AN EVALUATION OF CONGENITAL HYPOTHYROIDISM IN TEXAS 1992-1995

THESIS

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ABSTRACT

Congenital hypothyroidism is a biochemical defect that can have devastating effects on a child if undetected or untreated. The rate of congenital hypothyroidism in Texas has been on the increase since 1991. Rates in Texas far exceed observed rates nation wide.

This study is an attempt to characterize the distribution of congenital hypothyroidism in Texas. It examined the effects of race/ethnicity, gender and maternal age on the rate of congenital hypothyroidism. Research evidence points to these variables as possible risk factors in congenital anomalies, including congenital hypothyroidism. In addition, this study examined the seasonality of congenital hypothyroidism in order to assess the possibility of environmental effects.

The study spanned the period from 1992 to 1995 and covered the entire state of Texas. During that period, there were a total of 1,286,432 births of which 806 cases of congenital hypothyroidism were identified. Odds Ratio analysis and Logistic Regression were used to assess race/ethnicity, gender, and maternal age as risk factors. Time Series analysis was used to assess the seasonality effect. Results indicate that Hispanic race/ethnicity, female gender and advanced maternal age, in that order, significantly increase the rate of congenital hypothyroidism. The need for prenatal screening and outreach programs for at risk population was stressed. Further studies were suggested.

CHAPTER I

INTRODUCTION

Congenital hypothyroidism is a biochemical defect that involves inadequate production of thyroid hormone and consequently results in a deficiency in circulating thyroxine (Hannon et al., 1991; Tsai et als., 1992). This deficiency in thyroid hormone may be a result of the absence of the thyroid gland, incomplete gland development, thyroid inflammation resulting from autoimmune disorders, hereditary defects in thyroid hormone synthesis, or the inability to synthesize thyroxine because of dietary iodine deficiency.

Abnormalities directly affecting the thyroid's ability to secrete hormones are referred to as "primary hypothyroidism", and those indirectly affecting thyroid function are referred to as "secondary hypothyroidism". Both primary and secondary congenital hypothyroidism are considered serious infant diseases. If untreated, congenital deficiency of thyroid hormone may lead to decreased mental capacity and stunted growth.

The first description of congenital hypothyroidism is said to have been published by Thomas Curling in Britain in 1850 (Fisher, 1987). After World War II, availability of radioiodine led to important advances in the understanding of congenital hypothyroidism. It allowed scientists the ability to characterize disordered thyroid embryogenesis in infants with congenital hypothyroidism. Although beneficial effects of thyroid hormone treatment were well described by the 1930s, mental retardation remained a common feature of congenital hypothyroidism even after treatment. In the early 1970s, it was clearly documented that treatment before three months improves the prognosis for mental

retardation.

Advances in the understanding of fetal-neonatal thyroid physiology in addition to the availability of highly sensitive radioimmunoassay methods for the measurement of blood thyroxine (T4) and thyroid stimulating hormone (TSH) concentrations during the 1960s and early 1970s set the stage for newborn thyroid screening (Fisher, 1987). In 1974, mass population screening for congenital hypothyroidism was introduced in Quebec, Canada by Dussault and colleagues.

Early detection and treatment of congenital hypothyroidism is essential to prevent severe and irreversible mental retardation and physical deformities. For therapeutic effectiveness, congenital hypothyroidism must be detected and treated before the affected infant reaches three months of age. Treatment consists of the supplementation of the affected child with the appropriate dosage of l-thyroxine so as to maintain a normal thyroxine (T4) level (American Academy of Pediatrics, 1993).

The Texas Newborn Screening Program (NBS) tests for five newborn disorders. These are phenylketonuria, galactosemia, congenital hypothyroidism, hemoglobinopathies and congenital adrenal hyperplasia. Texas added congenital hypothyroidism to their screening program in 1980.

Table 1 shows the cases of congenital hypothyroidism detected through this program from 1989 to 1995.

Table 1. Cases of congenital hypothyroidism detected through the Newborn Screening Program in Texas.

	1989	1990	1991	1992	1993	1994	1995	Total
Cases	103	100	121	181	211	185	229	1130
Births	307,560	316,257	317,680	320,714	321,961	321,088	322,669	2,227,929
Rate(/100,000)	33.49	31.62	38.09	56.62	65.74	57.80	71.19	50.81
Ratio (1:	2,986	3,163	2,625	1,766	1,521	1,730	1,405	1,968

As Table 1 indicates, the rates of congenital hypothyroidism in Texas have been increasing since 1992. Congenital Hypothyroidism rates are much higher in Texas than they are nationwide. Since 1980, there were a total of 1,647 identified cases in Texas, an incidence of 1:3,200 births (Newborn Screening Program, 1996). In comparison, there is an incidence of 1:4,000 in the United States (American Academy of Pediatrics,1993).

Research Questions

This study is an attempt to answer the following questions:

1. Is there a relationship between maternal race/ethnicity and the incidence of congenital hyperthyroidism observed in Texas?
2. Is there a relationship between child's gender and the incidence of congenital hyperthyroidism observed in Texas?
3. Is there a relationship between maternal age and the incidence of congenital hyperthyroidism observed in Texas?
4. What are the relative effects of race/ethnicity, gender, and maternal age on incidence of congenital hyperthyroidism?
5. Is there seasonality in the incidence of congenital hypothyroidism? If so, is it related to environmental effects?

Several research studies point to race/ethnicity, gender, and maternal age as risk factors in congenital hypothyroidism as well as other congenital defects. Although maternal age has shown a relationship to such congenital defects as Down syndrome and gastroschisis, has not been examined as a possible factor for congenital hypothyroidism. Few studies explored the effect of environmental factors on congenital hypothyroidism. They tackled the relationship as a seasonality factor using Time Series Analysis. The results of these studies are presented in detail in Chapter II. Hypotheses are formulated in Chapter II based on the results of these earlier studies.

This study spanned the period from 1992 to 1995 and covered the entire state of

Texas. During that time, there were a total of 1,286,432 births of which 806 cases of congenital hypothyroidism were identified.

Statement of the Problem

It is vital to detect congenital hypothyroidism early in life due to the serious and irreversible outcomes that result if the disease is undetected and untreated. Currently, there is a high detection rate through newborn screening. On average, cases are confirmed within the first seven days of life and treatment initiated in the first month of life (Fisher et al., 1979). Knowledge of relationships between certain risk factors and the disease enhances detection methods by applying targeted education and earlier screening tests to those at risk. This has been observed in Down syndrome where the defect has a strong relation to advanced maternal age at delivery.

Significance of the Study

This study seeks to identify possible risk factors associated with congenital hypothyroidism. Understanding more about congenital hypothyroidism's causes and association with different factors will assist in its earlier detection through targeted comprehensive screening, possibly prenatally, of those identified to be at high risk of the disease. Outreach educational programs targeting at high-risk populations would contribute to an increased prevention, early detection, and treatment.

Definitions of Terms/Abbreviations

Galactosemia - Any of three recessive disorders of galactose metabolism; the classic form due to a deficiency of the enzyme galactose-1-phosphate uridyl transferase. It results in hepatomegaly, cataract, and mental retardation.

Hemoglobinopathies - Hematologic disorder due to alteration in the genetically determined molecular structure of hemoglobin and characteristic clinical and laboratory abnormalities and often overt anemia.

Odds Ratio (OR) - Odds of disease to non-disease among those with the risk factor.

Phenylketonuria - an inborn error of metabolism marked by an inability to convert phenylalanine into tyrosine, permitting accumulation of phenylalanine and its metabolic products in body fluids; it results in mental retardation, neurologic manifestations, light pigmentation, eczema and mousy odor, unless treated by a diet low in phenylalanine.

Radioimmunoassay - A highly sensitive and specific assay method that uses the competition between radio labeled and unlabeled substances in an antigen-antibody reaction to determine the concentration of the unlabeled substance which may be an antibody or a substance against which the specific antibodies can be produced.

Relative Risk - Ratio of risk of disease among the exposed to the risk among the unexposed.

	disease	no disease
exposed	A	B
unexposed	C	D

(A/(A+B)) / (C/(C+D))

Sickle Cell Disease - A disease where the patient develops sickling (irregular shapes) of cells in the blood.

T4 - Thyroxine - an iodine containing hormone secreted by the thyroid gland; its chief function is to increase the rate of cell metabolism.

TSH - Thyroid stimulating hormone - a glycoprotein produced and secreted by the anterior pituitary. This hormone activates adenylate cyclase in the thyroid gland to effect release of thyroid hormones.

CHAPTER II

LITERATURE REVIEW

Diagnosis of Hypothyroidism

Congenital hypothyroidism is one of the more common preventable causes of mental retardation (Fisher et al., 1979). It is very difficult to detect congenital hypothyroidism clinically because of the paucity of early signs and symptoms. The American Academy of Pediatrics recommends mass newborn screening using measurements of thyroxine (T4) and thyroid stimulation hormone (TSH) levels for the detection of congenital hypothyroidism (American Academy of Pediatrics, 1993). Screening is performed by initially using filter paper blood spot T4 measurement followed by a measurement of TSH in filter paper specimens with low T4. Infants with low T4 levels and TSH concentrations greater than 40 mu/L are considered to have primary hypothyroidism. These infants would need to be examined immediately and have confirmatory serum tests conducted to verify the diagnosis.

The American Academy of Pediatrics (1993) indicates that an affected fetus might be protected to a certain extent by placental transfer of maternal thyroid hormone; serum T4 levels in the cord blood. This would indicate that a child with congenital hypothyroidism would be at the highest risk of developing complications after birth, when the child is no longer supplemented with maternal thyroid hormone.

