THE RELATIONSHIP BETWEEN RECURRENT PLACENTAL PATHOLOGY AND RECURRENT POOR PREGNANCY OUTCOME

by
Cara Krulewitch

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APPROVAL SHEET

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Name of Candidate: Cara Krulewitch
Doctor of Philosophy, 1992

Thesis and Abstract Approved: [redacted]
Dr. Helen Kohler
Associate Professor
School of Nursing

Data Approved 5-4-92

CURRICULUM VITAE

NAME: Cara Joy Krulewitch

PERMANENT ADDRESS: [redacted]
Silver Spring, MD 20906

DEGREE AND DATE TO BE CONFERRED: Ph.D, 1992

BIRTHDATE: August 20, [redacted]

PLACE OF BIRTH: Chicago, Illinois

SECONDARY EDUCATION: New Trier West High School
Northfield, Illinois
1972

COLLEGIATE INSTITUTIONS ATTENDED:	DATES	DEGREE	DATE
University of Maryland at Baltimore Baltimore, Maryland	1988-92	Ph.D	Jun 1992
University of Illinois at Chicago Health Sciences Center Chicago, Illinois	1982-1984	M.S. Nursing	Aug 1984
University of Illinois at Chicago Health Sciences Center Chicago, Illinois	1981-1982	BSN Nursing	Aug 1981
Evanston Hospital School of Nursing Evanston, Illinois	1976-78	R.N. Diploma	Dec 1978
University of Illinois Champaign, Illinois	1972-76	B.S. Biology	June 1976

PROFESSIONAL PUBLICATIONS

Krulewtich, C. (1990). The Obstetrical Technician: A proposal to curb costs and alleviate stafing shortages in the nineties. *Proceedings the West Virginia Nurses' Association 1990 Research Symposium*, p.403-405.

PROFESSIONAL POSITIONS HELD

1991-PRESENT	Statistician (Demography) US Dept of HHS/PHS/CDC National Center for Health Statistics Hyattsville, MD
1990-PRESENT	Adjunct Instructor Columbia Union College Takoma Park, MD
1988-PRESENT	Registry RN Med-Force Inc Arlington, VA
1990-1991	Epidemiological Research Assistant US Dept of HHS/PHS/NIH National Institute of Child Health and Development Division of Prevention Research Bethesda, MD
Summer, 1990	NIH Summer Intramural Fellow National Institute of Child Health and Development Divsion Prevention Research Bethesda, MD
1988-1989	Clinical Research Associate Ganciclovir Study Center Biospherics Inc Laurel, MD
1987-1988	Instructor West Virginia University School of Nursing Morgantown, WV 26506
1986-1987	Assistant Clinical Director Maternal Child Health St. Francis Cabrini Hospital Chicago, Illinois 60611
1985-1986	Clinical Instructor St. Anne's Hospital School of Nursing Chicago, Illinois (Closed)
1981-1987	Clinical Nurse I University of Illinois Hospital Labor and Delivery Chicago, Illinois
1979-1981	Staff Nurse II Mercy Center Services Obstetric Unit Aurora, Illinois

ABSTRACT

Title of Dissertation: The Relationship Between Recurrent Placental Pathology and Recurrent Poor Pregnancy Outcome

Cara Joy Krulewitch, Doctor of Philosophy, 1992

Dissertation Directed by: Helen Kohler PhD RN, Associate Professor, School of Nursing; Frederick Suppe PhD, Professor, Schools of Nursing and Philosophy

Poor pregnancy outcome (PPO) is a top agenda item health and political arenas. Most prominent PPOs are low birth weight (LBW) and preterm delivery (PTD). Effective interventions to maximize pregnancy outcome will diminish their negative impact. The placenta is a diary of the infant's prenatal experiences. Changes in the placenta provide clues to the uterine environment during the pregnancy. Each placental pathology represents a different insult, including severity, duration and type.

The Collaborative Perinatal Project of the National Institute of Neurological and Communicative Disorders and Stroke was a longitudinal study of obstetric outcomes in women. The study was conducted from 1959 to 1966 and contains information for 53,518 pregnancies from 10,699 women, including examination of 31,494 placentas (59%). A nested case control study was conducted on this dataset. A sample of 7653 women of black and white races who had two pregnancies during the study period were examined to determine if a relationship existed between the recurrence of PPO and a recurrence of placental pathology.

Analysis used several statistical techniques including linear logistic regression and an experimental causal modelling program, TETRAD II. TETRAD II analysis indicated a relationship between marital status and educational incongruity and PPO along with a relationship between

recurrent chronic hypoxia and LBW and recurrent infection and PTD. This was the first time TETRAD II was used on real data.

Linear logistic regression confirmed these relationships. The risk of repeating LBW or PTD was 1.6 times greater if the woman was unmarried was 10% greater for each year of greater educational incongruity between the mother and father of the baby. Cigarette smoking in both pregnancies represented 2.1 (1.5-2.9) times greater risk of repeating LBW. There was a 4.2 (1.4-12) times greater risk of repeating PTD if placental chorionic villitis repeated, remaining significant after adjustment for cigarette smoking and social class. There was a 6.5 (1.4-31) times greater risk of repeating LBW if decidual necrosis repeated, remaining significant after adjustment for social class, but becoming marginal when cigarette smoking was included. The main implication of these findings involves the area of preconceptual care for women. This includes preconceptual treatment of infection and nursing support to women at high risk for repeating a PPO.

but those who hope in the Lord
will renew their strength.
They will soar on wings like
eagles;
They will run and not grow weary
They will walk and not be faint
(Isaiah 40:31, NIV)

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The rose is one of the most beautiful and delicate of God's creations.This beauty occurs in nature when the bush is untouched, but for the plant to produce the greatest number and the most beautiful blooms it requires the right amount of food, water, nurturing an pruning. The development of a scholar is quite similar. She or he will develop when left to their own, if the potential is there, but it takes nurturing, feeding and pruning for the full potential to be realized.

I thank my committee for providing me with those crucial needs. All of you added complementary parts to help draw out my potential.

Dr. Helen Kohler is the true gardener, her nurturing has been extra special, and has developed into a special friendship that I will cherish forever. She was there for countless phone calls at 11pm, reinforcing my abilities and being a sounding board for my new ideas. I will always remember the many meals at the Penn restaurant where we talked through the tough parts and shared good times. She is subtle in her guidance and has the ability to allow you to grow at your own pace, pruning as necessary and nurturing when needed.

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Dr. Fred Suppe added a philosophical perspective which led to the use of the TETRAD II program. It broadened the base of my research and also my knowledge. In addition to learning the program, I also learned how to overcome many obstacles to telecommunication and how to interface an IBM machine with a UNIX machine. Fred also has a unique calming influence, I guess it may relate to his enjoyment of my baking, which is an outlet for me.

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I am grateful to the creators of TETRAD II, Drs. Richard Scheines, Clark Glymour and Peter Spirtes of Carnegie-Mellon University. I offer a special thanks to Dr. Richard Scheines for devoting a full day and one-half to teaching me TETRAD II and helping me to develop the causal approach to my thesis. In addition, he gave me help on the phone when he was involved with other projects and offered all the support I needed to access the program.

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The development of any manuscript requires a good secretary or a great word processor and lots of time. I had the word processor but not the time. I want to thank Dottie Day for her help in preparing my tables and my TETRAD II models. The models were a definite challenge and took hours of work and I am pleased with the results.

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Lastly, a note to my dad: Pa, you finally have a doctor in the family!

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CHAPTER I
INTRODUCTION

INTRODUCTION

Pregnancy outcome refers to the state of health of the woman from conception to six weeks after delivery and the state of health of the infant to one year of life. If the state of health of the woman or infant becomes compromised during this time, then a poor pregnancy outcome (PPO) exists. Examples of PPO include, death of the infant (in utero or after delivery) or the woman, pregnancy induced hypertension (PIH, also referred to as pre-eclampsia or toxemia), other obstetric complications such as premature labor or hemorrhage, preterm birth or intrauterine growth retardation in the infant. The ultimate desired outcome of all pregnancies is a healthy woman and newborn infant. Failure to achieve this outcome can impact on the future of an entire society.

> *Each day in America 3548 infants are born to mothers who received less than adequate prenatal care; 719 infants are born low birthweight; and 105 infants die. . .A child doesn't have to be in a wheelchair to have a birth defect. Limiting a child's full potential even by a small amount, is going to have an effect on society. (Chiles, 1990).*

Today, in spite of its advanced medical technology, the United States ranks high in its infant mortality rate compared to other developed countries with a rate of 9.4 deaths per 1000 as of 1990 (NCHS, 1990). Most alarming about this rate is that progress in reducing the rate of infant mortality stalled in the 1980's (Chiles, 1990). This was compounded by the gap between white and black infant death rates, which widened. Currently

black infants have more than twice the chance to die than white infants (Chiles, 1990). Progress in lowering the percentage of low birthweight infants has diminished. The additional effects of poverty, lack of access to care, exposure to tobacco, alcohol and illicit substances have added additional risks to pregnant women for poor outcomes (Chiles, 1990).

The association of attributable risk of many factors to poor pregnancy outcome have been examined. The ability to determine causality is problematic since there is an interdependence between the fetus and the woman (Yerushalmy, 1956). Yankauer (1990) notes that questions asked over 20 years ago concerning factors that affect infant and perinatal mortality have remained unanswered. These questions include the extent and through what mediating channels the effect of both social and biologic factors operate on pregnancy outcome.

Identification of biologic factors in the obstetric history which may result in a poor pregnancy outcome may provide one set of predictors which will facilitate identification of a high risk situation which requires closer surveillance or intervention. The ultimate goal would be to use these predictors to provide closer surveillance or intervention to those who need it. Achievement of this goal would be a profound step in helping women attain optimum health. Research which identifies predictors of poor pregnancy outcomes will provide information that allows the nurse and other health professionals to identify those who most need surveillance, intervention or follow-up.

The participation of the nurse in detection of risks and causes of poor health outcomes can be traced back to Florence Nightingale who gathered detailed information concerning diseases and death rates. Caplan

(1974) notes that nurses have the most regular, frequent and intimate physical contact with patients and families which places them in an ideal position to serve as a bridge between the patient and the health care system. This is accomplished by mobilizing the environment:

> *Mobilizing the environment... is essentially the province of the nurse... In order to act as the bridge and the mediator between the patient and the specialists, the nurse must be regarded by each as being the same status level at their own group...(Caplan, 1974, p. 239)*

Poor pregnancy outcome (PPO) is one of the top agenda items in both the health and political arenas. The most prominent PPOs are low birth weight and preterm birth. These problems have placed a strain on the economy in high hospital costs, educational costs, and supportive care costs. Effective interventions directed at maximized pregnancy outcome will have a major impact on society from an economic standpoint as well.

One approach to begin answering some of these questions would be to identify a biological relationship between past pregnancy outcomes and the outcome of the current pregnancy. The placenta is a diary of the infant's prenatal experiences. Changes in the placenta provide clues to the environment that existed during the pregnancy. Each alteration from the norm such as cell changes, necrosis, invasion of macrophages or thrombosis represents a different insult that occurred. The area that is affected such as the membranes, which are far from the fetus and close to the mother, or the fetal umbilical cord which is close to the fetus, indicate the severity of the insult and provide information as to whether the event was acute or chronic. In addition, different changes occur if the insult

was infectious in nature as opposed to immunologic or even of unknown origin.

The relationship between placental development and pregnancy outcome has been identified by researchers (Andres, et al, 1990, Naeye, 1989, Emig, et al, 1961, Tenney and Parker, 1940, DeLee, 1917). In spite of this relationship, Altshuler (1984) notes that *...there has been relatively little investigation of placentally mediated fetal and perinatal afflictions...(p.4).* Even less attention has focused on the association between recurrent placental pathology and recurrent poor pregnancy outcome. One method to identify a biological relationship between past pregnancy outcomes and the outcome of the current pregnancy would be to examine the relationship between placental pathology and recurrent poor pregnancy outcome after controlling or eliminating the most commonly implicated factors or confounders. A study designed to explore this relationship would provide information that would add to the body of knowledge of recurrent poor pregnancy outcome.

BACKGROUND OF THE PROBLEM

Pregnancy outcome has been a topic of study for centuries. One of the earliest indicator of PPO was mortality. Edmonds (1835) identifies the infant mortality rate (birth to 2 years) for London, England in the 1730's as 60.3%. Abt (1923) reported the rate of infant mortality for Europe in the 1700's and 1800's as "extremely high". In 1914 infant mortality was identified as a subject of "profound social importance" (Kessel, 1986).

At the beginning of the century, the infant mortality rate in the United States was over 100/1000 live births. Included in the infant

mortality rate were infants who were born before term. In 1919 Ylppo introduced the concept of prematurity, proposing that infants with a birth weight of under 2500 grams were premature. In the 1930's the infant mortality rate had reduced to approximately 31/1000 live births. Yerushalmy (1939) attributed the majority of this decrease to improved child care and sanitation conditions. The definition of prematurity proposed by Ylppo was adopted by the American Academy of Pediatrics in the 1930's and the World Health Organization (WHO) in the 1940's.

In the 1930's investigations focused on the causes of infant mortality. Researchers such as Gardiner (1939), Yerushalmy (1938) and Breese (1939) began to trace the nature of the problem and begin to identify factors which related to infant mortality. These researchers investigated the effect of maternal age and parity on infant mortality. They noted that there was a curvelinear pattern with women of high and low ages experiencing higher infant mortality than women of ages 20-40. A similar pattern was noted for women of parity one and of parity greater than eight. Investigations involving the age of the father produced similar results.

In the 1950's it was noted that not all infants who weighed less than 2500 grams were born before term (measured as less than 9 months gestation at that time) and a new concept, "low birth weight" was proposed. This terminology was adopted by WHO in 1961. In the 1960's the issue of gestational age was promoted as the WHO changed their definition of "prematurity" to low birth weight. In 1967, Yerushalmy proposed that birth weight be evaluated in relation to gestational age.

