allow for a better understanding of the life circumstances and the perception of these circumstances by this population. In addition, a valid biomarker for stress should be determined, and blood samples should be collected for purposes of measuring this biomarker.

If the present results are valid and residual stress is a risk factor for NTDs, then the clinical and policy implications merit discussion. Health intervention strategies for women in the high residual stress category may require a comprehensive approach including social, emotional, medical, and financial assistance. Inadequate medical access information, diminished social support, deficient economic resources, and residential instability may predispose this group either to neglect or inconsistently seek medical care (Balcazar, Peterson, & Krull, 1997). Public health departments should educate women about the link between lack of *quality* social support and NTDs and encourage strong, healthy relationships in their lives. Obviously, the deeply personal nature of the risk factor limits intervention, but public health educators should work with mental health agencies to educate leaders in the community, including those of civic and church organizations, about the influence of limiting stress and the health of relationships on the health of an unborn child. These individuals could, in turn, reach out to women in their community to share this message. If these results are substantiated in further studies, clinicians may use this information to help them in recognizing a woman at risk for an NTD-affected pregnancy and take the proper steps to ensure prevention.

Overall rates of NTDs in the United States are declining, but the uneven decline in subgroups of NTD cases suggests an underlying multifactorial etiology of NTDs (Yen, et al., 1992). Moreover, differential access to prenatal care may be contributing, at least in part, to dissimilar declines in NTD rates in subgroups in the population (Yen, et al., 1992). Because of the etiologic heterogeneity suggested by the changing descriptive epidemiology of NTDs, it may be unlikely that total primary prevention of NTDs can be

achieved with folic acid supplementation in all ethnic groups (Yen et al., 1992). Folic acid has been shown to reduce the incidence of NTDs (Medical Research Council Vitamin Study Research Group, 1991), but whether or not the taking of folic acid-containing vitamins is related to a lifestyle that includes a high quality social support system remains to be determined. This study indicated that there is an association between residual stress, education, age, and NTDs. As social support and stress are considered as suspected risk factors for NTD-affected pregnancies in future studies, this relationship may be elucidated.

APPENDIX

Table 1. Residual Stress Score Derivation

Variable	Points Allocated
Marital Status	
Married	1
Single	0
Prenatal Care (B32)	
Yes	1
No	0
Number of close friends (J1)	
≥ 6	3
3 – 5	2
1 – 2	1
0	0
Number of close relatives (J2)	
≥ 6	3
3 - 5	2
1 –2	1
0	0
Participation in group meetings, community service groups, etc. (J3)	
More than 1 time a week	1
Weekly or almost weekly	1
1-2 times a month	1
Few times a year	0
Never	0
Family and friends understand (J4)	
Yes	1
No	0
Don't know	0
Feel useful to family and friends (J5)	
Yes	1
No	0
Don't know	0

Know what's happening with family and friends (J6)

Yes	1
No	0
Don't Know	0

Feel listened to by family and friends (J7)

Yes	1
No	0
Don't know	0

Definite role in family (J8)

Yes	1
No	0
Don't know	0

Count on family and friends in times of trouble (J9)

Yes	1
No	0
Don't know	0

Talk about deepest problem (J10)

Yes	1
No	0
Don't know	0

Satisfied with relationships with family and friends (J11)

Very	2
Somewhat	1
Not at all	0
Don't know	0

Attendance at religious worship services in the last year (J12)

More than 1 time a week	2
Weekly or almost weekly	2
1-2 times a month	1
Few times a year	0
Never	0

Involved in an accident or injured within 3 months prior to or after conception (A118)

Yes	-1
No	0

Number of people in household (C83)

> 8	-2
5-8	-1
1-4	0

Number of residences lived in for more than a month in year prior to conception (H43)

>2	-2
2	-1
1	0

Total number of occupations for mother and father 12 months prior to and 3 months after conception (based on I3 and I29)