Prenatal detection of congenital diseases is possible through amniocentesis. Amniocentesis is a medical procedure that is used in obtaining a small sample of amniotic fluid surrounding the fetus (March of Dimes, 1988). The amniotic fluid contains living cells from the fetus. These cells are grown in the laboratory and tested for chromosomal abnormalities or various genetic birth defects. Amniocentesis was developed in the 1800s and has long been used late in pregnancy to assess fetal anemia in Rh disease to discover if the fetal lungs are mature enough for delivery. Today, amniocentesis is often used in the second trimester of pregnancy to diagnose or rule out certain birth defects. It carries a small risk factor for infection or miscarriage.

Amniocentesis is offered as an optional test when there is an increased risk of chromosomal or genetic birth defect or certain malformations. It is usually recommended because of advanced maternal age at delivery (35 years or older), a previous child or pregnancy with a birth defect, or because of family history of a birth defect.

Screening Programs

Pilot programs for screening of newborn infants for congenital hypothyroidism began in Quebec in 1972 and Pittsburgh in 1973 (Fisher et al., 1979). Regional programs were subsequently established in Oregon, New England, and Toronto. The Quebec screening program began with filter paper spot sampling of heel-stick blood using phenylketonuria samples for T4 screening. Filter paper spot TSH testing of samples with the lowest 2% of the T4 concentrations was added to the process.

The Oregon and New England Regional programs also screen with filter paper spot T4 measurements and subsequent TSH radioimmunoassay of samples with the lowest 3% of T4 concentrations. Oregon runs a second filter-paper blood specimen which is obtained from each infant born within the state when the infant is 4 to 6 weeks of age. Pittsburgh began with the measurement of TSH in cord serum specimens. Currently they are using filter-paper spot TSH screening in collaboration with the Oregon Regional Program. The Toronto Program performs a cord serum T4 measurement on all infants, with supplemental TSH and T3 uptake measurements in the lowest 8 to 12% of the T4 results.

Data collected as of August 1978 indicated that out of the 1,046,362 screened infants in Oregon , there were 246 confirmed cases of primary congenital hypothyroidism, an overall incidence of one in 244,254 births. Out of the 246 confirmed cases, 239 were detected through the newborn screening and only 7 cases were missed. The study demonstrated the effectiveness of mass screening in the detection of congenital hypothyroidism.

Over five million infants have been screened for primary congenital hypothyroidism in California from 1980 to 1992 (Lorey et al., 1992). All babies born in California are tested for primary congenital hypothyroidism, phenylketonuria, galactosemia, sickle cell disease and other hemoglobinopathies through the Genetics Disease Program. A heel stick blood sample is spotted into the filter paper on a preprinted collection form. Demographic information, which includes ethnicity is completed at the place of birth. The first step is a serum T4 test. All samples with a value of 9.0 mg/dl or less are declared

presumptive positive. An additional 5% of the next lowest values are also declared presumptive positive. Those samples then undergo a TSH test and those with values of 25u/dl or more are declared positive for congenital hypothyroidism and examined for definitive diagnosis.

Georgia began a screening program to detect congenital hypothyroidism in February, 1979 (Brown et al., 1981). Blood samples are obtained from all neonates via heel puncture between the second and seventh day of life and are collected on filter paper. Initially the sample is tested for T4 by radioimmunoassay. Tests with T4 values less than 2.3 standard deviations from the mean for age matched infants are considered abnormal and repeated in duplicate. TSH assays are then performed in duplicate on all specimens with T4 concentrations equal to or less than 5.0 ug/dl. Serum is obtained from those infants with a low T4 and a TSH value greater than 25uU/ml for the establishment of a primary congenital hypothyroidism diagnosis.

Congenital Hypothyroidism screening began in Texas in February 1980 (Therrell et al., 1989). Filter paper specimens are grouped into two age groups (less than 7 days, more than 7 days) in accordance to age at time of specimen collection. Specimens are then analyzed using a T4 test. Those specimens with values in the lower 10% of the analytical run are repeated in duplicate while simultaneously performing duplicate analysis for TSH . Specimens with T4 results in the upper 90% are considered normal. T4 values in the lower 0.5% combined with TSH values greater than or equal to 30 uIU/mL are considered presumptive positive indicators for congenital hypothyroidism and followed up accordingly.

A study was conducted in Thailand to assess the cost benefit of mass screening (Rajatanavin et al., 1993). In Thailand, the incidence of congenital hypothyroidism ranges between one in 2,486 and one in 3,843 live births. This study was conducted at a hospital facility from August 1990 to March 1992. All births were screened for congenital hypothyroidism by first collecting cord blood samples at birth. The sera was saved for assay of TSH levels. The cost benefit of the screening process was estimated by calculating the cost per case finding. The opportunity cost spent was estimated using the principle of net present value by comparing the former and the latter parameters. The cost per case finding was 50,415.00 baht while the opportunity cost and supportive care spent was 81,156.00 baht. It was estimated that the cost savings (30,741.00 baht) gained from the early identification and treatment of an infant with congenital hypothyroidism were substantial enough to provide a case for the continuation of the screening program.

Treatment of Hypothyroidism

The American Academy of Pediatrics recommends the treatment of congenital hypothyroidism using 1-thyroxine. The 1-thyroxine given at appropriate dosages in proportion to the child's weight elevates the T4 levels of the child. This is particularly important, since there is evidence that low T4 levels during the first year in life may cause a decrease in IQ. This was supported by the Fisher et al. (1979) findings, indicated that when infants identified with congenital hypothyroidism were treated before one month of age, they developed normally.

In a study conducted in the United Kingdom by Tillotson et al. (1994), the effects of early treatment on the biochemical severity and intelligence of children with congenital hypothyroidism was examined. In the study 361 cases and 315 controls were examined. It was found that the T4 value at diagnosis was highly associated with the IQ of the child. Those children with a T4 level above 40 nmol/l had a higher mean IQ than the children with T4 levels of 40 nmol/l or less. However, unlike earlier studies, Tillotson et al. could not find any obvious trend in IQ with age at start of treatment (age range: 1-173 days). The study also failed to identify any association between IQ and the average dosage of thyroxine in the first year of life. It was concluded that benefits from screening and early treatment were questionable.

Race/Ethnicity as a Risk Factor

For the evaluation of the interaction between certain factors (i.e. race/ethnicity and gender) and congenital hypothyroidism, most studies compared incidence of the disease for each factor. The incidence was calculated by dividing the number of births into the number of identified cases in racial/ethnic groups and gender .

Research evidence indicates that race/ethnicity correlates with the incidence of congenital hypothyroidism. Native Americans and Hispanics were shown to have the highest incidence of congenital hypothyroidism. African Americans on the other hand had the lowest incidence. Lorey et al (1992) examined infants identified with congenital hypothyroidism in California and found a higher birth incidence of primary congenital

hypothyroidism in Native Americans (40.1 per 100,000 births) and Hispanics (35.6 per 100,000 births) than for the other racial categories (White, Asian: 24.0, 22.4 per 100,000 births). The lowest rate was observed in African Americans, at 9.1.

The Georgia program had also reported large racial differences in the incidence of primary congenital hypothyroidism when observing two years worth of data (Brown et al., 1981). The incidence of congenital hypothyroidism in blacks was one in 32,377 contrasted to one in 5,526 in whites. In Texas, a significant racial difference was observed for those infants who were screened positive for congenital hypothyroidism from February 1, 1980 to February 1, 1982 (Therrell et al., 1982) . Hispanics had the highest incidence (one in 1,228), while African Americans had the lowest (one in 8,564).

In the Northwest health region of England, newborn screening resulted in the identification of a significantly higher incidence of congenital hypothyroidism in Asian families (one in 918) compared to one in 3,391 in non-Asians (Rosenthal et al., 1988). A study conducted in Taiwan found that the prevalence of permanent primary congenital hypothyroidism was one in 5,788, almost one sixth of the incidence documented for Asians in the England study (Tsai et al., 1995).

Gender as a Risk Factor

Several studies were conducted to explore the relationship between the gender of the newborn infant and incidence of congenital hypothyroidism. These studies indicate that females tend to have a higher incidence of congenital hypothyroidism than males. In

the Lorey et al (1992) study there were twice as many females as there were males. However, the difference in gender was even more prominent when comparing gender differences within certain racial groups. There were three times as many Hispanic females than Hispanic males diagnosed with congenital hypothyroidism.

The Georgia program also noted gender differences in their affected population (Brown et al., 1981). The sex ratio was three females for each affected male. The Texas program indicated a 1.8 female to male ratio for primary congenital hypothyroidism (Therrell et al., 1982). Taiwan also noted a gender difference in their affected population giving a male to female ratio of 1:7 for detected cases of primary congenital hypothyroidism (Tsai et al., 1995).

Maternal Age as a Risk Factor

The effect of mother's age on incidence of congenital hypothyroidism was not studied. Several studies, however, were conducted to explore the relationship between maternal age and other congenital anomalies. These studies, together with studies of the effect of race/ethnicity and gender are reported in the following section.

Other Congenital Anomalies

In order to further assess the relationship between race/ethnicity, gender, maternal age, environmental effects and the rate of congenital hypothyroidism, other congenital

anomalies were examined. Relationships between certain congenital anomalies, such as neural tube defects, gastroschisis, Down syndrome, congenital heart defects and cleft palate have been extensively researched and are well documented in the literature.

In California, 29 in 1000 births have one or more serious birth defects each year. Birth defects were found in 16% of fetal deaths after 20 weeks gestation and in 31% of live-born children who died at infancy (California Births Defects Monitoring Program, 1994).