Other factors were added from the 1940's through the 1970's. These

factors included social class, education, living conditions, migration patterns of the family, medical history, marital status, maternal size, alcohol and drug use, interval between births, past obstetric history and woman's parents education and occupation (Anderson, et al, 1939, Feldstein, 1965). These factors and concepts are still the focus of present research (Papiernick, 1984, Wu Wen, 1990).

The repetition of PPO has been noted as early as the 1920's (Young, 1927). He identified a cycle which included stillbirth, low birthweight and toxemia. Many other researchers noted that PPO's have a repetitive nature (Howell and Eby, 1920, Eastman, 1944, McDonald, 1959, Warburton and Fraser, 1964, Funderburk, et al, 1976, Oats and Beischer, 1979, Harger, et al, 1983, Sutherland and Fischer, 1982, Khoury, et al, 1989, Verp, 1989). In one of the first prospective studies of its kind, Yerushalmy (1956) verified the strong repetitive character of PPO that had been identified by retrospective studies. In particular, he noted the repetition of fetal and infant deaths. He also noted that the stage of fetal or infant death (early in pregnancy, late in pregnancy, after birth) was repeated from the previous pregnancy. Yerushalmy identified three principal factors which influence the outcome of pregnancy: obstetric factors, external environmental factors and biologic factors. Biologic factors include the physiologic ability of the woman's body to support normal placental development.

Curiosity with the placenta and its relationship to pregnancy outcome has existed for over a century. Kobak (1930) reports studies on this topic from the 1800's. Talbot (1921) posed the question: *Is there any relation between some of the abnormalities of the placenta and the*

clinical events of the patient's pregnancy? (p.552). Early researchers evaluated the placenta and umbilical cord for inflammation and infiltration of leukocytes, and the relationship to infection (Slemons, 1916, 1922, Creadick, 1920, Brown, 1926, Siddall, 1928, Wohlwill and Bock, 1929, Kobak, 1930, Kuckens, 1938). Others investigated topics such as the composition of the placenta (Tenney, 1930), the pathology of the placenta (Strachan, 1926) and the relationship of placenta abnormalities to toxemia (Young, 1921, Tenney and Parker, 1940). These studies also discussed the relationship of these findings to pregnancy outcome.

As sophistication in analytic procedures increased, studies focused on histology and morphology of the placenta (Burstein, 1957, McKay et al, 1958, Blanc, 1959, Fox, 1968, Huber et al, 1961), and the relationship between placental insufficiency and poor outcome (Rumboltz, et al, 1961, Gruenwald, 1963). Introduction of serial measurements of estriols, placental alkaline phosphatase and human placental lactogen stimulated research into the association of abnormalities in these measurements and placental insufficiency (Laga, 1972).

During this time, histologic findings in the placenta gained greater attention. One finding of interest was a nonspecific inflammation of the chorionic villi (villitis) (Gruenwald, 1963, Altshuler, 1973, Russell, 1979). The etiology of this finding could not be determined (Russell, 1979, Sander, 1980, Altshuler, 1982, Mortimer, 1985). Case reports of villitis repeating in subsequent pregnancies began to be reported in the literature (Dollmann and Schmitz-Moormann, 1972, Altshuler and Russell, 1975, Russell, 1980). Redline and Abramowsky (1985) conducted a case control study which confirmed these observations, noting that although

there was variation from patient to patient, there was considerable similarity in the same patient from pregnancy to pregnancy. Sander and Stevens (1984) evaluated another placental finding, hemorrhagic endovasculitis (HEV), an inflammation of the blood vessels in the placenta. They noted that in a case control study that 48% of second pregnancies with HEV also had HEV in the first pregnancy, compared to a rate of 19.4% in the general population.

Naeye (1989) posed the question of the relationship between uteroplacental blood flow and premature birth and noted that there was a recurrence in placental pathology, indicative of diminished uteroplacental blood flow, with recurrence in poor pregnancy outcome. Andres, et al (1990) noted that maternal floor infarction of the placenta was related to poor pregnancy outcome and that 12.2% of those women who experienced this problem had experienced the same problem in previous pregnancies. These findings focus interest on the question of the recurrence of the same placental pathology when there is a recurrence of poor pregnancy outcome.

PURPOSE OF THE STUDY

The purpose of this study is to determine if the same placental pathology is observed in both cases when poor outcome occurs in both cases.

STATEMENT OF THE PROBLEM

Obstetric history is one measure of a woman's reproductive performance. Factors of poor obstetric history include: miscarriage, perinatal death, neurologically damaged neonates, low birth weight infant, preterm birth, multiple birth, congenital malformation, pregnancy induced hypertension, or antepartum hemorrhage (Newcombe, 1979, Herman, 1987).

There have been few research studies to investigate the relationship between recurrent placental pathology and recurrent poor pregnancy outcome. At present we do not know whether recurrent placental pathology is a predictor of pregnancy outcome. Also, if recurrent pathology were present, to what extent does the same pathophysiological process exist in both pregnancies.

These questions suggest three questions that, when asked consecutively, will create a group which has minimal confounders:

1. What social, demographic, medical, past obstetric factors represent a significant risk of repeating a poor pregnancy outcome?
2. When there is a recurrence of placental pathology, is there a significant risk of repeating a poor pregnancy outcome?
3. In the group of repeated poor pregnancies in, controlling for other risk factors, is there a recurrence of abnormal placental pathology?

THE THEORETICAL FRAMEWORK

The review of the literature on pregnancy outcome addresses two major categories: ***the maternal component*** and ***conceptus***. These categories portray the interrelationship between the woman and her external environment, and the developing infant and the placenta.

The first category, ***the maternal component***, is comprised of three subgroups: *biologic factors, external environmental factors* and *obstetric factors*. These subgroups were identified by Yerushalmy (1956) as he conducted the first prospective study of pregnancy outcome. The factors which he identified supported previous retrospective studies. The second category is ***the conceptus***. The *conceptus* is divided into the subgroups of *placental development* and *fetal growth*. Kretchmer, et al (1989) defines

growth as *an accretion of materials brought together in a synergism involving anabolism and catabolism...growth involves an increase in cell size and number and an increase in complexity (p. 169).* Placental development and fetal growth although independent, are interrelated. Kretchmer, et al (1989) note that the placenta is not a passive organ but works actively to provide nutrients and synthesize hormones and other proteins, for the growth of the fetus. The fetus in turn produces hormones which promote the reliable functioning of the placenta (Longo, 1984).

Pregnancy outcome includes all events that have occurred throughout the pregnancy. *Poor pregnancy outcomes* occur when the condition of the infant, the woman, or both is compromised. One subgroup of PPO is *repeated poor pregnancy outcome* (RPPO). This is defined as the group of women who experience PPO in more than one pregnancy.

The response of the maternal component to biologic, external environmental and medical factors impacts on the ability of the conceptus to develop normally. Development of the conceptus is dependent on both the development of the placenta and the growth of the fetus. There is an interrelationship between the maternal component and the conceptus. The result of this interrelationship is reflected in pregnancy outcome. This model is depicted in Figure 1.

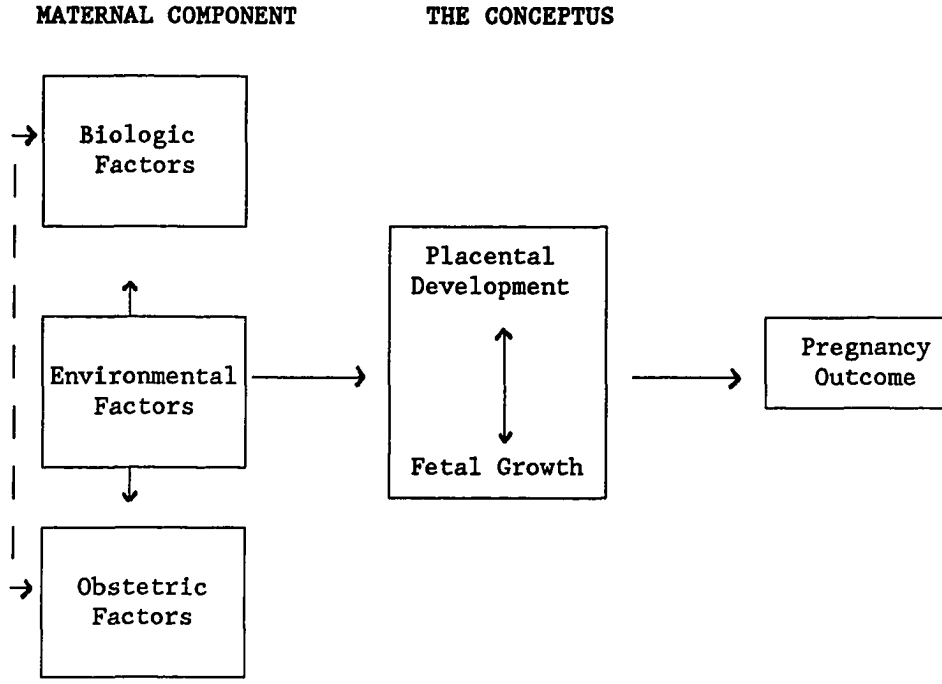


Figure 1: Model of Pregnancy Outcome

DEFINITIONS FOR THE CURRENT STUDY

The Maternal Component: All effects on pregnancy outcome which are experienced by the woman. This category is divided into three subgroups.

Biologic Factors: Medical/physical conditions which are not related to pregnancy but have been identified as having an effect on pregnancy outcome and that were present prior to conception: hypertension, cardiac disease, diabetes (except gestational), musculoskeletal disease, infection, congenital anomalies (of the woman). Biologic factors also include the physiological makeup of the woman such as her age, height and prepregnancy weight. Development of the placenta is dependent on the

physiologic response of the woman to the pregnancy and her body's ability to maintain homeostasis between the changes which occur due to the pregnancy and the external environment (Kretchmer et al, 1989).

External Environmental Factors: External environmental effects which have been identified in the literature to be associated with pregnancy outcome: socioeconomic status (measured by income, housing density, the woman's education, the father of the baby's education and the woman's father's education), race or ethnic background, substance abuse, social support, psychological disturbances, and mental retardation.

Obstetric Factors: Factors which are directly related to the current pregnancy. Current gravidity and parity, interpregnancy interval, deformities of the reproductive tract, medical conditions caused by pregnancy (such as: PIH or gestational diabetes), abnormal blood chemistries, anemia, premature labor or delivery, abnormal amounts of amniotic fluid and multiple gestation. Factors which have occurred in any previous pregnancies are also included in this subgroup. These are factors include low birthweight infants, growth retarded infants, stillbirth or miscarriage, induced abortion, preterm labor, preterm infant, abnormal amounts of amniotic fluid or abnormal blood chemistry and prior placental pathology.

The Conceptus: All effects on pregnancy outcome which are experienced by the conceptus (fetus and placenta).

Placental development: Factors which reflect development of the placenta, such as weight, presence of calcification, condition at delivery

and histology and morphology. Placental abnormalities which are noted: abruption, placenta previa and abnormal histology or morphology. Types of abnormal histology and morphology include inflammation or infarction in differing parts of the placenta (membranes, villi, decidua), placental vessels or umbilical cord and necrosis in differing parts of the placenta.

Growth of the fetus: Growth of the fetus is assessed by birth weight, length, head circumference and gestational age. Gestational age will be measured in days of gestation base on the last menstrual period.

Pregnancy outcome: The condition of the woman from conception until hospital discharge and the condition of the infant up to the first 7 days of life.

Poor pregnancy outcome: Any condition of the infant or woman which impacts on their health. In the infant, this includes preterm birth, small for gestational age, death, congenital defects, and low birthweight. In the woman this includes any condition which occurs as a result of the pregnancy, such as preeclampsia/eclampsia/PIH/Toxemia, gestational diabetes, hemorrhage, abnormalities of the placenta, premature labor/delivery, abnormal amounts of amniotic fluid and infection.

Repeat poor pregnancy outcome: More than one pregnancy resulting in a poor outcome in the obstetric history of a woman. This can include the current pregnancy or any previous pregnancies, regardless of a normal pregnancy outcome in between poor outcomes.

One of the poor outcomes which can occur is the death of the infant.

Death is classified into three subgroups: *early fetal death, late fetal death, neonatal death. Early fetal death* is the unintentional death of the fetus prior to 20 weeks gestation, commonly referred to as miscarriage or spontaneous abortion. *Late fetal death* is death of the fetus after 20 weeks gestation and before delivery, commonly referred to as stillborn. *Neonatal death* is death of the infant after delivery and prior to the 29th day of life.

Two other categories of death are commonly found in the literature, *infant death* and *perinatal death. Infant death* is death of the infant anytime in the first year of life. Infant death includes neonatal death. *Perinatal death* includes late fetal deaths and neonatal deaths.

STATEMENT OF HYPOTHESES

1. The variables identified in the literature as a significant risk for poor outcome will be demonstrated in this study.

2. There will be a significant the risk of repeating a poor pregnancy outcome when there is a recurrence of placental pathology.

3. In a group of repeaters of poor pregnancy outcome when the risk factors identified as significant are controlled for, the relationship between placental pathology and poor pregnancy outcome will remain significant.

IMPORTANCE OF THE STUDY

Caplan (1974) stresses the necessity of conservation of manpower by increasing collaborative efforts and focusing these efforts on those patients of the highest need where a remedy is possible. Nursing has a key vantage point from which to detect risk and intervene. The term "intelligent intervention" was coined by John Cassell during class lectures in the 1970's as a means of care provision. Intelligent

intervention refers to the prudent use of interventions when providing care. It involves consideration of economic impact and effect on the quality of care. Intervention is any action whose goal is to change or prevent an undesired outcome.

An example of intervention is a visit by a public health nurse to a postpartum woman. The goal of the visit is to identify potential problems such as illness in the woman or infant or developmental difficulties in the infants as early as possible so that treatment can be started early. Early treatments which are simple in nature may avert the need for more complicated and costly measures (such as identification of a minor infection where the treatment is an oral antibiotic as opposed to identification when the infection is massive infection and requires IV antibiotics and hospitalization). Since pregnancy outcome has as its goal the maximum health of the woman and the infant, intelligent intervention would identify those who are at risk for a PPO and would provide surveillance and intervention only to those who need it so that PPO can be minimized.