>3	-1
0	-1
1-3	0

Table 2. Demographic Profile of Cases and Controls*

Variable	Cases (n=125)		Controls (n=136)	
Age				
14-20	45	(36.0%)	39	(28.7%)
21-25	39	(31.2%)	38	(27.9%)
26-30	22	(17.6%)	37	(27.2%)
31-35	13	(10.4%)	18	(13.3%)
36-44	6	(4.8%)	4	(2.9%)
Marital Status				
Married	90	(72.0%)	105	(77.2%)
Single	35	(28.0%)	30	(22.1%)
Divorced	0	(0%)	1	(0.7%)
Ethnicity				
Hispanic	121	(96.8%)	131	(96.3%)
White/non-Hispanic	3	(2.4%)	4	(2.9%)
Black/non-Hispanic	0	(0%)	0	(0%)
Other	1	(0.8%)	1	(0.7%)
Hispanic group				
Mexican, Chicano, or Mexican-American	121	(96.8%)	131	(96.3%)
Other	0	(0%)	1	(0.7%)
No response	4	(3.2%)	4	(2.9%)
Income, in dollars				
$\leq$ 10,000	60	(48.0%)	59	(43.4%)
10,001 – 15,000	19	(15.2%)	23	(16.9%)
15,001 – 20,000	12	(9.6%)	11	(8.1%)
20,001 – 25,000	9	(7.2%)	14	(10.3%)
25,001 – 40,000	11	(8.8%)	13	(9.6%)
> 40,000	11	(8.8%)	14	(10.3%)
No response	3	(2.4%)	2	(1.5%)
Gravida†	2.5 $\pm$ 1.8		2.5 $\pm$ 1.6	
Education, in years†	10.2 $\pm$ 3.5		10.9 $\pm$ 3.4	

* Data presented as number (%), percentage totals may not equal 100 due to rounding;
† Continuous variables presented as mean $\pm$ standard deviation.

Table 3. Univariate Logistic Regression of Known and Suspected Risk Factors*

Variable	Controls	Cases	OR‡	CI‡
Country of origin				
Mexico	64 (47.1)	61 (48.8)	1.08	0.66 – 1.76
Other country	2 (1.5)	2 (1.6)	1.13	0.15 – 8.26
United States	70 (51.5)	62 (49.6)	Referent	
Use of multivitamins				
Yes	8 (5.9)	9 (7.2)	1.28	0.46 – 3.55
No	65 (47.8)	57 (45.6)	Referent	
Diabetes				
Yes	6 (4.4)	11 (8.8)	2.10	0.75 – 5.83
No	130 (95.6)	114 (91.2)	Referent	
Insulin use				
Yes	1 (0.7)	3 (2.4)	1.88	0.15 – 23.40
No	5 (3.7)	8 (6.4)	Referent	
Street drug or inhalant use				
Yes	2 (1.5)	7 (5.6)	2.10	0.25 – 17.59
No	3 (2.2)	5 (4.0)	Referent	
Cigarette smoking				
Yes	20 (14.7)	28 (22.4)	1.23	0.49 – 3.07
No	14 (10.3)	16 (12.8)	Referent	
Income				
< 10,000	59 (43.4)	60 (48.0)	1.25	0.64 – 2.43
10,000 – 25,000	48 (35.3)	40 (32.0)	1.02	0.51 – 2.06
> 25,000	27 (19.9)	22 (17.6)	Referent	

*All behavioral risk factors refer to 3 months prior to and 3 months after conception;
‡ OR, odds ratio; CI, 95% confidence interval