All racial/ethnic groups have overall birth defects rates around 2-3%. There are racial differences reflecting slight variation in most birth defects, while racial differences reflecting high variations are observed in only a few specific conditions. African American babies have the highest rate of all birth defects at 32.4 per 1,000 births. White and then Latino infants followed , at 29.5 and 27.8 per 1,000 births respectively. Asians have the lowest rate of 22.6 per 1,000 births. Although overall rates are similar, there are notable racial differences in rates of specific birth defects.

The overall rate of birth defects shows a slightly higher risk for mothers under 20 years and over 35 years of age. The greater risk to women over 35 years is largely due to the higher rates of births with chromosomal abnormalities, in particular trisomies and extra chromosomes.

Gastroschisis:

Gastroschisis is a birth defect where a child's intestine protrudes through a hole in

the abdomen (California Birth Defects Monitoring Program, 1994). The child can die without immediate corrective surgery and intensive hospital care. The incidence of gastroschisis is two for every 10,000 births in California. Young mothers are five times more likely than women in their late twenties to have a child with gastroschisis.

Down Syndrome:

Down syndrome is a combination of birth defects that manifest in mental retardation (March of Dimes Foundation, 1988). "Mental retardation" is when a child does not learn as quickly as other children, due to abnormal brain formation. Children with Down syndrome have heart abnormalities and may have respiratory problems. In most cases, Down syndrome is caused by the egg or the sperm cell contributing 24 chromosomes instead of 23, resulting in a total of 47 chromosomes instead of the normal 46.

The biggest risk factor for Down syndrome is the maternal age at pregnancy (The California Birth Defects Monitoring Program, 1994). The incidence of Down syndrome climbs dramatically at age 30. The incidence rate is also highest in Latinos, which is twice the rate in Whites. The difference is even more profound in mothers over 35 years of age. The incidence for mothers over 35 years ranges anywhere from twice to six times the rate in mothers under 35 years, depending on other risk factors such as race/ethnicity and gender of the infant.

Spina Bifida:

Spina bifida is a neural tube defect of the backbone (spinal column) often called "open spine" (March of Dimes, 1988). One in 2,000 babies are born with this condition each year in the United States. It is more frequent in the Appalachian Mountain region than in the western states, and is less common among Jewish people and African Americans. In California, it was found that Latinos had a 1.5 times higher incidence rate of Spina Bifida than Whites (The California Birth Defects Monitoring Program, 1994).

Congenital Heart Disease:

Congenital heart disease is the structural abnormality of the heart or the great vessels which are of potential functional importance. In a study by Fixler et al. (1993), prevalence rates of cardiac defects were estimated for three ethnic groups: African Americans, Whites and Hispanics. Congenital heart disease cases were identified from 379,561 live births in Dallas county, Texas for births from 1971 to 1984. Information on the cases were gathered from the birth certificates. Cases were ascertained by reviewing hospital records, office records, autopsy reports and county medical examiner records. The incidence of congenital heart disease by ethnic groups were based on the frequency of cases assigned to the specific ethnic group divided by the number of live births assigned to that ethnic group. The prevalence rates for congenital heart disease were significantly

higher for Whites (7.2 per 1, 000 births) than for African Americans (5.6) or Hispanics (5.9). After stratification for severity, the prevalence rates for those children with more severe disease (i.e. those that had cardiac catheterization, had surgery, or died) were similar.

Oral Clefts:

A cleft is an opening in the lip, the roof of the mouth (hard palate), or the soft tissue of the mouth (soft palate) (March of Dimes, 1988). These openings are normally present in early fetal development and usually close before birth. There are approximately one in 700 babies born with oral clefts in the United States. Clefts occur more often among Asians and certain groups of American Indians than among Whites. They occur less frequently among African Americans. In California, the rate of oral clefts is one in 550 births (The California Birth Defects Monitoring Program, 1994). More males than females are born with cleft lip, with or without a cleft palate, while more females than males are born with a cleft palate alone. Oral clefts are relatively rare in African Americans compared to other racial or ethnic groups.

Seasonality of Congenital Hypothyroidism

In a study by Miyai et al. (1994), 820 cases of congenital hypothyroidism were

identified in eight different areas in the world. The hypothyroid cases were either identified in hospitals in Japan, France, Pittsburgh and Philadelphia or through mass screening in Japan, Norway, Switzerland, Québec, Australia, Toronto, and Pennsylvania. Each country was examined separately. The distribution of the birth dates were analyzed statistically by the chi-square test. Each year was arbitrarily divided into four seasons. Birth rates variations were corrected for in this analysis. The study showed that there was a relationship between incidence of hypothyroidism and the four seasons in some areas. Higher incidence was observed during early summer and late autumn. The author refuted the possibility of climatic effects, but indicated that environmental factors may be a more plausible cause for the observed seasonality.

In another study by Reijneveld et al. (1993), a similar analysis was done in the Netherlands. Five hundred and thirty four cases of congenital hypothyroidism cases were identified. A chi-square test was conducted to find out if the number of cases varied according to the month of birth. The analysis did not find any statistically significant association between congenital hypothyroidism births and the month of the year.

Hypotheses

The above mentioned research leads to the formulation of five research hypothese as follows:

1. Hispanic mothers are more likely than Non-Hispanic mothers to give birth to infants with congenital hypothyroidism.

2. Female infants are more likely than male infants to be born with congenital hypothyroidism.
3. Infants born to mothers who are 35 years old and older are more likely to be born with congenital hypothyroidism.
4. Infants born to mothers who are younger than 18 years are more likely to be born with congenital hypothyroidism.
5. There is a correlation between incidence of congenital hypothyroidism and the month of birth.

CHAPTER III

METHODS

Data Source

Data on confirmed cases of congenital hypothyroidism for date of birth between 1992 and 1995 were obtained from the Texas Newborn Screening Program. The data set contained demographic information which included maternal age at delivery, child's race, county of residence at delivery, and child's gender. Appendix A includes the structure of the newborn screening data file.

Additional clinical data were obtained from the Texas Genetics Program. The Genetics Program follows all identified cases closely, collecting clinical and management information. Contained in the database are also cases that failed to be identified through the newborn screening, but were later identified through clinical means. The clinical database contained clinical data on the child's condition which included birth weight, type of hypothyroidism, and treatment. Both data sets provided a rich data source on cases with congenital hypothyroidism, providing both demographic, clinical, and management data on each identified case. Appendix B includes the structure of the clinical file.

Demographic and outcome data for all births between 1992 and 1995 were additionally obtained from the Texas Bureau of Vital Statistics. The birth file contained both information on the live birth and the mother. The data contained in this data set were mostly demographic, i.e. maternal age at delivery, child's race, county of residence at

delivery, and child's gender. Appendix C includes the structure of the vital statistics data file.

Data Preparation

The newborn screening data file on number of positive congenital hypothyroid cases was grouped by unique cases in order to examine unduplicated cases. The newborn screening file was then linked to the clinical file to produce one file containing demographic, screening and clinical data.

In examining the congenital hypothyroid data, it was found that maternal age was missing on a large proportion of the cases. Those were supplemented by matching the cases with vital statistics and completing missing data where matches were made.

The FoxPro 2.5 database program was used to compare, reorganize, and restructure the information from three source files into the study file. Appendix D includes the structure of the study data file.

Analysis Techniques

Measurement of Relative Risk (RR):

To measure the RR of the three independent variables, namely race/ethnicity, gender, and maternal age, the population identified with congenital hypothyroidism was

compared to a control population, namely those individuals who screened negative for congenital hypothyroidism. For ease of comparison, the whole birth file from which the hypothyroidism cases were extracted was used as the control population. This should not affect the results of the study significantly because of the large population size (1,286,432 births).

RR is an estimate of the magnitude of an association between exposure (i.e. ethnicity, gender, maternal age), and disease (i.e. congenital hypothyroidism) and an indication of the likelihood of developing the disease in the exposed group relative to those who are not exposed.

Odds Ratio Analysis:

Because the cases and non-cases are from two different populations, it would not have been possible to calculate the rate of the development of the disease given the presence or absence of exposure. The formulas utilized in the calculation of the relative risk in a cohort can not be applied to the data in this study. The relative risk can be estimated, however, by calculating the ratio of the odds of exposure among the cases to that among the non-cases. This calculation is referred to as the Odds Ratio (OR) and can be calculated using the following formula:

$$OR=(a/c)/(b/d)=ad/bc$$

Even though there may be differences between the numerical values of RR and OR, they tend to always point in the same direction. Table 2 indicates how race/ethnicity would be evaluated as a risk factor for the calculation of the OR.

Table 2. Odds Ratio Matrix.

		Congenital Hypothyroid?	
		Yes	No
Hispanic?	Yes	a	b
	No	c	d

$$(a/b) \times (c/d) = (a \times d) / (b \times c)$$

As shown in Table 2, the OR for the race/ethnicity factor is calculated by dividing the number of cases of congenital hypothyroidism in Hispanics (a) by the number of Hispanics births (b) (free of the disease) multiply the results by the number of cases in NonHispanics © divided by the number of non-Hispanics births (d). This ratio is equal to the number of cases in Hispanics (a) multiplied by non-Hispanic births (d) divided by the

number of Hispanic births (b) multiplied by the number of cases in non-Hispanics (c). A resulting odds ratio value of greater than 1 would indicate that the odds of the disease is greater when exposed to the specified risk factor.