The issue of quality of care has come to the forefront with the change to a DRG payment system. In addition, higher costs of care have created insurance costs that are affordable by fewer people. The rising amount of unpaid bills and lower payments from insurance companies and HMOs have resulted in cuts in provision of care. These problems have been compounded by a nursing shortage which has potentially compromised care as nurse to patient ratios are increased. Intelligent intervention would provide for only those services that are shown to improve the quality of care so that the strain on scare resources is kept to a minimum. Quality

of care has been separated into three major components, structure, process and outcome (Donabedian, 1980). Pregnancy outcome is one measure which has been used to evaluate the quality of care.

In order to improve pregnancy outcome, new technologies have been developed. These include high-tech neonatal intensive care equipment, fetal monitoring devices, ultrasonography equipment, and laboratory tests such as amniotic fluid evaluation. Once each of these new technologies was developed, it was quickly accepted and utilized. Many of these technologies are used for almost all patients, such as fetal monitoring devices and ultrasonography. Current studies have raised the questions of the safety and efficacy of these practices. Intelligent intervention would evaluate the necessity of these interventions for all patients and develop a method to identify patients at risk for poor outcome who would benefit from intervention.

Caplan (1954) noted the need to use the health care system prudently. He identified nurses as the key to prudent use of the system. Nurses have the best advantage to identify those at need and connect them with the necessary services since they have the most personal contact with patients. Caplan identified nurses as the bridge between the patient and the health care system.

Interventions which are low cost and non-invasive have the highest chance of being accepted by patients, health care institutions, economists and politicians. Nursing interventions are usually low cost and non-invasive. In the realm of pregnancy outcome, the key to cost-effective intervention is to identify those at risk for a poor outcome if they do not receive intervention. Once risk factors are identified, nurses

(especially those in the community health field) are in a position to identify those who need care.

As stated above, one measure of quality of care is pregnancy outcome. In the nursing and medical literature, there is much attention to development of prenatal care programs. Chiles (1990) notes that programs are developed which are focused on medical intervention when intervention in social, economic and behavioral areas is needed. These are concerns related to quality of care. Quality of care is closely related with the economic issues of efficacy, efficiency and effectiveness. Cost-benefit analyses are abundant in the literature. Pregnancy outcome is a common measure of effective treatment or positive benefit. As more technologies are developed to "improve" pregnancy outcome, research should also be focused on the factors which predispose women to experience poor pregnancy outcomes. One area of study where many questions remain unanswered is biological factors that are related to poor pregnancy outcome. Salafia and Vintzileos (1990) recommend examination of all placentas as a cost effective method to identify the populations at risk. Further investigation of the relationship between repeated placental abnormalities and repeated poor pregnancy outcome is warranted.

Chapter II
REVIEW OF THE LITERATURE

THE MATERNAL COMPONENT

Factors of Poor Outcome

The relationship between obstetric history and poor perinatal outcome has been investigated as early as the 1920's. Kellogg (1924) presented the concept of recurrent toxemia of pregnancy, using a case series of 400 consecutive toxemia cases to demonstrate this phenomenon as a unique entity from other toxemias. Young (1927) noted a relationship between toxemia of pregnancy, spontaneous abortion and premature birth, calling his observance "The abortion-premature birth-toxemia complex." In a study of 220 successive cases of toxemia, 31.9% of the cases of had experienced toxemia in a previous pregnancy. The complex Young (1927) identifies was defined as *...the condition in which, in association with one or more eclamptic pregnancies, there occurs an unbroken succession of gestations which end as abortion, premature or still-birth, sometimes in combination with accidental haemorrhage...(p. 282).*

Early investigations of the maternal contribution to pregnancy outcome focused on factors associated with poor outcome. Anderson, et al (1939) reviewed the literature of studies which evaluated factors of prematurity. They identified maternal age, parity and social class, marital status, order of birth ,medical abnormalities and previous premature infant as the most commonly reported factors. In a following study, they added race and sex of the infant to the list of factors (Anderson, et al, 1941).

Gardiner and Yerushalmy (1939) proposed that there was an expected family susceptibility to stillbirths and neonatal deaths. They used the epidemiological concept of secondary attack rate to measure recurrence of

poor outcome. This method involved comparing the proportion of neonatal and stillbirth rates of infants born into families with previous loss to the rates in families with no previous loss. They noted that there was a striking regularity with which both the stillbirth and neonatal mortality rates increased with an advancing number of previous losses. They suggested a relationship between prematurity and biologic or constitutional factors in the woman. They concluded that the increased mortality associated with previous infant loss is of a large magnitude and hence could not be reasonably explained by variations in external environmental and economic factors.

Yerushalmy, et al (1941) investigated the mortality of the woman in relation to previous pregnancy outcome. They evaluated 258,525 deliveries occurring in the three-year period 1936-38 and developed a "puerperal fatality rate" which was defined as "the number of deaths of women who were delivered either of a live birth or a stillbirth per 10,000 total deliveries (including those of stillbirths) (p. 1465)". All first births were eliminated because obstetric history was considered. There were 411 women who died in childbirth and the loss rate (per 1000) was 157.3, compared to a loss rate of 110.5 in a group with no past poor outcome and 230.7 in a group with poor outcome. They noted that the fatality of the woman and the infant are very strongly correlated and that the strong association between the rate for infant loss in the current delivery and the previous losses to the woman makes it difficult to study the relation between puerperal fatality and previous losses independently of fetal loss. They concluded that the causes which underlie repeated infant and fetal loss seem to affect puerperal fatality to a lesser degree than they

do stillbirth and neonatal rates. They also suggested that the father may play an important part in the cause of repeated loss.

Yerushalmy (1956) conducted the first prospective study of recurrence of pregnancy outcome on the island of Kauai and found and effect for order of pregnancy, pregnancy interval, age of the mother and previous obstetric history. MacDonald (1959) investigated recurrence of prematurity and found that women who deliver prematurely will repeat a premature delivery in the following pregnancy. They noted similar findings for delivery of an infant less than 2500 grams.

Feldstein (1965) identified a significant difference for maternal age, parity and social class. Kaminski, et al, 1973 performed multivariate analysis using two groups, high and low risk. They also identified maternal age, socioeconomic status and past obstetric history. de Araújo and Salzano (1975) evaluated birthweight, comparing whites and blacks in Brazil. They found no significant difference for race when socioeconomic status was apparently the same. They did find a significant effect for maternal height and weight. Funderburk, et al, 1976 noted a significant effect for past pregnancy outcome on the perinatal death rate, approaching 18% with three or more prior premature births. A variable effect for race, clinic classification and maternal illness was also noted.

Recurrence of Poor Outcome

A woman's past reproductive performance is an important predictor of pregnancy outcome. The effect of prior reproductive loss on a current pregnancy is not altered to any great extent by extraneous variables. However, past reproductive loss does alter the association between a

number of risk factors (age, parity, and interpregnancy interval) and poor pregnancy outcome (Herman, 1987). The relationship between a poor obstetric history and the outcome of a current pregnancy is complex. There appears to be a *recurrence effect* (Newcombe, 1979) in that the best predictor of a low birth weight in a current pregnancy is a low birth weight in a previous pregnancy and a previous preterm birth is the best predictor of a preterm birth in a current pregnancy (Bakketeig, 1977). Previous stillbirths and neonatal deaths were significant predictors of preterm birth and low birth weight even after stratifying and/or multivariate adjusting for other factors (Fedrick and Anderson, 1976; Fedrick and Adelstein, 1978; Kaminiski et al., 1973; Abernathy et al., 1966; Donahue and Wan, 1973; Meyer et al., 1976; Rantakallio, 1969; Terris and Gold, 1969; Papiernik, 1979; Guzick et al., 1984; Rumeau-Roquette et al., 1974). A past low birth weight baby predicts both low birth weight and preterm birth in subsequent pregnancies (Fedrick and Anderson, 1976; Fedrick and Adelstein, 1978; Kaminiski et al., 1973; Donahue and Wan, 1973; Rantakallio, 1969; Terris and Gold, 1969) but a past neonate weighing more than 4,000 g is protective against both low birth weight and preterm delivery (Fedrick and Anderson, 1976; Fedrick and Adelstein, 1978; Kaminiski, 1973).

Most studies use the outcome of all previous pregnancies as a measure of poor obstetric history. Some studies use the outcome of the next to last pregnancy as the measure of a poor obstetric history, or take into account the order of the outcomes. As pointed out by Newcombe (1979) it is important to differentiate between a poor outcome in the next to last pregnancy and poor outcome in any pregnancy if the object is to

elucidate the recurrence effect. Using the studies of Kaminiski et al. (1973) and Rumeau-Roquette et al. (1974). Newcombe showed that the risk of a low birth weight (LBW) in a current pregnancy is much higher given a LBW in the previous pregnancy than any history of LBW neonates. This effect was not noted for other poor outcomes. Alberman et al (1980) in a survey of pregnancies occurring in 3,502 women doctors examined this recurrence effect. The mean birth weight of neonates preceding a spontaneous abortion was lower than that of a live birth preceding another live birth. Women with repeated spontaneous abortions had neonates with decreasing birth weights with increasing parity. However, the birth weight of a live birth following a spontaneous abortion was as high as the birth weight of first pregnancies. If the objective is to assess the risk of a poor perinatal outcome in the presence of a positive past obstetric history then one should divide the risk into a number of categories: a poor outcome in the next to last pregnancy, any history of a poor outcome (excluding the next to last pregnancy), a history of more than one prior loss (excluding the next to last pregnancy), and no previous poor outcome. The group with more than one prior loss appears to be a group of repeaters. The studies of Resseguie (1973), Bakketeig et al. (1977, 1978), Fedrick and Adelstein (1977) and Roman et al. (1978) take account of the ordering of prior poor perinatal outcomes.

The recurrence effect may be a function of a factor or factors independent of the pregnancy. If this is so, then the risk of a poor outcome in a current pregnancy is truly independent of a previous outcome because the outcome of a previous pregnancy is only a proxy measure for the extraneous factor or factors. Candidates for such an extraneous

factor are: maternal nutrition, social class, and maternal habits such as smoking and alcohol consumption, materno-fetal incompatibility, anatomical anomalies of the uterus and chronic ill health of the woman (Verp, 1989; Papiernick, 1984; Glass and Globus, 1978; Anderson, et al., 1939). On the other hand the outcome of a previous pregnancy may have a direct effect on the outcome of a subsequent pregnancy.

The association between parity and pregnancy outcome is confounded by age, obstetric history, interpregnancy interval social class and maternal weight (Herman, 1987).

a) As age increases so does parity.

b) Women with a poor prior obstetric history tend to have higher parities.

c) Short interpregnancy intervals are associated with higher parities.

d) Women of a lower social class tend to have higher parities.

e) Maternal adiposity (measured by Quartelet's index) has been shown to increase with increasing parity and age (Heliovaara and Aromaa, 1981).

The relationship between parity and poor perinatal outcome is influenced by reproductive compensation and risk heterogeneity (Roman et al., 1984; Herman, 1987). Women who have had fetal losses compensate for these losses by having more pregnancies than women who have had live births (Roman et al., 1984; Golding, 1979; James, 1968; Bakketeig and Hoffman, 1979; Resseguie, 1973; Billewicz, 1973). It is common practice to assess this relationship using a cross-sectional analytic approach, i.e. women with different numbers of pregnancies are grouped together.

This analytic technique has been assumed to lead to an apparent U-shaped or J-shaped association between parity and perinatal outcome (Bakketeig and Hoffman, 1979).

A second approach to the analysis of parity and poor perinatal outcome is to stratify or restrict by gravidity or sibship size (i.e. the total number of pregnancies). In a stratified or restricted analysis the association between parity and poor perinatal outcome is not J-shaped (Roman et al., 1984; Bakketeig and Hoffman, 1979; Resseguie, 1973). Roman, et al. (1984) demonstrated that within gravidity groups the rates of fetal loss remained relatively constant only to fall to the lowest point in the last parity group. Thus women of gravidity 4 had fetal loss rates of 23%, 18%, 17%, and 10% in pregnancy orders one to four (Roman et al., 1984). They also illustrated the role of reproductive compensation in the association of parity and poor perinatal outcome. The continuation rate (the rate of having a subsequent pregnancy) following two, three or four pregnancies tends to fall as the number of live births increased.

Johnstone and Inglis (1974) evaluated sister/sister or sister/sister-in-law pairs and noted that there was a statistical similarity ($p < .05$) between sisters and sister-in-laws who had "light-for-dates" infants or premature infants but there was no statistical similarity if one sister/sister-in-law had a premature infant and the other had a "light-for-dates" infant.

The second reason given for the non-linear association between parity and poor outcome is risk heterogeneity. Different women have different risks of poor perinatal outcome. Those women with high risks tend to have reproductive compensation and are over-represented at higher

parities. This could explain the increasing risk with increasing pregnancy order. Reproductive compensation does not appear to be common after a first pregnancy, therefore women with first pregnancy losses are not over-represented in the second pregnancy group. Since the over-representation occurs in parity groups other than the second pregnancy, this group appears to have lower rates of poor outcome.

A primiparous woman is at a higher risk of having an intrauterine growth retarded neonate (Butler and Alberman, 1969), a preterm baby (Kaminski et al., 1973) or perinatal death (Butler and Bonham, 1963; Feldstein, 1965) when compared to a second pregnancy. Grand multiparous women (parity greater than 7) are at a higher risk of poor perinatal outcome than women of a lower parity.

To control for age, prior obstetric history, and other confounders some authors do a stratified analysis or restrict the analysis to specific age groups or to women without past poor perinatal outcomes (Fedrick and Anderson, 1976; Bakketeig and Hoffman, 1981). To control the confounding effect of a previous perinatal death Bakketeig and Hoffman (1981) restricted their analysis to sibships without previous perinatal deaths.