Table 4. Univariate Logistic Regression of Social Support and Stress Variables¶

Social Support Variable	Controls§	Cases§	OR‡	CI‡
Marital Status				
Single	30 (22.1)	35 (28.0)	Referent	
Married	105 (77.2)	90 (72.0)	0.73	0.42 – 1.29
Number of close friends				
≥ 3	30 (28.0)	28 (22.4)	Referent	
1 – 2	77 (56.7)	59 (47.2)	0.82	0.44 – 1.52
0	29 (21.3)	38 (30.4)	1.40	0.69 – 2.84
Number of close relatives				
≥3	57 (41.9)	42 (34.6)	Referent	
1 – 2	71 (52.2)	65 (52.0)	1.24	0.73 – 2.09
0	8 (5.9)	18 (14.4)	3.05*	1.21 – 7.68
Participation in group activities, meetings, community service†	69 (50.7)	56 (45.8)	0.86	0.60 – 1.24
Understood by family and friends†	132 (97.1)	106 (84.8)	0.17*	0.06 – 0.51
Useful to family and friends†	135 (99.3)	111 (88.8)	0.06*	0.01 –0.49
Knows what's happening with family and friends†	125 (91.9)	106 (84.8)	0.52	0.23 – 1.15
Listened to by family and friends†	132 (97.1)	109 (87.2)	0.21*	0.07 – 0.64
Definite role in family and friends†	132 (97.1)	106 (84.8)	0.17*	0.06 – 0.51
Can count on family and in times of trouble†	133 (97.8)	113 (90.4)	0.21*	0.06 – 0.77
Can talk about deepest problem†	125 (91.9)	100 (80.0)	0.35*	0.17 – 0.75

Satisfied with relationships				
Very	113 (83.1)	88 (70.4)	Referent	
Somewhat	19 (14.0)	25 (20.0)	1.69	0.87 – 3.26
Not at all	3 (2.2)	11 (8.8)	4.71*	1.27 – 17.39
Attended religious worship services in the last year				
At least weekly	43 (31.6)	51 (40.8)	Referent	
1 – 2 times a month	76 (55.9)	59 (47.2)	0.65	0.39 – 1.11
Few times a year/ never	17 (12.5)	15 (12.0)	0.74	0.33 – 1.66
Prenatal care†	127 (93.4)	110 (88.0)	0.52	0.22 – 1.23

Stress Variable	Controls	Cases	OR‡	CI‡
Involved in an accident or injured within 3 months prior to or after conception				
No	133 (97.8)	112 (89.6)	Referent	
Yes	3 (2.2)	13 (10.4)	5.15*	1.43 – 18.51
Total number of jobs in the last year for mother and father				
1-3	97 (71.3)	91 (72.8)	Referent	
0, >3	17 (12.5)	18 (14.4)	1.26	0.63 – 2.51
Number of people in household				
1 – 4	56 (41.2)	53 (42.4)	Referent	
5 – 8	67 (49.3)	56 (44.8)	0.88	0.53 – 1.48
> 8	13 (9.6)	16 (12.8)	1.30	0.57 – 2.96
Number of residences in last year				
1	108 (79.4)	74 (59.2)	Referent	
2	23 (16.9)	37 (29.6)	2.35**	1.29 – 4.27
>2	5 (3.7)	14 (11.2)	4.08**	1.41 – 11.81

¶ Percentages may not total 100 due to missing data; ‡ OR, odds ratio, CI, 95% confidence interval; § presented as number (%); † Variable is dichotomous, with the referent group as "no"; * Significant at $p < .05$; ** significant at $p < .01$

TABLE 5. Multivariate Logistic Regression of Social Support and Stress Variables*

Social Support Variable	OR‡	CI‡
Marital status		
Single	Referent	
Married	1.07	0.42 – 2.76
Number of close friends		
≥3	Referent	
1 – 2	0.66	0.28 – 1.54
0	0.87	0.23 – 2.54
Number of close relatives		
≥3	Referent	
1 – 2	0.79	0.39 – 1.64
0	1.32	0.25 – 6.97
Participating in group activities, meetings, community service†	0.69	0.41 – 1.18
Understood by family and friends†	0.18	0.02 – 1.61
Useful to family and friends†	0.18	0.02 – 1.74
Knows what's happening with family and friends†	0.68	0.21 – 2.19
Listened to by family and friends†	0.15	0.02 – 1.34
Definite role in family and friends†	0.13	0.02 – 1.16
Can count on family and friends in times of trouble†	§	
Can talk about deepest problem†	0.39	0.11 – 1.39
Satisfied with relationships		
Very	Referent	
Somewhat	1.63	0.61 – 4.40
Not at all	2.25	0.19 – 26.52