The OR was calculated for each of the following factors:

- Hispanic race/ethnicity of the mother
- Newborn female gender
- Advanced maternal age (≥35 years)
- Teenage pregnancies (<18 years)

The confidence interval (C.I.)for the Odds Ratio was calculated at a 95% rate utilizing the following formula:

$$95\%\ C.I. = (ad/bc)\exp(\pm 1.96\sqrt{(1/a)+(1/b)+(1/c)+(1/d)})$$

Logistic Regression:

Logistic regression, known as logit analysis, was utilized, in addition to the OR, to analyze the significance of race/ethnicity, gender and maternal age on cases of congenital hypothyroidism. Logistic regression is a form of regression in which the criterion variable is dichotomous. Since logit analysis estimates coefficients from dichotomous variables,

the prediction that an event will occur is maximized. If the predicted probability is greater than 0.50, then the event will occur, if it is less than 0.50 then the event will not occur. The formula for the calculation of the estimated probability for an event to occur is as follows:

$$Prob = 1 / (1+e^{-Z})$$

$$Z = B_0 + B_1X_1 + B_2X_2 + B_3X_3 + \ldots$$

In order to use logit analysis, the data was transformed into a dichotomy of 1 and 0, where 1 represented the presence of the value of the independent variables under study, namely Hispanic race/ethnicity, female birth, or maternal age greater than or equal to 35 years of age; and 0 represented the absence of these values. Logistic regression was used to estimate the probability of predicting the occurrence of congenital hypothyroidism from these independent variables.

Time Series Analysis - ARIMA:

In order to analyze the possibility of seasonality, Auto Regressive Integrated Moving Average (ARIMA) analysis was conducted. ARIMA is a general model widely used in time series analysis. Based upon prior investigation of the behavior of a series, three numbers are specified: the order of autoregression (p), the degree of differencing (d),

and the order of moving average (q). The general model is written as ARIMA(p,d,q) and the formula for this model is as follows:

$$\hat{Y}_t = \beta_1 \hat{Y}_{t-1} + \beta_2 \hat{Y}_{t-2} + \ldots + \beta_k \hat{Y}_{t-k} + MA_t + \hat{\alpha}_1 MA_{t-1} + \hat{\alpha}_2 MA_{t-2} + \ldots + \hat{\alpha}_j MA_{t-j}$$

The OR, logistic regression, and ARIMA analyses were conducted using the SPSS-8.0 Statistical Package.

CHAPTER IV

RESULTS

As may be recalled from Chapter III, the OR analysis was conducted to measure the risk factor of three independent variables, race/ethnicity, gender, and maternal age, on incidence of congenital hypothyroidism.

Race/Ethnicity as a Risk Factor

Table 3 reflects the odds of hypothyroidism in mothers with a Hispanic race/ethnicity.

Table 3. Odds Ratio Matrix of Cases of Congenital Hypothyroidism in Hispanic Race/Ethnicity.

		Congenital Hypothyroid?	
		Yes	No
Hispanic?	Yes	359	525,229
	No	447	756,294

Calculating the OR from the data in Table 3 resulted in a value of 1.16 (95% CI = 1.01, 1.33) for births to mothers of Hispanic origin, indicating that the risk for congenital hypothyroidism does increase with deliveries to Hispanic mothers.

The results of the logistic regression did not indicate any significant effects of Hispanic race/ethnicity on congenital hypothyroidism at the 95 percent confidence level. The significance level of the Wald's statistic was 0.116 and therefore was not significant. In addition, the R value was less than .01 for this risk factor, further indicating a lack of correlation. The results of the logistic regression that are related to the mother's Hispanic race/ethnicity can be found in Appendix F.

The results of the logistic regression are contradictory to the results of the odds ratio. It may be noticed that the absolute value of the regression coefficient (B) was large, which resulted in an estimated standard error that is too large as well. This produced a Wald statistic that was too small, leading us to fail to reject the null hypothesis that the coefficient is 0, when in fact we should. Therefore, it is recommended that whenever we have a large coefficient, we should not rely on the Wald statistics for hypothesis testing (Norusis, 1997).

Figure 1 illustrates the effect of race/ethnicity by comparing the rate of cases of hypothyroidism for mothers of different race/ethnicity.

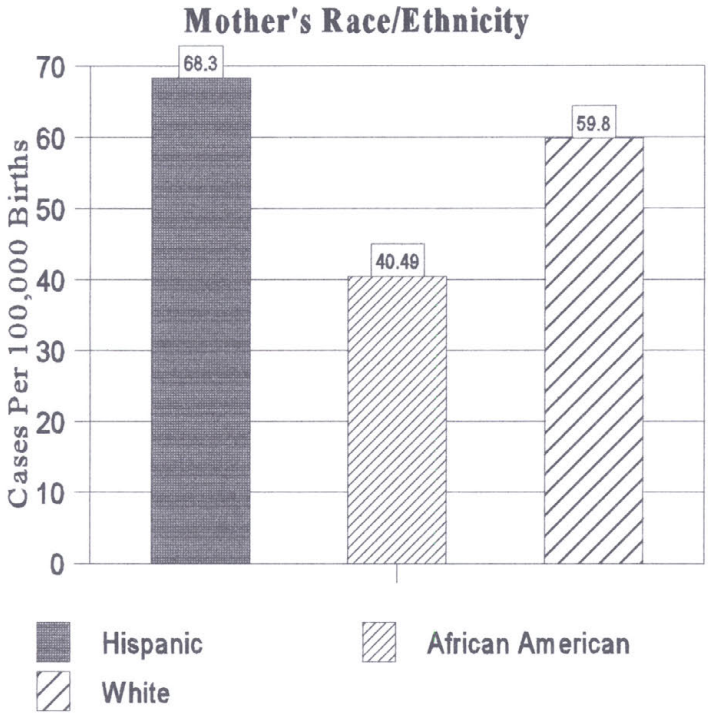

Figure 1. Cases of Congenital Hypothyroidism Per 100,000 Births by Mother's Race/Ethnicity in Texas.

Gender as a Risk Factor

Table 4 records the odds of congenital hypothyroidism in female births.

Table 4. Odds Ratio Matrix of Cases of Congenital Hypothyroidism in Females Births.

		Congenital Hypothyroid?	
		Yes	No
Female Gender	Yes	411	626,601
	No	395	654,922

When calculating the OR from the data in Table 4 a value of 1.09 (CI = 0.95,1.25) was obtained for deliveries resulting in a female child, indicating that the risk for congenital hypothyroidism does not significantly increase in female newborns.

The results of the logistic regression did not indicate any significant effects of newborn female gender on congenital hypothyroidism at the 95 percent confidence level. The significance level of the Wald's statistic was 0.268 and therefore was not significant. In addition, the R value was less than .01 for this risk factor, further indicating a lack of correlation. The results of the logistic regression that are related to the newborn female gender can be found in Appendix F.

The results of the logistic regression were supported the results of the odds ratio results. However, it may be noticed that the estimated standard error is too large as well. This produced a Wald statistic that was too small, leading us to fail to reject the null hypothesis that the coefficient is 0, when in fact we should.

Figure 2 compares the rate of cases of congenital hypothyroidism by gender.

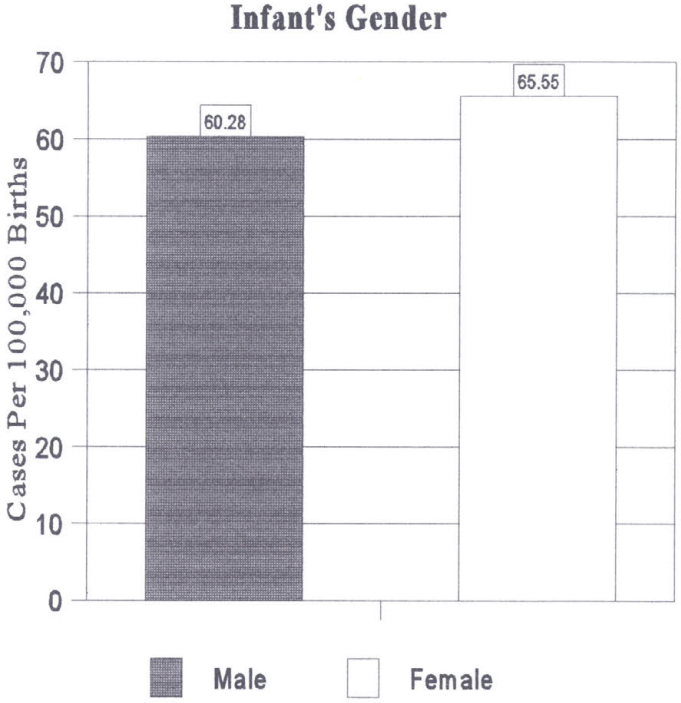

Figure 2. Cases of Congenital Hypothyroidism per 100,000 Births in Males and Females in Texas.

Maternal Age as a Risk Factor

Cases of congenital hypothyroid and births with a missing maternal age were eliminated from the calculations included in the analysis. Since the maternal age was missing on 7% of the cases (56 cases), the results may be skewed.

Figure 3 compares the rate of congenital hypothyroidism cases by mother's age at delivery.