Birth weight and gestational age increase with increasing parity and rates of perinatal death decrease with increasing parity. Parity was a predictor of gestational age and crown heel length but not of birth weight in models of Abernathy et al. (1966). Meyer et al. (1976) used a combined age-parity variable in a multiple logistic regression model. This variable was a predictor of preterm birth and low birth weight. Parity was one of the 15 most powerful predictors of low birth weight in the discriminant analysis of Rantakallio (1966). Parity was a significant

predictor of birth weight (for whites) in the multiple linear regression of de Araújo and Salzano (1975).

The association between interpregnancy interval and perinatal outcome is confounded by gestational age, maternal age, parity, past obstetric history, and social class. If the interpregnancy interval is measured as the interval between two deliveries the shorter interpregnancy intervals will contain a higher rate of preterm births, simply because the length of gestation is contained in the interval measured (Eastman, 1944). The appropriate measure of this interval is delivery to last menstrual period interval or last menstrual period to last menstrual period interval.

Women who become pregnant at an early age tend to have high parity and shorter interpregnancy intervals. These women usually come from lower social classes (Fedrick and Adelstein, 1973). Women from lower social classes were twice as likely as women in higher social classes to conceive within six months (Fedrick and Adelstein, 1973). Teenagers were at a much higher risk of becoming pregnant within 6 months of a previous pregnancy.

Women who have a pregnancy loss will tend to replace that loss and therefore have a shortened interpregnancy interval. A short interpregnancy interval (less than 1 year) and a long interval (more than 5 years) were both associated with increased rates of low birth weight and perinatal mortality in the index as well as in the preceding pregnancy (Erikson and Bjerkedal, 1978). When Erikson and Bjerkedal (1978) restricted the analysis to livebirths the association between interpregnancy interval and the effect of the birth weight was diminished. The stillbirth rate for the first born of a pair is higher at short

interpregnancy intervals. At long interpregnancy intervals the later born of the pair was at a higher risk of being stillborn. A prolonged interpregnancy interval probably reflects relative infertility. Berkowitz (1981) has shown that infertility is a predictor of preterm birth.

If the previous pregnancy had ended in an adverse outcome (e.g. a spontaneous abortion or a perinatal death) the probability of becoming pregnant within 6 months was higher than if the preceding pregnancy had been successful (Fedrick and Adelstein, 1973). Because of the recurrence effect Fedrick and Adelstein (1973) restricted their analysis to pregnancies in which the preceding pregnancy resulted in a liveborn baby and found that the risk of a stillbirth increases with an increasing interpregnancy interval. The proportion of low birth weight neonates was greatest with both short and long interpregnancy intervals. Eisner and his colleagues (1979) comparing women with short interpregnancy intervals (less than 6 months) to women with longer intervals found that the risk of low birth weight was increased 1.5-fold in women with shorter pregnancy intervals.

Previous spontaneous abortions have been shown to be important predictors of poor perinatal outcome (Warburton and Fraser, 1964; Rantakallio, 1969; Guzick et al., 1984). It has been reported that women who have had a therapeutic abortion are more likely to have a subsequent preterm delivery. A review by Atrash and Hogue (1990) suggest that women whose first pregnancy was terminated by induced abortion have a higher risk of low birthweight than women who carried their first pregnancy to term which indicates that induced abortion is not protective of the risk of low birthweight for first-born offspring. They also note that pregnancy

termination by dilatation and evacuation may result in an increased risk of subsequent low birthweight baby, especially in the case when this group is compared to a group of women who are gravida 2 para 1. They stress that very little has been published and no conclusions can be made. They suggest that an increased risk of preterm birth is probably brought about by an increased incidence of cervical incompetence following a therapeutic abortion. An intervening pregnancy appears to reduce this risk (Berkowitz, 1981).

THE CONCEPTUS

Historical Aspects

Realdus Columbus is believed to have introduced the term placenta in 1559 when he used the Latin word for *circular cake* (Pritchard, et al, 1985). Investigations into the relationship between placental abnormalities and poor pregnancy outcome can be traced back to the previous century. Lubsarsch (1871) experimented with pregnant sheep by inoculating them with bacteria and examined the fetal organs, as well as the placenta. Many of the early studies identified placental inflammation as a sign of infection (Slemons, 1916, 1922; Young, 1921; Siddall, 1928; Wohlvil and Bock, 1926; Creadick, 1920; Laubscher, 1924, Graeff, 1927; Kobak, 1930).

Kobak (1930) conducted a study which examined placentas for presence of infection, abnormal pathology or inflammation and the fetal outcome, including cord culture and autopsy in the event of fetal death. In addition, he compared the length of the time interval between rupture of membranes and delivery and the outcomes observed. He concluded that infection will result in abnormal placental pathology when there is

prolonged insult and may affect the outcome of the fetus.

Tenny and Parker (1940) noted a lesion of the placenta that is associated with toxemia. They described this lesion as a sign of premature aging where the amount of syncytial degeneration was increased. They also identified marked congestion of the villus blood vessels associated with clinical findings of albuminuria, indicating that placental damage precedes clinical signs of toxemia and that placental damage is an accurate indicator of severity of the disease.

Rumboltz, et al (1961) described placental insufficiency as an etiologic factor of poor pregnancy outcome, especially the low birthweight infant at term gestation. He noted that there is a definite relationship between the size, weight and pathologic condition of the placenta, and the growth, weight and survival of the infant.

Gruenwald (1963) explored the problem of low birthweight due to growth retardation in utero. He noted that there was no effort in the literature to distinguish between infants who normally have lower birthweights and those who have abnormally low birthweights due to intrauterine deprivation or other causes. He observed autopsies of infants who had died in utero, noting that they were malnourished and retarded in growth and presumed that the growth retardation was due to placental dysfunction. He coined the term *chronic fetal distress* to describe this condition and noted that *subacute fetal distress* was characterized by wasting. He stated that there was evidence of prolonged stress in both conditions. It was noted that approximately one third of all infants with low birthweight are not truly premature.

Chronic fetal distress is a non-specific condition caused by

disturbances similar to acute perinatal distress and shock. Fetal distress is a spectrum of insult to the fetus. The most severe form of chronic distress results in death in utero with significant growth retardation. The least severe from is acute fetal distress which last for a few days and does not cause wasting. Subacute distress is not severe enough to cause death or significant growth retardation, but will cause wasting (Gruenwald, 1963).

Recurrent placental inflammation of unknown etiology (villitis) was first reported by Dollmann and Schmitz-Moormann (1972). Russell (1979) noted that this condition had only been recognized for the past two decades and that the etiology had not been determined. The condition was associated with intrauterine growth retardation and was noted to recur in successive pregnancies and was not associated with maternal age, socioeconomic status, marital status or gestational age. Additional case reports continued to describe the condition without explanation of etiology (Russell, 1980; LaBarrere, et al, 1982; Redline and Abramowsky, 1985).

Interest in the placenta and increased knowledge about morphology and histology produced other identified abnormalities. Maternal floor infarction (Naeye, 1985; Andres, et al, 1990), hemorrhagic endovasculitis (Sander, 1980; Sander and Stevens, 1984) and other abnormalities (Ornov, et al, 1981; De Wolf, et al, 1980) have been reported. All these abnormalities have been reported to repeat in subsequent pregnancies at a rate higher that the general population.

Placental Development

The embryonic or fetal membranes include the amnion, chorion, yolk

sac and allantois which all develop from the zygote. There are two components of the placenta: the fetal portion which arises from the chorion and the maternal portion which forms from the endometrium. The functional layer of the endometrium is know as the decidua. The decidua has three regions that are identified by their association to the implantation site. The *decidua basalis* underlies the conceptus and forms the maternal component of the placenta. The *decidua capsularis* is the superficial portion that overlies the conceptus. The remaining uterine mucosa is the *decidua parietalis* (Moore, 1982).

Approximately three and one-half days after fertilization, the dividing zygote develops into a blastocyst and reaches the uterus (Croxtto, et al, 1972, Moore, 1982). The blastocyst separates into two parts as it develops. The two parts are separated by fluid which fills the blastocyst cavity. A group of cells which is centrally located and is called the *inner cell mass* gives rise to the embryo. An outer cell layer which gives rise to the placenta is known as the *trophoblast*. The trophoblast adheres to the endometrial epithelium and begins to differentiate into an inner layer called the *cytotrophoblast* is mitotically active and the *syncytiotrophoblast* which is composed of a multinucleated protoplasmic mass with no apparent cell boundaries. This layer becomes syncytial (Moore, 1982).

The syncytiotrophoblast begins to penetrate the endometrium between epithelial cells. It shares junctions with the uterine cells, resulting in minimal displacement of uterine lumen (Ender, 1981). After the epithelial cells are displaced, they grow back over the blastocyst and contribute to the decidua capsularis. Several masses of

syncytiotrophoblast extend into the endometrium. These masses expand irregularly and surround the maternal capillaries (Harris, 1966). The syncytiotrophoblast changes from a group of irregular masses to a tunnelled continuum with individual layers that are close to one cell thick (Ender, 1981). This establishes a series of intrasyncytial lacunae that become filled with circulating blood by the end of the blastocyst period (Hamilton, 1960). These spaces collectively form a large blood sinus called the *intervillous space* which is bounded by the chorionic plate and the decidual basalis (Moore, 1982).

Development of placental villi begins when masses of cytotrophoblast extend through the syncytium into the junction of the endometrium. Cell columns continue to proliferate when they reach the endometrium and form a *cytotrophoblastic shell* around the conceptus (Ender, 1981). The villi cover the entire surface of the chorionic sac until about the eighth week. Those villi which cover the decidua capsularis degenerate as they become compressed as the sac grows. This area become avascular and is called *smooth chorion.* In the decidual basalis, the villi rapidly increase in number, branching, and size. This area of the chorion is called the *chorion frondosum.* The chorionic plate and the chorionic villi arising from it form the fetal component of the placenta. The decidual basalis forms the maternal component (Moore, 1982).

The cytotrophoblastic shell anchors the fetal placenta villous chorion to the decidual basalis (Moore, 1982).

Placental Pathophysiology

When examining the placenta grossly, certain features have been

associated with perinatal complications or poor perinatal outcome. A circumvallate insertion of the external membranes has been associated with chronic oligohydramnios, amnion rupture, maternal smoking and other conditions of uterine vascular insufficiency (Salafia & Vintzileos, 1990).

Microscopic examination of the placenta, when several sites are sampled, can reveal the presence of amniotic infection, its duration and severity, the location of the inflammatory process and the pathway of the infection. These findings are of two primary groups, those that are infection related and those that are representative of hypoxic insult. Chorioamnionitis is defined as *...an acute, diffuse, inflammatory process in the extraplacental membranes, the plate of the placenta and the umbilical cord... (Herman, 1987).* The term, *acute placental inflammation*, was coined by Herman to describe this phenomenon. Acute placental inflammation includes one or more of the following: chorionic vessels (chorionic vasculitis), chorionic plate of the placenta (placental chorionitis), the umbilical cord vessels (vasculitis), wharton's jelly of the umbilical cord (funisitis). These are discussed in more detail below. When the inflammatory process becomes more advanced, it involves more than the extraplacental membranes as it ascends from the cervix and invades the amniotic cavity, attracting fetal leukocytes (Altshuler and Herman, 1989).

This information is significant in identification of subclinical infection or infection in a carrier of an organism, such as streptococcus where there is an abnormal cellular and humoral response and treatment should be initiated because of a high risk for developing neonatal sepsis (Salafia & Vintzileos, 1990).

Herman (1987) divides the placental response to an infective agent

into a maternal and fetal response. The fetal response consists of vasculitis, and in more extreme cases, funisitis.

Vasculitis: Consists of polymorphonuclear leukocytes present within the walls of the blood vessels of the cord and/or within the walls of the chorionic plate. Herman notes that some authors consider margination of the polymorphonuclear leukocytes along the endothelium within the lumen as evidence of early vasculitis.

Funisitis: The next stage of the fetal response is indicated by the presence of fetal polymorphonuclear leukocytes in Wharton's jelly of the umbilical cord.

The maternal response consists of membranitis, a deciduitis, or a subchorial intervillositis.

Membranitis: The infiltration of polymorphonuclear leukocytes into the extraplacental membranes.

Deciduitis: Polymorphonuclear leukocytes in the decidua of the placental plate.

Subchorial intervillositis: An accumulation of polymorphonuclear leukocytes in the intervillous space immediately below the chorionic plate. These polymorphonuclear leukocytes may also be found to extend upwards into the chorionic plate. Commonly with chorioamnionitis, acute villous edema is observed. Villous edema is associated with a decrease in the oxygen

supply to the fetus and birth asphyxia (Herman, 1987).

A second grouping of placental pathology involves factors which represent decreased blood flow, resulting in hypoxic damage. This damage can be the result of a long term problem (chronic) or relatively short term problem (acute). Pathologic findings of chronic hypoxic damage include necrosis of the decidua, thrombosis and inflammation around the villi. Meconium filled macrophages are indicative of acute hypoxia. These findings can be found in three layers of the placenta, marginal, capsularis or basalis. Salafia and Vintzileos (1990) define chronic villitis as *a chronic inflammatory infiltrate of the placental villi composed of plasma cells, lymphocytes and histiocytes or macrophages (p.1287)*. Chronic villitis has been associated with viral infection and maternal immunopathology. An associated feature of chronic villitis is hemorrhagic endovasculitis. Salafia and Vintzileos (1990) credit Sanders (1984) with coining the term. They describe it as a lesion observed in cases of unexplained poor pregnancy outcome. The observed lesion may affect any or all levels of the placental circulation and typically appears as a vasoocclusive process with endothelial damage, fibroblast proliferation with scalloping of the vessel outline, erythrocyte fragmentation and bleeding within the vessel wall and in the villous stroma. Only erythrocyte fragmentation and vascular damage is present at the capillary level. Although previously believed to be of immunologic origin, the current interpretation believes the origin to be related to abnormal blood flow.