Attended religious worship services in the last year		
At least weekly	Referent	
1 – 2 times a month	0.73	0.35 – 1.53
Few times a year/ never	0.83	0.28 – 2.50
Prenatal care†	0.69	0.11 – 4.46

Stress Variable	OR‡	CI‡
Involved in an accident or injured within 3 months prior to or after conception		
No	Referent	
Yes	§	
Total number of jobs for mother and father in the last year		
1-3	Referent	
0, >3	2.53	0.75 – 8.58
Number of people in household		
1 – 4	Referent	
5 – 8	1.17	0.57 – 2.39
> 8	1.61	0.43 – 5.96
Number of residences in last year		
1	Referent	
2	1.39	0.58 – 3.34
>2	1.46	0.37 – 5.83

* Adjusted for periconceptional vitamin use, education, age, and country of origin; †Variable is dichotomous, with the referent group as "no"; ‡ OR, odds ratio, CI, 95% confidence interval; § Odds ratios not calculable due to few numbers in cells.

Table 6. Residual Stress Scale Frequencies*

Category	Inclusive Scores	No. Controls		No. Cases	
Low	(15 – 19)	49	(38.0%)	33	(28.0%)
Moderate	(13 – 14)	40	(31.0%)	30	(25.4%)
High	(-2 – 12)	40	(31.0%)	55	(46.6%)

* Data are missing for 7 controls and 7 cases.

Table 7. Univariate Logistic Regression of Residual Stress Categories

Category	OR‡	CI‡
Low	Referent	
Moderate	1.11	0.58 – 2.13
High	2.04*	1.12 – 3.72

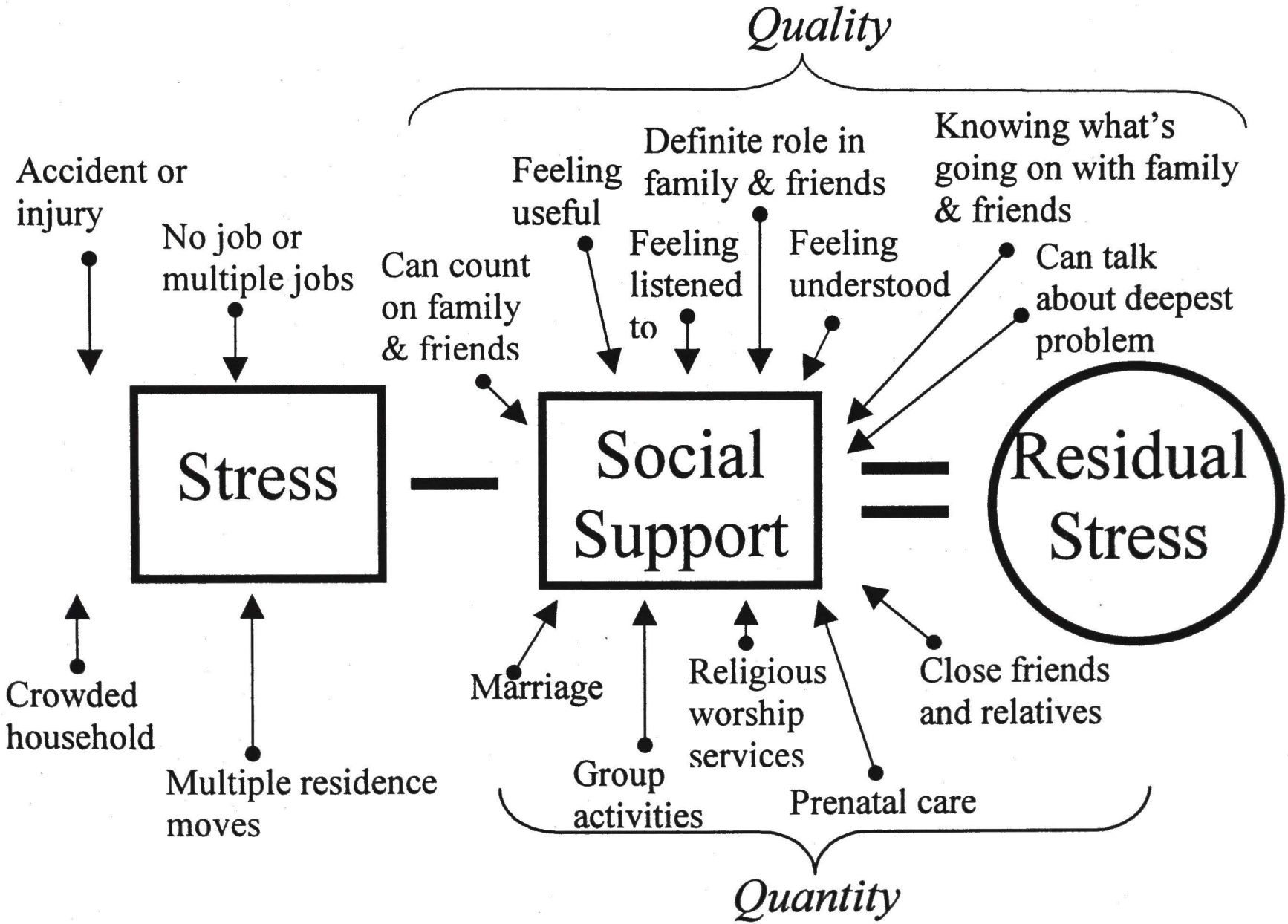
p = .02; ‡ OR, odds ratio, CI, 95% confidence interval