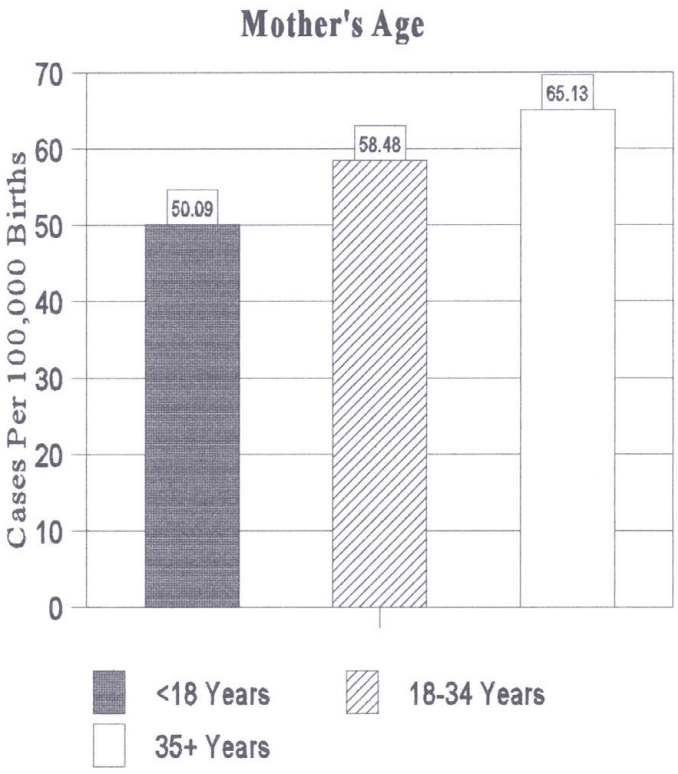

Figure 3. Cases of Congenital Hypothyroidism per 100,000 Births by Mother's Age at Delivery in Texas.

It was observed from the above graph that the rate of congenital hypothyroidism increased with maternal age. In order to test the relationship between maternal age and congenital hypothyroidism, a chi-square test was conducted on the data. Table 5 shows the data input for the chi-square analysis which utilized the statistical software Epi Info.

Table 5. Chi-Square Input Table for the Relationship of Maternal Age to Congenital Hypothyroidism.

Mother's Age	**Cases**	**Controls**
<18 Years	43	85,805
18-34 Years	634	1,083,561
35+ Years	73	112,010

The results of the chi-square analysis produced a chi-square value for linear trend of 1.861 with a p-value of 0.17255 Therefore, the maternal age did not have a significant effect on congenital hypothyroidism.

Advanced Maternal Age:

Table 6 records the odds of congenital hypothyroidism in mothers 35 years and older at delivery.

Table 6. Odds Ratio Matrix of Cases of Congenital Hypothyroidism in Mothers 35 Years of Age and Older at Delivery.

		Congenital Hypothyroid?	
		Yes	No
Maternal Age ≥35 Years?	Yes	73	112,010
	No	677	1,169,513

Calculating the OR from the data in Table 6 results in a value of 1.13 (CI = 0.88, 1.43) for mothers 35 years and older, indicating that the risk for congenital hypothyroidism does not significantly increase with deliveries to mothers with an advanced maternal age.

The logistic regression results indicated a significant effect of advanced maternal age on congenital hypothyroidism. This is based on a significance level of Wald statistics that is different than 0 using a significance level of 0.05. The Wald statistic was 1,486 with a significance level of less than .01. The R value was 0.316, which indicates a small partial contribution to the model. The results of the logistic regression related to advanced maternal age can be found in appendix F.

Teenage Mothers:

Table 7 records the odds of congenital hypothyroidism in mothers less than 18 years at delivery.

Table 7 Odds Ratio Matrix of Cases of Congenital Hypothyroidism in Mothers Less than 18 Years of Age at Delivery.

		Congenital Hypothyroid?	
		Yes	No
Maternal Age <18 Years?	Yes	43	85,805
	No	707	1,195,571

Calculating the OR from the data in Table 7 resulted in a value of 0.85 (CI = 0.62, 1.15) for mothers who were younger than 18 years, indicating that the risk for congenital hypothyroidism is not affected substantially with deliveries to teenage mothers.

Comparison of the Three Risk Factors

Table 8 records the odds of congenital hypothyroidism for mother Hispanic ethnicity/race, mother's age greater than or equal to 35 years and female infants.

Table 8. Odds Ratio Matrix of Cases of Congenital Hypothyroidism for Hispanic Race/Ethnicity, Mother's Age Greater than or Equal to 35 Years and Female Infants.

		Congenital Hypothyroid?	
		Yes	No
All three factors	Yes	12	17,983
	No	784	1,263,505

When calculating the OR from the data in Table 7 a value of 1.08 (CI = 0.61, 1.90) was obtained for mother Hispanic ethnicity/race, mother's age greater than or equal to 35 years and female infants indicating that the risk for congenital hypothyroidism does not significantly increase with all three factors.

Figure 4 compares the relative risk of race/ethnicity, gender, and maternal age by plotting the rate of cases of congenital hypothyroidism, related to these factors.

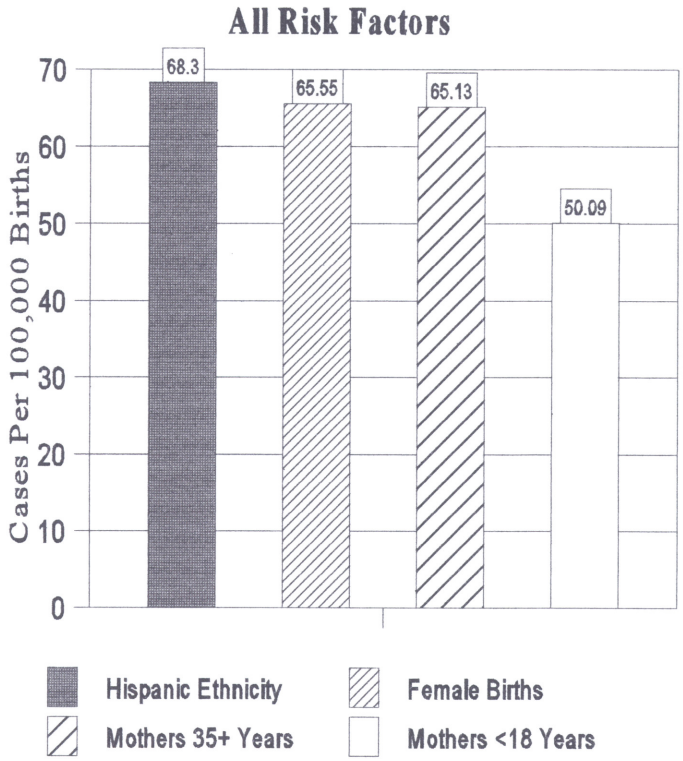

Figure 4. Comparison of the Cases of Congenital Hypothyroidism per 100,000 Births by Hispanic Race/Ethnicity, Female Gender, and Maternal Age (<18 and ≥35 years) in Texas.

Figure 4 demonstrates how the rates of congenital hypothyroidism differs between the three risk factors. It shows how Hispanic ethnicity has the highest rate, followed by female births, followed by mothers who are 35 years of age and older, and finally mothers less than 18 years of age.

Table 9 contains the correlation matrix for the three risk factors and demonstrates

the relationship between these factors. This matrix was produced as part of the logistic regression statistic run.

Table 9. Correlation Matrix for Maternal Age ≥35, Hispanic Race/Ethnicity and Female Gender.

	Constant	Age >34	Hispanic	Female Gender
Constant	**1.00000**	.00000	-.00001	-.95503
Age >34	.00000	**1.00000**	.00019	-.00081
Hispanic	-.00001	.00019	**1.00000**	-.29650
Female Gender	-.95503	-.00081	-.29650	**1.00000**

The results of the correlation matrix shown in table 9 above indicate that there is no correlation between the variables of advanced maternal age, Hispanic race or female gender of the newborn.

Seasonality as a Risk Factor

To study the effect of seasonality on cases of congenital hypothyroidism the number of infants born with the disease during each month of the year per 1,000 births were compared. Variance in the rate of cases occurring in the different birth months would indicate the seasonality effect. Figure 5 plots the number of the cases during each month.

The values for each month were produced by combining the values of the cases and the births for each of the months for the entire study period.

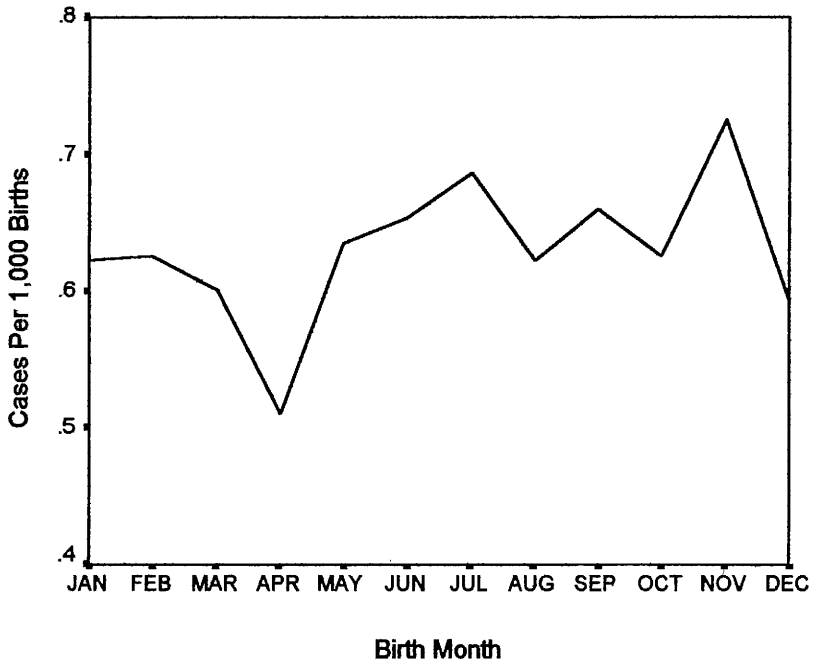

Figure 5. Plot of Rate of Congenital Hypothyroidism Cases Per 1,000 Births Against Month of Birth.

Figure 5 shows that the rate of infants born with congenital hypothyroidism fluctuated from one month to the other, with the lowest rate occurring during the month of April and the highest during the month of November.

To explore seasonality in depth, the rate of congenital hypothyroidism was studied from month to month from 1992 to 1995. This comparison would indicate if cases during a certain month remained consistently higher or lower from year to year. Figure 6

illustrates this relationship of month and year of birth.