Epidemiology Aspects

Hypertensive women with previous stillbirth had a greater risk of a

positive contraction stress test than hypertensive women without a previous stillbirth (Freeman, et al, 1985).

An increased risk of spontaneous abortions, antepartum late fetal death, neonatal death and IUGR have been noted in association with recurrent placental villitis (Redline & Abramowsky, 1985). Rayburn (1985) examined 89 stillborns, including placental pathology, and observed that the only statistically significant finding was the presence of placental vascular insufficiency with a diagnosis of hypertension or diabetes mellitus.

Berman, et al (1987) identify that recurrent preterm birth and early neonatal deaths have been associated with acute placental inflammation. The possible mechanism is that low socio-economic status women have recurrent bacterial vaginosis during pregnancy. The authors demonstrate an interaction between mycoplasma hominis cervicitis and a prior obstetric history of spontaneous abortion in the prediction of low birth weight.

McGregor (1988a) investigated the relationship between preterm labor and premature rupture of membranes and cervicovaginal microorganisms. His review of the literature discussed previous work in the area which indicated a relationship between microorganism invasion, inflammation and preterm labor. He approached the problem by conducting a double-blind randomized placebo-controlled trial of erythromycin treatment. He reported that in a subset of the sample where cervical dilatation and effacement preterm was demonstrated, there was a prolongation of pregnancy, increased birth weight and decreased duration of intensive nursery care. He suggests that women who are at risk for preterm birth because of microbial-host inflammatory mechanisms may be identified and

receive treatment which reduces the risk of preterm birth. He posits the question : *...How can women at risk for preterm labor due to infection be identified and the risk of preterm delivery be reduced...(p. 10)*

Low uteroplacental blood flow, identified by excessive syncytial knots and placental infarcts, was associated with higher rates of preeclampsia and premature birth. This phenomenon was noted to repeat at a rate over twice that of those without low uteroplacental blood flow in the first pregnancy (Naeye, 1989).

A case control study of 60 cases of maternal floor infarction was associated with a 40% fetal loss rate and a 51% intrauterine growth retardation rate. A recurrence of 39% was reported (Andres, et al, 1990).

These findings suggest a recurrent nature of different placental pathologies which can result in the same outcome (fetal death, growth retardation, prematurity). Each study identified a specific placental pathology and reported its recurrence, along with several poor outcomes. A study which identifies the recurrence of a specific pathology to a specific outcome has not been reported in the literature.

Growth of the Fetus

As discussed previously, the blastocyst separates into two parts, the embryo and the trophoblast. The trophoblast develops into the placenta and the embryo develops into the fetus. The embryonic stage of development ends as the essential structures of the fetus are formed by the eighth week (Pritchard, et al, 1987).

CHAPTER III
METHODOLOGY

APPROACH

The purpose of this study is to determine if the same placental pathology is observed in both cases when poor outcome recurs. To accomplish this purpose, secondary analysis was done on the data collected for the Collaborative Perinatal Project (CPP) of the National Institute of Neurological and Communicative Disorders and Stroke (Naeye and Peters, 1978).

Over the eight years of the CPP, 8442 (78%) of the women had two pregnancies, 1850 (17%) women had three pregnancies and 1407 (13%) had more than three pregnancies. Data were collected from 1959 to 1966 from women being cared for in 12 medical-school affiliated hospitals in different regions of the United States. One hospital drew its sample from a private patient population in a metropolitan area in the northeast. The other hospitals drew their samples from clinic populations in metropolitan and inner city areas throughout the country. The sample includes 53,518 pregnancies in 10,699 women and examination of 31,494 (59% of all pregnancies) placentas. It contains over 1000 demographic, hereditary, social, medical and postmortem variables. In addition information on pregnancy, labor and delivery, and the neonatal period was collected Placenta data is available on 86% of late fetal deaths and infant deaths. Placentas were evaluated by four specially trained technicians and all nonroutine abnormalities were examined by a senior pathologist (Naeye and Peters, 1978).

Most data analyses in health care research involve the use of new data which is collected for a specific research purpose. This is defined as primary analysis (Woods, 1988). The amount of data which nursing

collects and generates during research and clinical practice is immense. This is true of other disciplines such as medicine, public health, life sciences and social sciences as well. At the conclusion of primary analysis, there usually exist relationships among the variables which have not been examined and data which has not been utilized. Secondary analysis is a method to increase the utility of this data. Many definitions of secondary analysis exist in the literature (Hyman, 1972, Glaser, 1963, Polit and Hungler, 1978, Woods, 1988, McArt and McDougal, 1985, Glass, 1976 and Churchill, 1983). Common to all these definitions is analysis of data which had been gathered for other purposes by looking at a different set of research questions and hypotheses.

Lobo (1988) and McArt and McDougal (1985) identify rationales for proposing secondary analysis as a nursing research strategy:

1. Identification of significant variables which were not analyzed in the original study.
2. Exploration of different relationships among the variables.
3. Utilization of a different unit analysis.
4. Subsample analysis specific to one segment of the sample.
5. Utilization of a different statistical analysis.
6. Utilization of data not analyzed in the original study.
7. Analysis of two sets of data on comparable research questions.

Methods

Case-Control Designs

This study was a nested case-control study. A case-control study begins by identification of a specific outcome or disease process and selects subjects based on the presence or absence of this outcome. Those

subjects with the outcome are identified as *cases* and those without the outcome are the *controls*. The cases and controls are compared with respect to selected attributes and exposure to identified risk factors. The cases in this study are broadly defined as women experiencing poor pregnancy outcome and the controls as those women experiencing normal pregnancy outcome. This study differs from a cohort study which identifies a group (cohort) of individuals and collects information, following the subjects over a specified period of time looking for the identified outcome to occur.

Cases and controls were selected from a cohort of women identified during pregnancy and followed over time. Endpoints in the CPP include almost all aspects of a continuum of reproductive casualty (such as early fetal death, late fetal death, preterm labor and intrauterine growth retardation, neonatal and infant mortality, neonatal morbidity and long term neurological and intellectual deficits. This study used some of these endpoints of reproductive casualty as the outcome of interest, in particular mortality (early, late, neonatal, infant). Indicators of fetal growth were also available, including gestational age and birth weight, these were also used for this study.

Case-control studies are the most common form of analytic epidemiologic studies (Kelsey, et al, 1986). They offer the advantage of time and economy over cohort studies. In addition, because the subjects are selected based on their outcome status, adequate sample size is more easily obtained (Hennekens and Buring, 1987). On the other hand, case-control studies have the disadvantage of control of extraneous variables which occurred during exposure, making selection of an appropriate

comparison group difficult. In this study, this is minimized by using two measurements from the same individual.

Case-control studies can be *exploratory* or *analytic*. Exploratory studies are conducted when little is known. Schlesselman (1982) refers to exploratory case-control studies as a "fishing expedition (p. 16)". When specific hypotheses are proposed and tested, the case control study is analytic.

Modern case-control studies date back to the 1920's in papers by Lane-Claypon (1926) and Broders (1920). The method became formalized and used in the sociological field in the 1920's and 1930's. The importance of the use of controls was emphasized in a study by Schreck and Lenowitz in 1947 when they conducted a case-control study of carcinoma of the penis. A control group for comparison with the cases identified the absence of circumcision and poor sex hygiene as etiologic factors (Schlesselman, 1982). Researchers in the 1920's and 30's noted a rapid increase in the rate of lung cancer that was much greater than the expected risk. Until the 1950's only descriptive studies were available to explore this phenomenon. A classic epidemiological investigation used a case-control study to identify a causal relationship between cigarette smoking and cancer (Hennekens and Buring, 1987). Case-control studies are also useful when the disease is rare. This makes the case-control approach useful for this study since poor pregnancy outcome is a relatively rare event. Schlesselman (1982) also notes that statistical methods such as relative risk determination and chi square tests of association were shown to be efficiently estimated from case control data.

Logistic Regression

Logistic regression is a specialized form of multiple regression and is commonly used in case-control studies (Herman, 1987, Schlesselman, 1982). Logistic regression, used when the outcome is binary, such as in a case-control study where the outcome is present or absent, provides an estimate of the magnitude of the association between the outcome and a set of risk factors. This estimate is the probability of the outcome being present conditional upon the values of the set of risk factors. The probability is known as the **"log odds"** or **logit** (Hennekens and Buring, 1987). The odds of developing the outcome is calculated as follows:

$$\text{odds} = \frac{P}{(P-1)}$$

The log odds (logit) is calculated by taking the natural logarithm (ln) of this value. The multiple regression formula can be written to represent a logistic regression as follows:

$$\ln\left[\frac{P}{(P-1)}\right] = \alpha + \sum_{i=1}^{k} X_i\beta_i$$

Where: α = a constant; β = the regression coefficient and X =independent variable

The logit transformation of the probability forces the predicted probabilities to lie between 0 and 1 (Herman, 1987, Hennekens and Buring, 1987). In logistic regression, the dependent variable is defined as the natural logarithm (ln) of the odds of the outcome.

To represent the probability of the outcome occurring, the equation is rewritten on the following page:

$$Y = \frac{1}{1 + e^{-(\Sigma i \beta i)}}$$

In multiple regression, the β's are known as regression coefficients, in like manner, in logistic regression, the β's are referred to as **logistic regression coefficients** (Schlesselman, 1982). These coefficients are always between 0 and 1 (by definition), therefore, they denote the magnitude of the increase or decrease in the log odds which is produced by one unit change in the value of the independent variable. They indicate the effect of an individual factor on the log odds of the outcome when all remaining variables are held constant. This offers convenience in epidemiological research since these coefficients can be directly converted to an odds ratio (Hennekens and Buring, 1987).

The coefficient for each independent variable in a logistic regression can be converted to an odds ratio (OR). Schlesselman (1987) defines an OR *...the odds of disease in exposed individuals relative to the odds of disease in the unexposed (p. 34).* The OR is an estimate of the relative risk (RR) which represents the magnitude of the association between that factor and the outcome, controlling for the effects of the other variables. This is accomplished by taking the antilogarithm of the coefficient:

RR $(X_1) = e^{bi}$ and the 95% confidence intervals = $e^{(bi \pm 1.96SEbi)}$

In this study, two outcomes were of interest: survival of the infant and growth. Survival was measured as live birth or the period during gestation when death occurred Growth of the infant was described as term or premature gestation (less than 259 days) and normal or low birth

weight (less than 2500 grams).

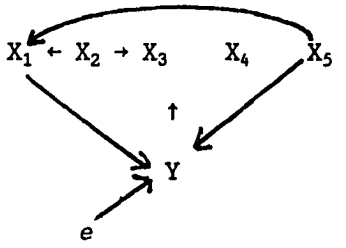
Causal Modelling

An important objective of epidemiology is to judge whether an association between exposure and disease is causal (Hennekens and Buring, 1987). This can become problematic since research is conducted using human subjects, making structured control as in the laboratory impossible. Thus, any associations may be due to an alternative explanation from the hypothesis that is tested.

Linear modelling or structural modelling provides a means to increase the ability to establish causality. Spirtes, et al (1990) identifies four parts to a structural equation model or linear causal model: A set of random variables with a joint distribution, a set of linear equations among the random variables, distribution assumptions about the random variables and a set of causal relations among the random variables. There are many standard programs that estimate the parameters of models. These estimations provide a means to test hypotheses.

These models differ from basic statistical packages such as multiple or logistic regression because they seek to define the causal relationship. Multiple or logistic regression seek to explain the amount of influence each independent variable contributes to the prediction of the dependent variable. These "influences" are derived as weighting factors in a linear or log-linear equation. The problem of using regression equations to infer causality arises in the way in which each predictor is evaluated. Each independent variable (predictor) is evaluated based on the amount of covariation relative to all the other independent variables in the equation. Unmeasured (latent) causes are not

considered. This may result in measuring the effect of the variable which is identified as the dependent variable or the variable of interest. Spirtes, et al, (1991) illustrate this problem in the example below.



In this example, X_1 ... X_5 are independent variables (predictors) that influence Y and *e* represents the effect of correlated errors. The effect of X_4 on X_1 and Y on X_3 will cause regression techniques to falsely state that X_1 X_2 X_3 and X_5 are causes of (causally connected to) Y. Tetrad II (Spirtes, et al, 1991) is a method of analysis designed to overcome this problem. It evaluates the variables in pairs and so will only identify X_1 and X_5 as causes of Y.

Another problem encountered in developing a causal model is that there may be many separate dependencies that can be described by using a set of simultaneous equations, also called structural equations. The problem lies in determining which dependencies are correct.

EQS (Bentler, 1985) and LISREL VI (Joreskog and Sorbom, 1984) are two of the most common computer programs which specify structural models. The models produced by these programs include linear, factor analytic and path analytic models. The result of the analysis is a structural equation model which allows the expression of a causal hypothesis as a linear equation. EQS and LISREL VI involve an automatic search procedure which

takes an initial model and data and produce a unique recommendation for revision of the model (Spirtes, et al, 1990).

These programs have been criticized because they involve assumptions of linearity and multinormality which are rarely tested and often do not hold. This criticism has been minimized by careful data analysis and a program for LISREL IV called PRELIS. The assumptions are often confirmed by those analyses. Secondly, the formation of a structural equation model and the demonstration that it does not fail a statistical test does not confirm the causal assumption. There may be many alternative linear causal models that meet the same criteria but differ in very important respects to the one chosen by the researcher. In addition, a model which correctly specifies the causal relationship but has minute failures to the assumptions of linearity or normality in the process that generated the data, will fail a chi-square test of goodness of fit in large samples (Spirtes, et al, 1990). An alternative approach that has been proposed is to use the sample data to modify an initial model by suggesting additional causal connections or correlated errors that were not included in the initial model.

Tetrad II is an experimental program which uses graph analysis algorithms, as opposed to numerical techniques. It relies on heuristic search techniques that are characteristic of many artificial intelligence programs (Spirtes, et al, 1990). In contrast to EQS and LISREL which provide unique model recommendations, it provides a set of alternative revisions to an initial model.