Table 8. Multivariate Logistic Regression of Residual Stress Categories*

Category	OR‡	CI‡
Low	Referent	
Moderate	1.38	0.56 – 3.42
High	2.53†	0.98 – 6.57

* Adjusted for periconceptional vitamin use, education, age, and country of origin. ‡ OR, odds ratio, CI, 95% confidence interval; †p = .056

Figure 1. Relationship between Stress, Social Support, and Residual Stress



SECTION J: STRESS AND SOCIAL SUPPORT

Not including your spouse/partner, of all your friends, how many people are there that you can talk to about private matters or can call on for help?	# friends ⌊__⌋⌊__⌋
Not including your spouse/partner, how many relatives do you have that you can talk to about private matters or can call on for help?	# relatives ⌊__⌋⌊__⌋
How often do you participate in or attend group meetings or activities, for example, social clubs, PTA, sporting events, or other community service groups?	more than 1 time/wk . 1 weekly or almost weekly 2 1-2 times/mo . . . . . 3 few times/yr . . . . . 4 never 5
Do family and friends understand you?	YES . . . . . 1 NO . . . . . 2 DK 8
Do you feel useful to family and friends?	YES . . . . . 1 NO . . . . . 2 DK 8
Do you know what's happening with family and friends?	YES . . . . . 1 NO . . . . . 2 DK 8
Do you feel listened to by family and friends?	YES . . . . . 1 NO . . . . . 2 DK 8
Do you feel you have a definite role in family and among friends?	YES . . . . . 1 NO . . . . . 2 DK 8
Can you count on family and friends in times of trouble?	YES . . . . . 1 NO . . . . . 2 DK 8
Can you talk about your deepest problem?	YES . . . . . 1 NO . . . . . 2 DK 8
How satisfied are you with relationships with family and friends?	very . . . . . 1 somewhat . . . . . 2 not at all . . . . . 3 DK 8
On average, how often have you attended religious worship services during the last year?	more than 1 time/wk . 1 weekly or almost weekly 2 1-2 times/mo . . . . . 3 few times/yr . . . . . 4 never 5

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