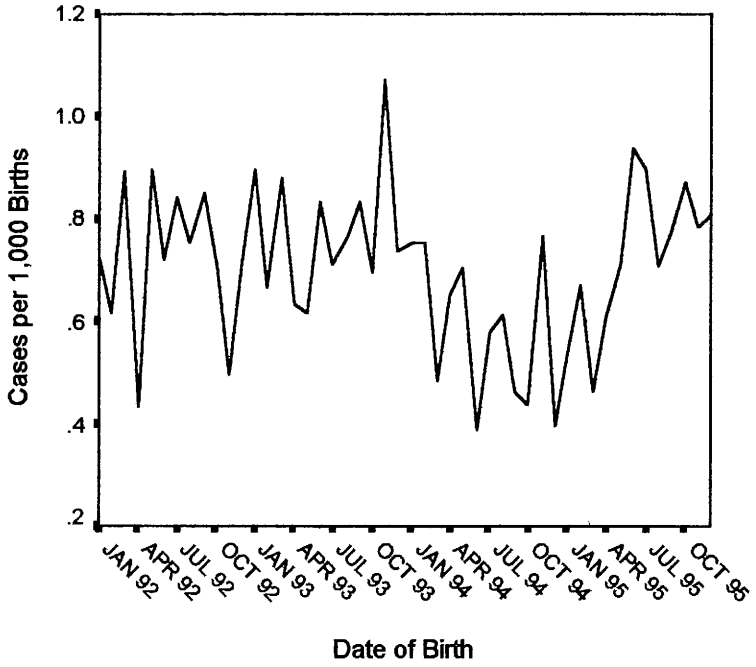

Figure 6. Plot of Rate of Congenital Hypothyroidism Cases Per 1,000 Births Against Month and Year of Birth.

Figure 6 indicates that when the number of hypothyroid cases per 1,000 births were plotted against the month and year of birth for the children born between 1992 and 1995, the relationship between the rate and month of delivery was not consistent from one year to the other. For example, even though the congenital hypothyroid rates were lowest in the month of April for the years 1992, 1993 and 1995. It was relatively higher during 1994.

Time series analysis was conducted to find out if the relationship between cases of

congenital hypothyroidism and the month of birth was significant. The results of this analysis indicated that there is no seasonality between month of birth and cases of congenital hypothyroidism. The results of the ARIMA analysis can be found in Appendix E. A spectral graph was produced to confirm the results of the ARIMA. The resulting graph is illustrated in figure 7.

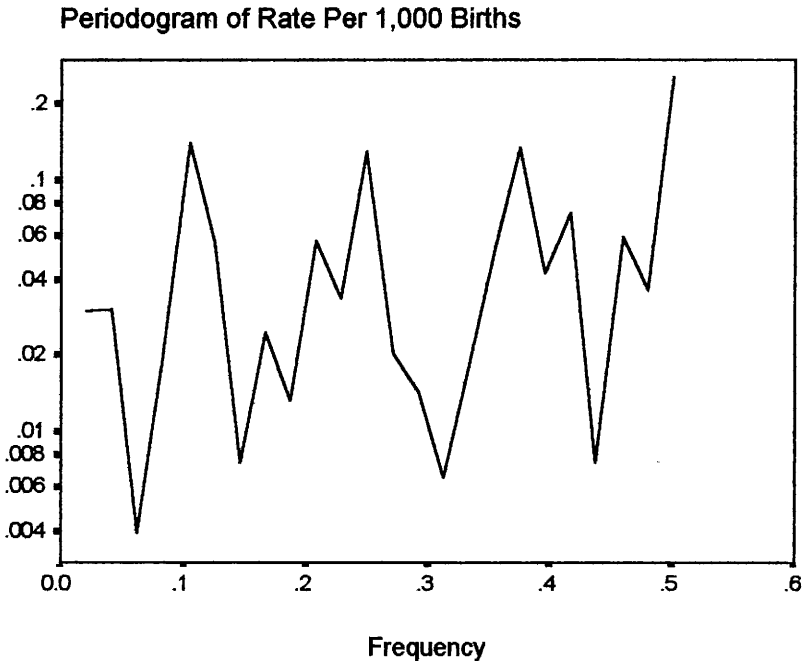

Figure 7. Plot of Spectral Analysis for the Effect of Month of Birth on Rate of Congenital Hypothyroidism Cases Per 1,000 Births.

The spectral analysis plot in Figure 7 did not show any consistent pattern. It can only be concluded that there was no seasonal effect established by the month of birth on congenital hypothyroidism.

CHAPTER V

DISCUSSION AND CONCLUSION

The rate of congenital hypothyroidism in Texas has more than doubled (2.1 times) from 1989 to 1995. Texas congenital hypothyroidism rates far surpassed rates in other states. The present study was conducted to investigate risk factors that may have lead to the increase in the cases of congenital hypothyroidism in Texas. Four risk factors were studied, the race/ethnicity of the mother, the gender of the infant, the maternal age, and seasonality of the disease.

Five hypotheses were formulated based on the results of research in the field. The first hypothesis stated that Hispanic mothers are more likely than Non-Hispanic mothers to give birth to infants with congenital hypothyroidism. The results of the OR analysis confirms this hypothesis. These results are in agreement with other research evidence. In California, the highest rate of congenital hypothyroidism was observed in Hispanics where the rate was estimated at 35.6 per 100,000 births (Lorey et al., 1992). Evidence from a similar study (Therrell et al., 1982) suggests that Hispanics have the highest incidence of hypothyroidism in Texas for almost a decade.

The second hypothesis stated that female infants are more likely than male infants to be born with congenital hypothyroidism. This hypothesis was not confirmed by either the odds ratio or the logistic regression results. The results of the OR analysis did not indicate the same results obtained in other studies which showed that females are more at

risk for congenital hypothyroidism than males (Brown et al., 1981; Therrell et al., 1982; Leroy et al., 1992; and Tsai et al., 1995).

The third hypothesis stated that infants born to mothers who are 35 years old and older are more likely to be born with congenital hypothyroidism. Although the results of the odds ratio did not show any significant relationship, the logistic regression seemed to indicate a relationship between advanced maternal age and congenital hypothyroidism. To the best knowledge of the researcher there were no other studies conducted to investigate the effect of maternal age on incidence of congenital hypothyroidism. However, studies that were conducted to investigate the effect of maternal age on other anomalies, such as Down's syndrome, found increased incidence of these anomalies in infants born to older mothers (California Birth Defects Monitoring Program, 1994).

A fourth research hypothesis stated that infants born to mothers who are younger than 18 years are more likely to be born with congenital hypothyroidism. This hypothesis was not confirmed. The OR of teenage mothers to give birth to infants with congenital hypothyroidism was less than 1. These results are not in agreement with a study that found infants born to teenage mothers to be at risk of gastroschisis (California Birth Defects Monitoring Program, 1994). The conflicting results may be due to the difference in the nature of congenital hypothyroidism and gastroschisis. The difference between the results of the two studies may be also due to the difference in the measurements used and/or the rate of occurrence of the two diseases.

Comparison between the potency of the three risk factors, race/ethnicity, gender, and maternal age indicated that race results in the highest incidence of congenital

hypothyroidism, followed by gender, followed by maternal age. These results are in general agreement with the research in this area. For in spite of the fact that none of the studies reported compared the effects of these three risk factors they tended to yield higher rates of congenital hypothyroidism when race/ethnicity was studied (up to 6 times in the study conducted by Tsai et al., 1995) than when gender was (up to 3 times in the study conducted by Brown et al., 1981).

The fifth research hypothesis stated that there may be a correlation between incidence of congenital hypothyroidism and the month of birth. This hypothesis was not confirmed.

The strong relationship of congenital hypothyroidism with Hispanic race/ethnicity may also explain the higher incidence of congenital hypothyroidism since 1992. Hispanic births have increased from 39.3 percent of the total births in 1992 to 42.4 percent of the total births in 1995.

This study further found that logistic regression did not work well with the large population (1.29 million) and its relatively small case size (806 cases). The classification table showed an extremely high (99.94) percent prediction, which was a direct result of the high number of live births and not a result of a strong relationship between the factors under study and congenital hypothyroidism. It is therefore recommended that further studies concentrate on statistical techniques such as odds ratio and chi-square.

Results of studies that researched the seasonality of congenital hypothyroidism were conflicting, suggesting a need for further investigation in this area.

The results of the present study leads to the following conclusions:

1. There is a need for careful postnatal screening of populations at risk of congenital hypothyroidism in Texas, namely Hispanics, female infants, and infants born to mothers 35 years and older.
2. There is a need for prenatal screening of populations that are highest at risk of congenital hypothyroidism , namely Hispanic mothers who are 35 years of age or older and expecting a female infant. The higher cost of prenatal screening would be offset by targeting fewer number of the population with the highest risk of the disease.
3. There is a need for educational programs specifically targeting the populations that are at risk of congenital hypothyroidism to increase their awareness of the risk involved and the need for pre- and post-natal screening. This educational programs could be incorporated in existing programs offered to mothers through family planning and genetic counseling.
4. Further research is needed to explore in depth the combined effects of several risk factors on incidence of congenital hypothyroidism.
5. Further studies are needed to investigate the effects of environmental factors on congenital hypothyroidism. These studies may explore regional as well as temporal environmental aspects such as air and water pollutants.