The information produced by TETRAD II allows the user to construct pictures which are called directed graphs. A directed graph consists of

a set of nodes which represent random variables, and edges that indicate direction and connect some of the nodes. An example of a directed edge is: X → Y. This can be interpreted as "X influences Y and Y is a function of at least X (Spirtes, et al, 1991, p. 3)." The example represents an *edge* because one node (X) is connected to another node (Y). It is *directed* because the connection is an arrow pointing a direction going from X to Y. An undirected edge would be a straight line connection which does not give direction.

Tetrad II is designed to include information concerning the time order of the variables.

Tetrad II uses a "tetrad difference" to build the graph. The tetrad difference is the determinant of a 2 X 2 submatrix of the covariance matrix. It uses the assumption that this difference will be zero in the population and that the sampling distribution of tetrad differences is normal. The variables are evaluated in groups of 4 (thus the name tetrad), producing three tetrad differences. Two of these are evaluated to see if they "vanish" in the population. Tetrad II is programmed to take this information and follow three fundamental principles:

> *Falsification principle: Other things being equal, prefer models that do not strongly imply constraints that are judged not to hold in the population.*
>
> *Explanatory Principle: Other things being equal, prefer models that strongly imply constraints that are judged to hold in the population.*
>
> *Simplicity Principle: Other things being equal, prefer simpler models (i.e. models with higher degrees of freedom)*
>
> *(Spirtes, et al, 1990, p. 13)*

Tetrad II does not provide parameter estimates or compute a goodness-of-fit but it can be used in conjunction with EQS or LISREL VI which do

provide parameter estimates (Spirtes, et al, 1991).

Spirtes, et al (1990) asked the question "how reliable are these procedures as guides to the truth?" They compared the reliability of EQS, LISREL VI and TETRAD II on computer simulated data which involved 80 data sets that were generated by Monte Carlo methods from each of nine different structural equation models that included a variety of structural equation errors. Half the data sets had a sample size of 200 and half had a sample size of 2000. They found that the TETRAD II program provided more reliable but less precise information. They also found that for the large sample size, TETRAD II was correct 95% of the time in respecifying the model by analysis of the data, LISREL VI was correct 18.8% of the time and EQS 13.3% of the time. Spirtes, et al (1990) authors stress that they limited the scope of their study to automatic respecification of models by EQS and LISREL VI. They also note that authors of both packages provide ample warning about the reliability of the results and that they should be used in conjunction with knowledge of the content area.

There are many alternative models to explain pregnancy outcome, recurrence of poor outcome and the relationship of biological effects, environmental effects and the effects of obstetric history on the current pregnancy, placental development and infant outcome. Based on the information presented by Spirtes, et al, (1990), TETRAD II offers a heuristic tool to evaluate the proposed model of this study.

The procedure that will be used for this study is the TETRAD II BUILD procedure. Raw data in categories from 0 to 4 inclusive can be entered into the program. In addition, information regarding the time order of the variables can be entered. When data from a system that is not

causally sufficient (that is there are latent or hidden variables in the model) is entered into the BUILD procedure, TETRAD II provides a pattern called a *partial oriented inducing graph* , using a 0.05 alpha level. The pattern includes a series of directed edges (A → B, Y → Z, etc) which identify relationships among the variables. When the TETRAD II program provides a directed edge from A to B, it can be interpreted that "A influences B" or that in the true causal graph there is a sequence of directed edges from A to B (Spirtes, et al, 1991, p. 76). The directed edges can be evaluated and a final graph can be constructed.

Data Analysis Plan

The sample for this study consisted of the group of women who had a second pregnancy during the study period. Only singleton births were used in the analysis. Since the sample size is very small in other race groups (341 or 4% total singleton births), the analysis will be restricted to the 7653 white and black women who experienced singleton pregnancies.

Each woman was matched to her first pregnancy in the study period. Included in the identification number of each woman is a code for the number of the pregnancy event during the data collection. Matching was accomplished by separating the data into "event number" groups (event #1 = the first pregnancy, event #2 = the second pregnancy, etc), separating single from multiple births and then match-merging by identification number (without the event code). All variables that were present in both pregnancies were renamed for the second pregnancy so that the final data set includes information for pregnancy 1 and pregnancy 2.

Frequencies of each variable used in the analysis were run for the total sample and by race. Appendix A includes tables of these frequencies.

Once the variables were selected, they were categorized in 5 categories logistic regression and TETRAD II analysis. The categories were determined by the following criteria:

1. If there are logical or common use divisions in the data (eg birth weight, gestational age, etc) use those.
2. If there are no logical or common use divisions, then divide the groups so that they have equal numbers.

Comparison groups were constructed based on birth weight, gestational age and survival. These groups considered the effects of social class and gynecologic age for groups of women who had never been pregnant, had never delivered a viable infant and who had been pregnant and delivered one or viable infants before the study period.

Recurrence of poor outcome was defined as poor outcome occurring in both pregnancies in the study. Groups were included only if exact replication (outcome occurred in both pregnancies) occurred. Poor outcome groups were assigned based on observations in previous research that noted a cycle of poor outcomes including death, prematurity and low birth weight (Young, 1927, Harger, et al, 1983). Therefore, these outcomes were considered together as well as separately. The complete list of combinations of outcome groups is listed in Appendix B.

Analysis was conducted in stages, asking the following questions.

1. Which variables are causally adjacent to each other?

The TETRAD II BUILD program was run.

2. What social, demographic, medical, past obstetric factors represent a significant risk of repeating a poor pregnancy outcome?

Univariate and linear logistic regression were performed.

3. When there is a recurrence of placental pathology, is there a significant risk of repeating a poor pregnancy outcome?

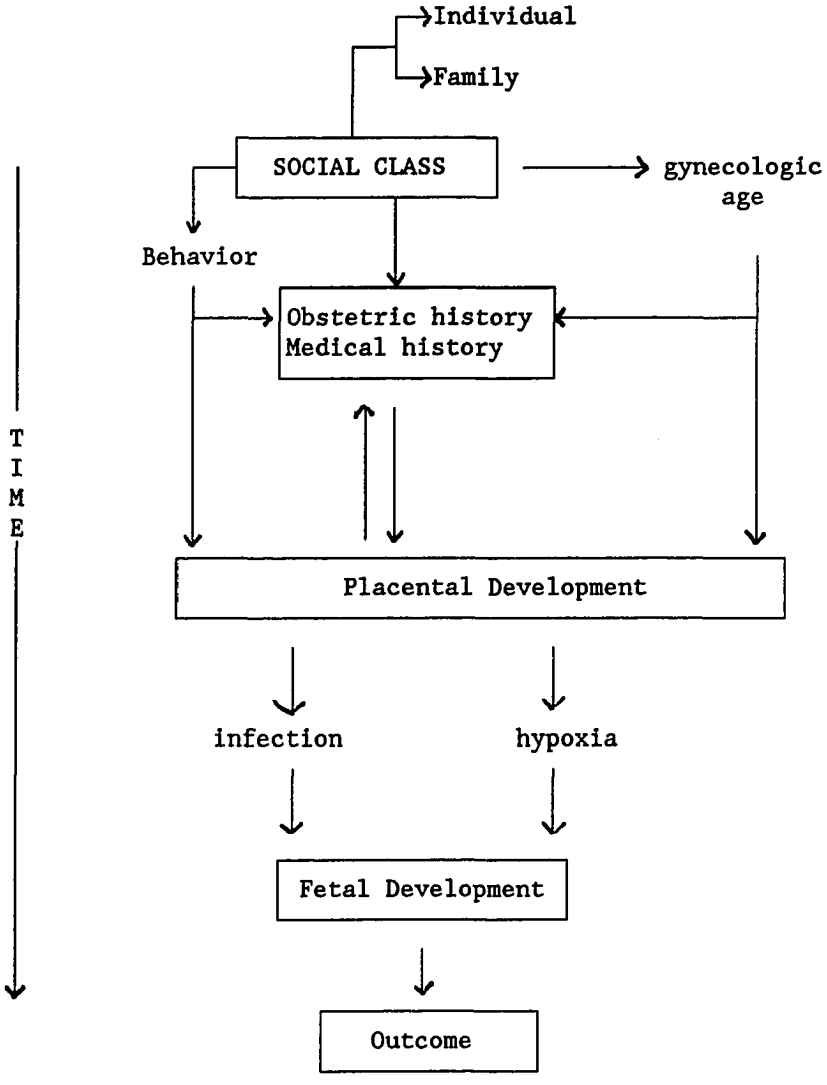
Linear logistic regression was performed

4. In the group of repeated poor pregnancies when, controlling for other significant risk factors, is there a recurrence of abnormal placental pathology?

A logistic regression and cross-tabulations were performed.

The logistic and TETRAD II models used for these analyses are listed in the data analysis plan in Appendix B.

The effects of social class, gynecologic age and other factors were evaluated in the following time order:



Variables used in this study are listed below:

Social Class: Education (Including expected education) family social class, occupation, per capita income

Gynecological Age: (Age at pregnancy - Age at menarche)

Behavior: Cigarettes smoked per day

Obstetric History: Survival, birth weight, number and type of poor outcome

Medical History: Includes metabolic disorders, cardiovascular, pulmonary, venereal genitourinary diseases, infection

Placental Pathology: Recurrence of microscopic pathology (chronic, acute, sub-acute hypoxic changes, inflammatory changes, infectious changes

Fetal Development: Birth weight, gestational age

Outcome: Recurrence of early fetal death, late fetal death, neonatal death, infant death, low birth weight, intrauterine growth retardation, live birth (normal birth weight and gestational age)

The model proposed notes that social class mediates both gynecologic age (Age at pregnancy-age at menarche), behavior and obstetric history. All these may have an effect on placental development.

Since the social environment of the woman is different at different ages, an additional variable was calculated which considered the potential for completed education. Those women under 25 years of age may not have completed their education. If education were completed to the highest level (graduate school), it would require 12 years of primary school, 4 years of college and 4 years of graduate school, a total of 20 years. Since school usually begins at age 6, education should be completed by age 26. Women who were less than 25 years of age may have incompleted education. Therefore, an additional variable "expected education" will be calculated which reflects this:

expected education = (Age - 6) - actual education

Expected education should equal 0 if expected education is the actual education attained.

A second subdivision was based on marital status. In women who were married, education or expected education is the social class variable.

Women who were unmarried, were probably living at home, therefore, education is conditional on maternal grandfather's occupation. Another variable, social class incongruity, which is reflected in the difference between mother's education and father's: (Education of the woman) - (Education of the father of the baby).

CHAPTER IV
FINDINGS

OVERVIEW

This study involved a two-part analysis. The first part used the TETRAD II BUILD algorithm described in chapter III along with univariate analysis. The second part involved bivariate analysis and linear logistic regression.

A preliminary Tetrad analysis using the social class variables (education, occupation, expected education, per capita income, marital status and family social class), gynecologic age, obstetric history and early fetal death, late fetal death, neonatal death, infant death for each pregnancy was performed using the raw data in discrete groups. There were 8442 women in the total sample who experienced a second pregnancy event during the course of the study. They were primarily married (73%), of non-professional occupation (94%), having at least some high school (83%), 5% had a gynecologic age of less than 4 and a greater proportion had per capita income (1960 dollars) less than $2000 (70%). A complete description of all variables used in these analyses are described in Appendix A.

A raw data analysis using TETRAD II requires that all the data have no missing entries for any observations. The full sample of 8442 women yielded a sample of 4440 women for this initial TETRAD II analysis. The analysis revealed a causal pathway from the social class variables through obstetric history, suggesting a confirmation of the proposed model identified in Chapter III. This relationship raised questions about the effect of past history on current pregnancy outcome, in particular, to what extent social class affects a woman's first pregnancy. This could indicate that the effects of social class interact with obstetric history

to result in current poor pregnancy outcome.

To control for the potential interaction of previous obstetric history, only those women who were nulligravid (no previous pregnancies) upon entry into the study were considered for further TETRAD II analysis. A total of 2935 women were nulligravid upon entry into the study. A greater proportion of these women were married (83%), a slightly greater proportion had professional occupations (9% versus 6%), slightly more educated (89% with some high school), with higher incomes (60% had per capita income less than $2000), and almost half the proportion of women with a gynecologic age of less than 4 (2.7%).

Marital status was chosen as a proxy for social class for TETRAD II analyses. Therefore, a third group was created. This group was a subgroup of all women who were nulligravid upon entry into the study and were married at their second pregnancy. This group contained 2462 married women who had slightly more professional occupations (10.5%), 90% with some high school education, 2% with a gynecologic age of less than 4, and per capita income about the same as the full nulligravid group.

PART I: Tetrad II Analysis

The TETRAD II BUILD algorithm is a structural modelling technique that provides a means to increase the ability to establish causality. It operates by examining sample data and providing a set of directed graphs as output. As discussed in chapter III, a directed graph consists of a set of nodes which represent random variables, and edges that indicate direction and connect some of the nodes. An example of a directed edge is: $X \rightarrow Y$. This can be interpreted as "X influences Y and Y is a function of at least X (Spirtes, et al, 1991, p. 3)."

Variable Selection

Analysis of the group of women who were nulligravid upon entering the study began with categorization of the poor outcome into the recurrence groups as described in Chapter III. Categorization schemes for outcome and placental variables were listed in the Data Analysis Plan, Appendix B. In the group of nulligravid women the total number of recurrence of mortality followed by poor outcome was 77 (3%). In addition, the total group of 5 early fetal deaths had missing information on 2 or more of the social class variables. Due to concerns with the predictive power of using the mortality group for this analysis, a decision was made to use the groups of exact recurrence of low birth weight (LBW) and preterm delivery (PTD) for further analysis. The number of exact recurrence of low birth weight or prematurity was 255 (9%). In addition, only exact recurrence of outcomes and placental changes were evaluated. The exact recurrence was evaluated by creating four combinations of the outcomes.

Two groups of "any PTD and any LBW" were used because these two groups represent a different sampling schemes. The computer selection procedure performs sampling without replacement. The order of the sampling is determined by the subsetting *if* statements. In group 1, all preterm births are sampled first, then low birth weight births are sampled from the remainder. This creates a group of preterm births and a group of term gestation low birth weight births. In the second group, all low birth weight births are sampled first and preterm births were sampled from the remainder. This group contains all low birth weight births and a group of normal weight preterm births. This explains why there are different

numbers in groups 1 and 2 in table 1 on the following page. Five placental outcome recurrence variables were prepared and graded on severity as described in Appendix B.

The frequencies for exact recurrence of outcome and placental changes of the nulligravid sample are listed in Table 1 and 2 below.

The four outcome groups were divided as follows:

Group	Level 0	Level 1	Level 2
1	No recurrence	all PTD	all term LBW
2	No recurrence	all LBW	all normal birth weight PTD
3	No recurrence	PTD with LBW	PTD without LBW
4	No recurrence	LBW with PTD	LBW without PTD

TABLE 1
RECURRENCE OF POOR OUTCOME GROUPS
NULLIGRAVIDAS (N=2935)

Group	Level 0	Level 1	Level 2	Missing
1	1860 (88%)	210 (10%)	42 (2%)	823 (28%)
2	1860 (88%)	94 (5%)	158 (8%)	823 (28%)
3	1860 (88%)	80 (4%)	52 (3%)	943 (32%)
4	1860 (88%)	52 (3%)	11 (1%)	1012 (34%)

TABLE 2
RECURRENCE OF CHANGES IN THE PLACENTA
NULLIGRAVIDAS (N=2935)

INFECTION CHANGES		SUB-ACUTE HYPOXIC CHANGES	
Not present	1193 (95%)	Not present	2209(95%)
Mild	20 (2%)	Mild	125 (5%)
Moderate	3 (<1%)	Moderate	0 (0%)
Severe	46 (4%)	Severe	0 (0%)
Very severe	0 (0%)	Very severe	0 (0%)
Total	1262	Total	2334
Missing	1673 (57%)	Missing	601(20%)
INFLAMMATORY CHANGES		CHRONIC HYPOXIC CHANGES	
Not present	1403 (66%)	Not present	1162(62%)
Mild	646 (30%)	Mild	15 (1%)
Moderate	77 (4%)	Moderate	645(34%)
Severe	3 (<1%)	Severe	57 (3%)
Very severe	0 (0%)	Very severe	4(<1%)
Total	2129	Total	1883
Missing	806 (27%)	Missing	1052(36%)

ACUTE HYPOXIC CHANGES	Preterm	Term
Not present	0	0
Mild	1 (<1%)	7(<1%)
Moderate	140 (99%)	2117 (99%)
Severe	0	0
Very severe	0	0
Total	141	2124
Missing		770 (26%)

TETRAD II Findings

TETRAD II analysis was conducted using covariance matrices and the models, except model 3 (including medical history), in the data analysis plan outlined in Appendix B. The choice to use covariance matrices on the continuous variables versus raw data on discrete groups was made so that more of the observations were used for each variable. When raw data is used, there must be complete information for every variable in that observation. When covariance matrices are used, there must be complete information for each pair separately.

Each model was run on all four of the outcome groups. Since TETRAD II bases assumptions on linearity and multinormality, the choice of significance level became a concern. In a sample size of over 2000 it is possible that small violations of these assumptions exist and the usual choice of a significance level of 0.05 might cause TETRAD II to reject edges that are actually true. It was suggested that the models be run over a range of significance levels and the more robust edges be identified as part of the model (Scheines, 1992).

TETRAD II analyses were run at significances of 0.4, 0.2, 0.1, 0.05, and 0.01 for each model and group, not assuming causal sufficiency. The models that resulted from these analyses can be found in Appendix C. An edge was almost always present from expected education to actual education. The findings of all models also indicated that marital status and gynecologic age were edges in the majority of treks (paths) and this trek continued to recurrence of outcome in some cases. This raised the question of the relationship of marital status as a proxy of the other social class variables. It also confirmed the section of the model that

connects social class to gynecologic age.

Relationships were identified between recurrent placental changes and recurrent outcome. An edge connecting recurrent chronic hypoxia and recurrence of poor outcome was present which was not connected to any of the social class variables. This edge was robust through all models that included recurrent chronic hypoxia and it was also robust throughout different significance levels in each model. An edge between recurrent placental infection and outcome also appeared in several of the groups. While present, it not as robust as recurrent chronic hypoxia. Recurrent placental infection was also connected to marital status and gynecologic age in some of the models. When only recurrent chronic hypoxia and recurrent placental infection were included with social class and gynecologic age, an edge between placental infection and occupation appeared in two models. An edge between recurrent inflammation and marital status was also robust for several significance levels when only inflammation, social class and gynecologic age were included in the model. This edge was not observed when all placental variables were included in the model. It is possible that the stronger edge between recurrent chronic hypoxia and recurrent outcome caused this edge to vanish. When only placental variables and outcome were analyzed, no edges appeared. This indicates that there may be a latent variable which operates through the social class and/or gynecologic age variables and the placental variables to produce recurrent poor outcome.

To evaluate the relationships identified by TETRAD II, univariate analysis was conducted. Table 3-7 summarize the univariate analyses.

TABLE 3
UNIVARIATE ANALYSIS
MARITAL STATUS
FULL NULLIGRAVID GROUP (N=2935)

Variable	DF	Chi-Square	Probability	Cramer's V
Expected Education	4	5.923	0.205	0.050
Actual Education	4	62.323	0.000	0.151
Occupation	3	115.523	0.000	0.218
Gynecologic Age	4	142.168	0.000	0.221
Per Capita Income	4	302.840	0.000	0.332
Family Social Class	3	16.514	0.001	0.080

The results in Table 3 indicate that there was a significant relationship between marital status and all social class variables except expected education. This confirms the relationships identified in the TETRAD II analysis. The nonsignificant relationship between expected education and marital status is probably masked by actual education since the TETRAD II analysis indicates an edge between expected education and actual education that is robust in almost all analyses.

TABLE 4
UNIVARIATE ANALYSIS
RECURRENCE OF ANY PREMATURITY, ANY LOW BIRTH WEIGHT
FULL NULLIGRAVID GROUP (N=2935)

Variable	DF	Chi-Square	Probability	Cramer's V
SOCIAL CLASS				
Marital Status	2	27.611	0.000	0.114
Family Social Class	6	6.507	0.369	0.042
Per Capita Income	8	59.303	0.000	0.122
Actual Education	8	15.048	0.058	0.062
Expected Education	8	12.080	0.148	0.060
Occupation	6	17.545	0.007	0.070
Gynecologic Age	8	54.744	0.000	0.114
PLACENTA RECURRENCE				
Placental Infection	6	3.237	0.78	0.042
Acute Hypoxia	2	0.386	0.824	0.015
Sub-acute Hypoxia	2	6.281	0.043	0.060
Chronic Hypoxia	8	67.853	0.000	0.158
Inflammation	6	25.977	0.000	0.092

TABLE 5
UNIVARIATE ANALYSIS
RECURRENCE OF ANY LOW BIRTH WEIGHT, ANY PREMATURITY
FULL NULLIGRAVID GROUP (N=2935)

Variable	DF	Chi-Square	Probability	Cramer's V
SOCIAL CLASS				
Marital Status	2	28.019	0.000	0.115
Family Social Class	6	2.335	0.886	0.025
Per Capita Income	8	62.290	0.000	0.125
Actual Education	8	20.691	0.008	0.0738
Expected Education		15.439	0.051	0.068
Occupation	6	21.408	0.002	0.077
Gynecologic Age	8	51.281	0.000	0.110
PLACENTA RECURRENCE				
Placental Infection	6	2.856	0.83	0.039
Acute Hypoxia	2	0.990	0.609	0.025
Sub-acute Hypoxia	2	5.755	0.058	0.058
Chronic Hypoxia	8	56.583	0.000	0.144
Inflammation	6	25.209	0.000	0.091

TABLE 6
UNIVARIATE ANALYSIS
RECURRENCE OF PREMATURITY WITH LBW, PREMATURITY WITHOUT LBW
NULLIGRAVID GROUP (N=2935)

Variable	DF	Chi-Square	Probability	Cramer's V
SOCIAL CLASS				
Marital Status	2	19.98	0.000	0.10
Family Social Class	6	2.71	0.84	0.03
Per Capita Income	8	43.9	0.000	0.11
Actual Education	8	16.57	0.035	0.11
Expected Education	8	24.394	0.002	0.09
Occupation	6	10.0	0.122	0.05
Gynecologic Age	8	34.6	0.000	0.09
PLACENTA RECURRENCE				
Placental Infection	6	2.989	0.81	0.041
Acute Hypoxia	2	2.398	0.301	0.04
Sub-acute Hypoxia	2	2.015	0.365	0.035
Chronic Hypoxia	8	25.216	0.001	0.09
Inflammation	6	12.138	0.059	0.065

TABLE 7
UNIVARIATE ANALYSIS
RECURRENCE OF ANY LBW, WITH PREMATURITY, LBW WITHOUT PREMATURITY
NULLIGRAVID GROUP (N=2935)

Variable	DF	Chi-Square	Probability	Cramer's V
SOCIAL CLASS				
Marital Status	2	15.0	0.001	0.08
Family Social Class	6	7.	0.30	0.04
Per Capita Income	8	23.8	0.002	0.08
Actual Education	8	16.6	0.035	0.07
Expected Education	8	22.5	0.004	0.08
Occupation	6	5.6	0.5	0.04
Gynecologic Age	8	22.3	0.004	0.08
PLACENTA RECURRENCE				
Placental Infection	6	2.683	0.84	0.039
Acute Hypoxia	2	0.201	0.904	0.012
Sub-acute Hypoxia	2	1.264	0.532	0.028
Chronic Hypoxia	8	51.177	0.000	0.143
Inflammation	6	9.712	0.137	0.059

The results of the univariate analyses presented in tables 4-7 above support the findings of the TETRAD II modelling. Marital status which had many robust edges in the TETRAD II modelling was also significantly related to all the social class variables, except actual education, and it was related to all of the four selected recurrent outcomes. Per capita income, occupation, gynecologic age and actual education were connected by edges in TETRAD II modelling and also had significant chi-square and Cramer's V statistics. The significant relationships between recurrent inflammation and recurrent outcome, and recurrent sub-acute hypoxia and recurrent outcome were noted in the univariate analysis but were not demonstrated by the TETRAD II analysis. It is possible that these relationships were hidden edges in the TETRAD II analysis by the stronger relationships such as recurrent chronic hypoxia which is highly significant and is very robust.

During the course of TETRAD II analysis, it was noted that per capita income was producing a covariance of 0 for some samples. A further analysis of per capita income revealed a variance of greater than 600,000. Box plot and quartile evaluation revealed that the variable was skewed toward the left (lower incomes) with a skewness of greater than -3. Analysis by hospital center revealed that two of the twelve hospitals had higher incomes, education and occupation than the other hospitals, in particular one center contained almost all the observations where the per capita income was greater than $3999. This indicated that center should be considered as a covariate for further analysis and that per capita income requires transformation. TETRAD II analysis was then conducted removing per capita income from the model the relationships described for

the full model remained.

To control for the effects of marital status, the subsample of the nulligravid group which contained only married women was created, as described above, and assessed with TETRAD II. This group contained 2462 observations. When marital status was controlled, edges between occupation and gynecologic age and occupation and per capita income appeared and were robust at difference significance levels and different groups. The edge between social class variables and recurrent outcome became less robust, appearing at only one significance level and only in one of the groups (prematurity with/without lbw). It did not appear in the other groups. Other weak edges appeared between recurrent infection and recurrent subacute hypoxia, recurrent chronic hypoxia and infection, occupation and recurrent subacute hypoxia and expected education and recurrent poor outcome. All these weak edges were produced at a significance level of 0.4, which is very close to pure chance. The edge between recurrent chronic hypoxia and recurrent outcome remained robust for the both the model with all placental recurrence and with recurrent chronic hypoxia alone it was robust for different significance levels for each model.

In summary, Tetrad II BUILD analyses were run at multiple significance levels. The an edge was almost always present from expected education to actual education. In addition, there were edges from marital status and gynecologic age and the other social class variables. Relationships were identified between recurrent placental changes and recurrent outcome. An edge connecting recurrent chronic hypoxia and recurrent poor outcome. This edge was not connected to any of the social

class variables. This edge was robust throughout different significance levels in each model. There was an edge connecting placental infection and recurrent outcome which was less robust than the chronic hypoxia variable. Univariate analysis confirmed these findings. The TETRAD II models can be found in Appendix C.

PART II-Statistical Analysis

Variable Selection

The relationships identified in the TETRAD II analysis supported the proposed model which identified social class, gynecologic age, recurrence of placental pathology and the growth outcomes of birth weight and gestational age. The variables used for the statistical analysis were derived from the TETRAD II analysis and the proposed model. Social class variables were marital status, family social class (measured as the difference in woman's education - father's education), education in years, occupation (trichotomized as professional, skilled, unskilled) and transformed per capita income ($2 + \log_2$ (per capita income)). Per capita income was transformed because of the problems discovered during the TETRAD II analysis. The original variance for per capita income was greater than 600,00 and the skewness was greater than -3. After transformation, the variance became 0.85 and the skewness became -0.95.

Since the relationship between expected education and actual education and marital status and gynecologic age proved to be very robust in the Tetrad II analysis, a concern for effects of multicollinearity arose. In many of the models where marital status was considered, an edge between gynecologic age and marital status was also present, therefore gynecologic age was also not included in the model due to concerns of mulitcollinearity. The same was true for expected education and actual education. This was one of the most robust edges in the TETRAD II modelling. Expected education was also not included as a factor in the analysis. Cigarette smoking, which has been demonstrated to be a risk factor for poor outcome was included as a cofactor.