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APPENDIX A

Structure of the Newborn Screening Data File

Field	Field Name	Type	Width	Dec
1	SAMTEST	Character	1	Test result
2	TSHRSLTCOD	Character	3	TSH result code
3	T4RSLTCODE	Character	3	T4 result code
4	SAMSUBMID	Character	8	Submitter ID
5	SAMPHONE	Character	10	Telephone number
6	SAMZIPCODE	Character	9	Zip Code
7	SAMSTATE	Character	2	State
8	SAMCITY	Character	11	City
9	SAMSTREET	Character	15	Street
10	SAMMOTHERS	Character	9	Mother's social security number
11	SAMMOTHERA	Character	2	Mother's age
12	SAMMLNAME	Character	11	Mother's last name
13	SAMMFNAME	Character	8	Mother's first name
14	SAMREF_NO	Character	12	Reference number
15	SAMBIRTHWT	Numeric	5	Birth weight
16	SAMRACE	Character	1	Child's race
17	SAMSEX	Character	1	Child's gender
18	SAMBIRTHDT	Date	8	Child's birth date
19	SAMMEDICAI	Character	9	Child's Medicaid ID
20	SAMMEDELIG	Character	1	
21	SAMMEDREC	Character	10	Child's medical record number
22	SAMLNAME	Character	11	Child's last name
23	SAMFNAME	Character	8	Child's first name
24	SAMLABNO	Character	9	Lab number

APPENDIX B

Structure of the Clinical Data File

Field	Field Name	Type	Width	Dec
1	DIAGCODE	Character	2	Diagnosis code
2	LABNO	Character	9	Lab number
3	CASENO	Character	4	Case number
4	LNAME	Character	15	Child's last name
5	AKA	Character	15	Child's AKA
6	FNAME	Character	10	Child's last name
7	SEX	Character	1	Child's gender
8	RACE	Character	1	Child's race
9	DOB	Date	8	Child's date of birth
10	WHTINGRAMS	Character	4	Weight in grams
11	CITY	Character	15	City
12	COUNTY	Character	3	County
13	PHR	Character	2	Public health region
14	INITIALTST	Character	2	Initial test result
15	INITSTRECD	Date	8	Initial test date
16	AGESCREEN	Character	2	Age at screening
17	SECONDSCRN	Character	2	Second test result
18	SECSCRRECD	Date	8	Second test date
19	SECSCRNLAB	Character	9	Second screen lab number
20	DXDATE	Date	8	Diagnosis date
21	AGEDX	Numeric	3	Age at diagnosis
22	JULIANDX	Character	3	Julian date at diagnosis
23	TDHDX	Character	3	TDH diagnosis code
24	PHYSICIAN	Character	15	Physician name
25	CONSULTANT	Character	4	Consultant
26	CONFIRMTDH	Character	1	Confirmed by TDH
27	T4SCREEN	Character	5	T4 screen results
28	CUTOFFSCN	Character	5	Cutoff screen
29	T41	Character	5	First T4 level
30	CUTOFF1	Character	5	Cutoff for first T4
31	T42	Character	5	Second T4 level
32	CUTOFF2	Character	5	Cutoff for second T4
33	TSH1	Character	4	First TSH level
34	TSH2	Character	4	Second TSH level
35	SCREENCAH	Character	5	CAH screen
36	SCRNCUTOFF	Character	5	Screen cutoff
37	RETESTCAH	Character	5	First retest for CAH
38	RETESTCAH2	Character	5	Second retest for CAH
39	RETESTCUTO	Character	5	Retest cutoff
40	SERUMT3U	Character	5	Serum T3U level
41	SERUMT4	Character	5	Serum T4 level
42	SERUMTSH	Character	5	Serum TSH level
43	SERUMTBG	Character	5	Serum TBG level
44	OTHER	Character	40	Other

APPENDIX C

Structure of the Bureau of Vital Statistics Data File

Field	Field Name	Type	Width	Dec
1	FILE_NO	Character	6	File number
2	MOTHER_AGE	Character	2	Mother's age
3	CITY	Character	2	City
4	COUNTY	Character	3	County
5	ZIP	Character	5	Zip code
6	STATE	Character	2	State
7	MOM_RACE	Character	2	Mother's race
8	MOM_HISP	Character	1	Mother's Hispanic origin
9	MOM_ETH	Character	1	Mother's ethnicity
10	BIRTH_MO	Character	2	Birth month
11	BIRTH_DAY	Character	2	Birth day
12	BIRTH_YR	Character	2	Birth year
13	SEX	Character	1	Sex of child
14	WEIGHT	Character	2	Birth weight
15	DOB	Date	8	Date of birth

APPENDIX D

Structure of the Present Study Data File

Field	Field Name	Type	Width	Dec
1	FILEYEAR	Character	8	Birth year
2	FILE_NO	Character	6	File number
3	CASES	Character	1	Case (Y/N)
4	DIAG_CODE	Character	2	Diagnosis code
5	LAB_NO	Character	9	Lab number
6	CASE_NO	Character	4	Case number
7	AGE_DX	Numeric	3	Age at diagnosis
8	DX_DATE	Date	8	Diagnosis date
9	MOTHER_AGE	Numeric	2	Mother's age
10	CITY_NAME	Character	15	City name
11	CITY	Character	2	City
12	COUNTY	Character	3	County
13	CNTY	Character	3	County - 2
14	ZIP	Character	5	Zip code
15	STATE	Character	2	State
16	MOM_RACE	Character	2	Mom's race
17	RACE	Character	1	Mom's race - 2
18	MOM_HISP	Character	1	Mom's Hispanic ethnicity
19	MOM_ETH	Character	1	Mom's ethnicity
20	BIRTH_MO	Character	2	Birth month
21	BIRTH_DAY	Character	2	Birth day
22	BIRTH_YR	Character	2	Birth year
23	SEX	Character	1	Sex
24	WEIGHT_LBS	Numeric	2	Weight in pounds
25	WEIGHT_GMS	Numeric	4	Weight in grams
26	BIRTH_CITY	Character	2	Birth city
27	BIRTH_CNTY	Character	3	Birth county
28	BTH_CNTY	Character	3	Birth county - 2
29	DOB	Date	8	Date of birth

APPENDIX E

ARIMA

```
MODEL:  MOD_3

Model Description:

Variable:   RATE
Regressors: DOB

Non-seasonal differencing: 2
No seasonal component in model.

Parameters:
AR1       _________  < value originating from estimation >
AR2       _________  < value originating from estimation >
AR3       _________  < value originating from estimation >
AR4       _________  < value originating from estimation >
AR5       _________  < value originating from estimation >
AR6       _________  < value originating from estimation >
MA1       _________  < value originating from estimation >
MA2       _________  < value originating from estimation >
MA3       _________  < value originating from estimation >
MA4       _________  < value originating from estimation >
DOB       _________  < value originating from estimation >
CONSTANT  _________  < value originating from estimation >

95.00 percent confidence intervals will be generated.

Split group number: 1  Series length: 48
No missing data.
Melard's algorithm will be used for estimation.



Termination criteria:
Parameter epsilon: .001
Maximum Marquardt constant: 1.00E+09
SSQ Percentage: .001
Maximum number of iterations: 10

Initial values:

AR1      -1.13700
AR2      -1.08382
AR3       -.40108
AR4        .38063
AR5        .59857
AR6        .36412
MA1        .13524
MA2       -.30847
MA3        .12979
MA4        .17958
```

```
DOB         .00000
CONSTANT    .00025

Marquardt constant = .001
Adjusted sum of squares = 2.2715939

              Iteration History:

  Iteration    Adj. Sum of Squares     Marquardt Constant

          1            2.2528350               .001000
          2            2.0544354               .000100
          3            1.9936543               .100000
          4            1.7401476              1.000000
          5            1.7388933               .100000
          6            1.6899934              1.000000
          7            1.6847375             10.000000
          8            1.6812234              1.000000
          9            1.6644979               .100000


Conclusion of estimation phase.
Estimation terminated at iteration number 10 because:
   Maximum number of iterations was exceeded.

FINAL PARAMETERS:

Number of residuals  46
Standard error       .19702293
Log likelihood       11.051265
AIC                  1.8974697
SBC                  23.841166

            Analysis of Variance:

               DF  Adj. Sum of Squares     Residual Variance

Residuals      34            1.6615347            .03881803

           Variables in the Model:

                        B           SEB       T-RATIO   APPROX. PROB.

AR1          -1.12282783     .67534068    -1.6626095       .10558398
AR2           -.91557909    1.18891705     -.7700950       .44656155
AR3           -.52022399    1.52817559     -.3404216       .73563349
AR4            .33049302    1.49889929      .2204905       .82680786
AR5            .64121636     .98173388      .6531468       .51805432
AR6            .46531222     .40724130     1.1425958       .26118888
MA1            .36377013   18.46790509      .0196974       .98439989
MA2           -.36776247   15.99967535     -.0229856       .98179612
MA3            .37044154   18.22943332      .0203211       .98390604
MA4            .62795894   12.13763377      .0517365       .95904141
DOB            .00000000     .00000000     .              .
CONSTANT       .00052229     .00277220     .1884010       .85168231

Covariance Matrix:
```

	AR1	AR2	AR3	AR4	AR5	AR6
AR1	.45609	.77411	.99325	.96425	.59811	.24034
AR2	.77411	1.41352	1.80275	1.76692	1.14026	.45134
AR3	.99325	1.80275	2.33532	2.28496	1.47529	.59725
AR4	.96425	1.76692	2.28496	2.24670	1.45425	.58527
AR5	.59811	1.14026	1.47529	1.45425	.96380	.38771
AR6	.24034	.45134	.59725	.58527	.38771	.16585
MA1	11.13765	20.71832	26.37115	25.99878	16.88706	6.62691
MA2	8.40543	15.56552	20.15427	19.28803	12.52639	5.22275
MA3	10.58237	19.74790	25.03053	24.89682	16.18209	6.23926
MA4	5.86937	11.17969	13.97153	14.18837	9.29443	3.43171

	MA1	MA2	MA3	MA4
AR1	11.13765	8.40543	10.58237	5.86937
AR2	20.71832	15.56552	19.74790	11.17969
AR3	26.37115	20.15427	25.03053	13.97153
AR4	25.99878	19.28803	24.89682	14.18837
AR5	16.88706	12.52639	16.18209	9.29443
AR6	6.62691	5.22275	6.23926	3.43171
MA1	341.06352	242.12312	330.89049	195.00867
MA2	242.12312	255.98961	204.19374	83.98036
MA3	330.89049	204.19374	332.31224	209.18498
MA4	195.00867	83.98036	209.18498	147.32215

Correlation Matrix:

	AR1	AR2	AR3	AR4	AR5	AR6
AR1	1.0000000	.9641076	.9624122	.9525613	.9021189	.8738680
AR2	.9641076	1.0000000	.9922284	.9915009	.9769171	.9321755
AR3	.9624122	.9922284	1.0000000	.9975449	.9833527	.9596887
AR4	.9525613	.9915009	.9975449	1.0000000	.9882606	.9588012
AR5	.9021189	.9769171	.9833527	.9882606	1.0000000	.9697496
AR6	.8738680	.9321755	.9596887	.9588012	.9697496	1.0000000
MA1	.8930031	.9435946	.9344115	.9392102	.9314135	

```
.8811328
MA2        .7779038     .8182783     .8242952     .8042745     .7974822
.8015599
MA3        .8595808     .9111632     .8985116     .9111677     .9042067
.8404429
MA4        .7160352     .7747191     .7532456     .7798770     .7800008
.6942631


                MA1          MA2          MA3          MA4

AR1         .8930031     .7779038     .8595808     .7160352
AR2         .9435946     .8182783     .9111632     .7747191
AR3         .9344115     .8242952     .8985116     .7532456
AR4         .9392102     .8042745     .9111677     .7798770
AR5         .9314135     .7974822     .9042067     .7800008
AR6         .8811328     .8015599     .8404429     .6942631
MA1        1.0000000     .8194217     .9828641     .8699660
MA2         .8194217    1.0000000     .7000968     .4324466
MA3         .9828641     .7000968    1.0000000     .9454168
MA4         .8699660     .4324466     .9454168    1.0000000

Regressor Covariance Matrix:

                   DOB      CONSTANT

DOB          .00000000    .00000000
CONSTANT     .00000000    .00000769

Regressor Correlation Matrix:

                   DOB      CONSTANT

DOB         1.0000000     .0040131
CONSTANT     .0040131    1.0000000



>Warning # 16567.  Command name: ARIMA
>Our tests have determined that the estimated model lies close to the
>boundary of the invertibility region.  Although the moving average
>parameters are probably correctly estimated, their standard errors and
>covariances should be considered suspect.


The following new variables are being created:

  Name         Label

  FIT_1        Fit for RATE from ARIMA, MOD_3 CON
  ERR_1        Error for RATE from ARIMA, MOD_3 CON
  LCL_1        95% LCL for RATE from ARIMA, MOD_3 CON
  UCL_1        95% UCL for RATE from ARIMA, MOD_3 CON
  SEP_1        SE of fit for RATE from ARIMA, MOD_3 CON
```

APPENDIX F

Logistic Regression

```
      Total number of cases:      1282329 (Unweighted)
      Number of selected cases:   1282329
      Number of unselected cases: 0

      Number of selected cases:                  1282329
      Number rejected because of missing data:   0
      Number of cases included in the analysis:  1282329


Dependent Variable Encoding:

Original        Internal
Value           Value
0               0
1               1


                          Parameter
              Value   Freq  Coding
                              (1)     (2)
HISP_RAC
                  0 756738  1.000    .000
                  1 525588   .000   1.000
                        3   .000    .000
MAGE_M34
                  01170043  1.000    .000
                  1 112083   .000   1.000
                       203   .000    .000
SEX
                  0 655317  1.000
                  1 627012   .000


Dependent Variable..   CASES

Beginning Block Number  0.  Initial Log Likelihood Function

-2 Log Likelihood   13495.326

* Constant is included in the model.


Beginning Block Number  1.  Method: Enter

>Error # 18085
>The object(s) listed above must be removed since they contain missing
(or
>out of range) values in all sets.
```

>This command not executed.

Variable(s) Entered on Step Number
1.. MAGE_M34
HISP_RAC HISP_RACE
SEX

Estimation terminated at iteration number 9 because
Log Likelihood decreased by less than .01 percent.

Iteration History:

Iteration	Log Likelihood	Constant	MAGE_M34(1)	MAGE_M34(2)	HISP_RAC(1)
1	-164708.89	2.356382	-1.0687536	-1.0684257	-3.285371
2	-57441.25	4.091468	-2.1250112	-2.1239494	-5.094476
3	-23145.06	5.995198	-3.1549508	-3.1519097	-6.998043
4	-11493.95	7.941884	-4.1328512	-4.1245719	-8.945280
5	-7690.45	9.840129	-5.0388813	-5.0174537	-10.846336
6	-6638.47	11.595389	-5.7957722	-5.7455228	-12.607985
7	-6451.05	13.075066	-6.2752785	-6.1799621	-14.097776
8	-6439.15	14.235085	-6.4347474	-6.3064776	-15.265423
9	-6439.07	15.249770	-6.4490794	-6.3152184	-16.281493

HISP_RAC(2)	SEX(1)
-3.285002	-.00019577
-5.093283	-.00063124
-6.994628	-.00179913
-8.935994	-.00488346
-10.822344	-.01261635
-12.551919	-.02953884
-13.991958	-.05598165
-15.123351	-.07550597
-16.133147	-.07895023

-2 Log Likelihood	12878.143
Goodness of Fit	1280937.97
Cox & Snell - R^2	.000
Nagelkerke - R^2	.000

	Chi-Square	df	Significance
Model	617.183	5	.0000

Block	617.183	5	.0000
Step	617.183	5	.0000

---------- Hosmer and Lemeshow Goodness-of-Fit Test----------

	CASES = 0		CASES = 1		
Group	Observed	Expected	Observed	Expected	Total
1	.000	.000	.000	.000	.000
2	.000	.000	.000	Nan	.000
3	.000	.000	.000	Nan	.000
4	.000	.000	.000	.000	.000
5	.000	.000	.000-1.53353+121		.000
6	.000	.000	.000	.000	.000
7	.000	.000	.000	.000	.000
8	.000	.000	.000	.000	.000
9	.000	.000	.000	.000	.000

	Chi-Square	df	Significance
Goodness-of-fit test	Nan	7	1.000

Classification Table for CASES
The Cut Value is .50

			Predicted 0		Predicted 1	Percent Correct
			0	I	1	
Observed						
0	0	I	1281523	I	0	I 100.00%
1	1	I	803	I	3	I .37%
					Overall	99.94%

------------------- Variables in the Equation -------------------

Variable	B	S.E.	Wald	df	Sig	R
MAGE_M34			1552.905	2	.0000	.3388
MAGE_M34(1)	-6.4491	.1638	1549.693	1	.0000	-.3386
MAGE_M34(2)	-6.3152	.1978	1019.415	1	.0000	-.2746
HISP_RAC			4.3112	2	.1158	.0048
HISP_RAC(1)	-16.2815	81.3518	.0401	1	.8414	.0000
HISP_RAC(2)	-16.1331	81.3518	.0393	1	.8428	.0000
SEX(1)	-.0790	.0713	1.2275	1	.2679	.0000
Constant	15.2498	81.3520	.0351	1	.8513	

		95% CI for Exp(B)	
Variable	Exp(B)	Lower	Upper
MAGE_M34(1)	.0016	.0011	.0022
MAGE_M34(2)	.0018	.0012	.0027
HISP_RAC(1)	.0000	.0000	1.499E+62

HISP_RAC(2)	.0000	.0000	1.739E+62
SEX(1)	.9241	.8036	1.0626

Correlation Matrix:

	Constant	MAGE_M34(1)	MAGE_M34(2)	HISP_RAC(1)	HISP_RAC(2)
Constant	1.00000	-.00201	-.00157	-1.00000	-1.00000
MAGE_M34(1)	-.00201	1.00000	.78272	.00011	.00011
MAGE_M34(2)	-.00157	.78272	1.00000	-.00002	.00002
HISP_RAC(1)	-1.00000	.00011	-.00002	1.00000	1.00000
HISP_RAC(2)	-1.00000	.00011	.00002	1.00000	1.00000
SEX(1)	.00002	-.00963	-.00763	-.00043	-.00043

	SEX(1)
Constant	.00002
MAGE_M34(1)	-.00963
MAGE_M34(2)	-.00763
HISP_RAC(1)	-.00043
HISP_RAC(2)	-.00043
SEX(1)	1.00000

Observed Groups and Predicted Probabilities

```
 1600000 +                                                             +
         I                                                             I
         I                                                             I
F        I0                                                            I
R1200000 +0                                                            +
E        I0                                                            I
Q        I0                                                            I
U        I0                                                            I
E 800000 +0                                                            +
N        I0                                                            I
C        I0                                                            I
Y        I0                                                            I
  400000 +0                                                            +
         I0                                                            I
         I0                                                            I
         I0                                                            I
Predicted ---------------+---------------+---------------+---------------
  Prob:   0              .25             .5              .75             1
  Group:  00000000000000000000000000000011111111111111111111111111111111
```

Predicted Probability is of Membership for 1
The Cut Value is .50
Symbols: 0 - 0
1 - 1
Each Symbol Represents 100000 Cases.