The placental variables were divided by the medical significance of their pathology as it was discussed in chapter II. Two groups were evaluated for analysis: those indicating acute placental inflammation (cord vasculitis, chorionic vasculitis, funisitis and placental chorionitis) and those indicating hypoxia (nucleated red blood cells, nuclear clumping in the syncytiotrophoblast, decidual necrosis, fibrin deposition or cystic changes in the cytotrophoblast, infarcts, fibrosis, villous edema, increased number of Hofbauer cells or excessive Langhans layer, vessel thrombosis and macrophages containing meconium in the amnion, chorion or decidua). The outcomes of interest, as discussed previously were recurrence of low birth weight (less than 2500 grams) and recurrence of preterm delivery (less than 259 days gestation). Intrauterine growth retardation (greater than 259 days gestation and less than 2500 grams) was found to repeat in only 11 (< 1%) of the pregnancies and was eliminated from the analysis due to inadequate sample size.

The four outcome groups used in the TETRAD II analysis were combined into two groups for linear logistic regression because of their similarity and of the small number of recurrence of low birth weight without preterm delivery. In addition, the two combinations of preterm delivery and low birth weight (levels 1 and 2) produced very similar TETRAD II models. The final groups used for statistical analysis were all preterm births and all low birth weight births.

The research questions were first analyzed by evaluating the crude odds ratio as an estimate of the relative risk. When the outcome is relatively uncommon, the odds ratio is a close estimate of the relative risk. Since poor pregnancy outcome is relatively uncommon (less than 10%

in the population exposed to the risk factor) this estimate was possible (Altshuler and Herman, 1989).

Analysis began on the nulligravid dataset of 2935 women. Two-by-two tables were constructed using the two recurrent outcomes described above. It soon became apparent that there were many empty cells. The empty cells prevented calculation of odds ratios for those tables and convergence of the logistic models. This necessitated using the full data set of 7653 women for any further analyses. A series of univariate cross-tabulations were developed comparing each of the social class variables and gynecologic age at the second pregnancy with each outcome, similar to the univariate analysis described in Part 1.

Placental pathologies were crossed in a "super table" (2 X k X 2 X 2) which considered presence or absence of pathology at the first and second pregnancy crossed with the selected outcome at each pregnancy. These tabulations provided crude odds ratios and identified those variables that demonstrated a crude risk of repeating a poor outcome. The placental pathologies were identified as indicative of infection or hypoxia. The complete description is provided in the Data Analysis Plan in Appendix B.

Placental pathologies that were included in the recurrent chronic hypoxia variable used in the TETRAD II analysis (nuclear clumping in the syncytiotrophoblast and nucleated red blood cells, micro infarcts, pathologic edema of the villi) did not demonstrate significance in the two-by-two tables. However, placental pathologies that were used in the recurrent inflammation variable used in the TETRAD II analysis (marginal, capsularis and basalis decidual necrosis) were significant, these

pathologies are also indicative of hypoxia. Another recurrent hypoxia indicator was macrophages filled with meconium. This pathology was also significant in the 2 X 2 tables.

Significant pathologies indicative of recurrent infection were chorionic vasculitis and placental chorionitis. In addition, there was a weak relationship between cord vasculitis of the umbilical vein and funisitis. These pathologies were part of the infection variable created for TETRAD II analysis. They are also part of the syndrome identified previously as acute placental inflammation. These pathologies were grouped and examined as acute placental inflammation and each infection related pathology was examined separately in further analyses.

There were two groups of variables used in the TETRAD II analysis that were not significant. The pathologies included in the acute hypoxia variable of the TETRAD II analysis (decidual vessel thrombosis, fibrinoid decidual vessels, fibrin deposition/cystic changes in the cytotrophoblast) and some of the placental pathologies indicative of infection that were nonsignificant were acute epithelial placental membranitis of the amnion and chorion, squamous metaplasia of the amnion and amnion nodosum. All of the nonsignificant variables had recurrence samples of less than 10. Their nonsignificance could have been due to lack of power.

The placental pathologies identified above as significant were then entered into logistic regression models along with all the selected social class variables and cigarette smoking.

Statistical Analysis Findings

Research Question 1: Which variables represent significant risks of repeating a poor outcome

A linear logistic regression analysis revealed 1.6 (1.2-2.3) greater

risk of repeating a low birth weight or preterm delivery if the woman was unmarried. This remained unchanged when adjusted for all other social class factors and cigarette smoking. Educational incongruity was evaluated as a continuous variable in years of education. There was a 10% greater risk of repeating a low birth weight or preterm delivery for each year of greater incongruity. Recalling that educational incongruity was calculated as (education of the woman - the education of the father of the baby), this means that women who are highly educated with fathers of the baby who are poorly educated are at the greatest risk of repeating a preterm or low birth weight infant. The risk of repeating a preterm delivery was 7.2 (3.8-13.5) times greater for women of skilled professions before adjustment. This became a protective effect of 0.6 (0.4-0.8) after adjustment. This may indicate that the effect of skilled education is a proxy for other social factors. Occupation was not a significant risk factor for repeating a low birth weight birth after adjustment. Education did not provide a significant risk in either group. This could have been hidden by the stronger relationship to educational incongruity which contains education. Cigarette smoking was significant as a risk for preterm delivery before adjustment (3.6, 3.0-4.4), but became non significant after adjustment (1.4, 0.8-2.4). Again, this may indicate that the effect of cigarette smoking is a proxy for other factors of social class. When cigarette smoking occurred in both pregnancies, there was a significant a risk of repeating a low birth weight birth even after adjustment (2.1, 1.5-2.9).

Research Question 2: Is there a significant risk of repeating a poor outcome if placental pathology repeats?

Evaluation of two-by-two tables identified two key significant

relationships between recurrence of placental pathology and recurrence of preterm delivery or low birth weight. First, an increased risk of preterm delivery when there was a recurrence of acute placental inflammation was demonstrated with a crude odds ratio of 1.6, (1.1-2.3). When analyzed alone, recurrence of chorionic vasculitis represented a 4.5 (4.3-4.6) times greater risk of repeating a preterm delivery and recurrence of placental chorionitis which represents a 16 times greater risk of repeating a preterm delivery. The remaining pathologies included in the recurrence of acute placental inflammation (cord vasculitis of the vein and funisitis) did not demonstrate significance. The sample size of these two groups was also very small. These findings are summarized in Table 8.

Secondly, two of the hypoxia pathologies were significant. An increased risk of low birth weight was demonstrated with a recurrence of meconium filled macrophages and recurrent decidual necrosis examined together, crude odds ratio 2.6, (2.4-2.8). When analyzed alone, there as a 6.5 (1.4-31) times greater risk of repeating a low birth weight birth if there was recurrence of decidual necrosis. Recurrence of meconium filled macrophages represented a 6.5 (5.3-7.9) times greater risk of repeating a low birth weight birth. These findings are summarized in Table 9.

Research Question 3: *Does the risk of recurrence of poor outcome if placental pathology repeats remain significant after controlling for social class factors?*

This question was examined using linear logistic regression. Three models were used for each placental pathology. The first model included the recurrence of placental pathology and the outcome variable. The second model added the social class variables and the third model added both the social class and cigarette smoking. This process was done for

each recurrent placental pathology, acute placental inflammation and hypoxia and each hypoxia variable.

Two of the placental pathologies remained significant after adjustment. Recurrent chorionic vasculitis remained significant after adjustment with a 4.2 (1.4-12) greater risk of repeating a preterm delivery. Recurrent decidual necrosis also remained a significant risk (5.5, 1.1-27.6) of repeating a low birth weight birth after adjustment.

The other pathologies indicative of infection that were significant before adjustment became nonsignificant. Recurrent acute placental inflammation did not remain significant as a grouped variable after adjustment (1.2, 0.7-2.1) and recurrent placental chorionitis also became nonsignificant after adjustment (0.7, 0.2-2.8).

The other pathologies indicative of hypoxia that were significant before adjustment became nonsignificant after adjustment. Recurrence of meconium filled macrophages became nonsignificant (4.9, 0.6-42) as well as the combination of meconium filled macrophages and decidual necrosis (1.5, 0.4-7.5). This suggests that cigarette smoking may operate through meconium filled macrophages. The findings of the logistic regression analysis are summarized in tables 8 and 9 below.

TABLE 8
THE RISK OF PRETERM DELIVERY BY SOCIAL CLASS, CIGARETTE SMOKING ACUTE PLACENTAL INFLAMMATION (API)

RISK FACTORS	PRETERM DELIVERY -/-[1]	PRETERM DELIVERY +/+[2]	OR[3](95% CI)	OR[4] 95% CI
Social Class				
Marital Status				
Married	4992 (85)[5]	292 (78)	1 (Reference)	1 (Reference)
Unmarried	903 (15)	82 (22)	1.6 (1.2-2.1)	1.6 (1.2-2.3)
Occupation				
Professional	322 (7)	24 (5)	1 (Reference)	1 (Reference)
Skilled	1448 (32)	183 (40)	7.2 (3.8-13.5)	0.6 (0.4-0.8)
Unskilled	2826 (61)	251 (54)	4.1 (3.4-5.0)	0.9 (0.8-1.6)
Education/[6]*	-/-	+/+		
(Completed years)	10.5(2.3, 9-12)[7]	10.75(2.3, 9-12)[7]		0.9 (0.9-1.0)
Educational[6]*	-/-	+/+		
Incongruity	0.6(2.4, -1 - 1)[7]	-0.2(2.5, -2 - 1)[7]		1.1 (1.0-1.1)
Cigarette Smoking				
-/-[1]	2311 (51)	235 (47)	1 (Reference)	1 (Reference)
+/+[2]	2247 (49)	265 (53)	3.6 (3.0-4.4)	1.4 (0.8-2.4)
Acute Placental Inflammation				
-/-[1]	4124 (96)	445 (92)	1 (Reference)	1 (Reference)
+/+[2]	225 (4)	38 (8)	1.6 (1.1-2.3)	1.2 (0.7-2.1)
Cord Vasculitis only				
-/-[1]	4350 (98)	493 (97)	1 (Reference)	1 (Reference)
+/+[2]	111 (2)	13 (3)	1.0 (0.9-1.1)	1.4 (0.8-2.4)
Chorionic vasculitis only				
-/-	3666 (98)	281 (91)	1 (Reference)	1 (Reference)
+/+	82 (2)	28 (9)	4.5 (4.3-4.6)	4.2 (1.4-12)
Funisitis only				
-/-	3949 (99)	312 (99)	1 (Reference)	1 (Reference)
+/+	28 (1)	7 (1)	3.2 (3.0-3.4)	1.1 (0.1-2.1)
Placental chorionitis only				
-/-	3429 (99)	248 (90)	1 (Reference)	1 (Reference)
+/+	24 (1)	28 (10)	16.1 (16-16.2)	0.7 (0.2-2.8)

(1) Absent both pregnancies
(2) Present both pregnancies
(3) Crude odds ratio
(4) Adjusted odds ratio (adjusted for social class and smoking)
(5) Column percentage
(6) Change in odds for each year of education
(7) Mean (standard deviation, inter-quartile difference)
*T-Test for continuous variables not significant

TABLE 9
THE RISK OF LOW BIRTH WEIGHT BY SOCIAL CLASS, CIGARETTE SMOKING MECONIUM FILLED MACROPHAGES AND DECIDUAL NECROSIS

RISK FACTORS	LOW BIRTH WEIGHT -/-[1]	+/+[2]	OR[3] 95% CI	OR[4] 95% CI
Social Class				
Marital Status				
Married	4992 (85)[5]	292 (78)	1 (Reference)	1 (Reference)
Unmarried	903 (15)	82 (22)	1.6 (1.2-2.1)	1.6 (1.2-2.3)
Occupation				
Professional	336 (6)	6 (55)	1 (Reference)	1 (Reference)
Skilled	3093 (61)	168 (55)	1.6 (0.7-4.2)	0.8 (0.6-1.1)
Unskilled	1678 (33)	127 (42)	5.6 (5.3-5.9)	1.0 (0.7-1.5)
Education/[6]*	-/-	+/+		
(Completed years)	10.7 (2.3, 9-12)[7]	10.8 (2.3, 9-12)[7]		0.9 (0.8-0.9)
Educational[6]*	-/-	+/+		
Incongruity	-0.2 (2.5, -2 - 1)[7]	-0.2 (2.5, -2 - 1)[7]		1.1 (1.0-1.2)
Cigarette Smoking				
-/-	2679 (88)	111 (33)	1 (Reference)	1 (Reference)
+/+	349 (12)	222 (66)	4.5 (3.9-5.2)	2.1 (1.5-2.9)
Meconium filled macrophages/ Decidual Necrosis				
-/-	4866 (98)	290 (95)	1 (Reference)	1 (Reference)
+/+	104 (2)	16 (5)	2.6 (1.5-4.5)	1.5 (0.4-7.5)
Decidual Necrosis only				
-/-	4862 (98)	291 (96)	1 (Reference)	1 (Reference)
+/+	107 (2)	13 (4)	6.5 (1.4-31)	5.2 (1.0-30)
Meconium filled macrophages only				
-/-	4495 (97)	5 (83)	1 (Reference)	1 (Reference)
+/+	216 (3)	1 (17)	6.5 (5.3-7.9)	4.9 (0.6-42)

(1) Absent both pregnancies
(2) Present both deliveries
(3) Crude odds ratio
(4) Adjusted odds ratios (adjusted for social class and smoking)
(5) Column percentages
(6) Mean (standard deviation, inter-quartile difference)
(7) Change in odds for each year of education
*T-test for continuous variables nonsignificant

CHAPTER V
SUMMARY AND CONCLUSIONS

Summary

A nested case-control design was used to conduct an exploratory analysis of the relationship between placental pathology and the poor pregnancy outcomes of either low birth weight or preterm delivery.

The purpose of the study was to determine if repeating a particular placental pathology or placental pathology syndrome was predictive of an increased risk of repeating a poor outcome.

This research involved a two-part analysis using data from the Collaborative Perinatal Project of the National Institute of Neurological and Communicative Disorders and Stroke. Data were collected from 1959 to 1966 from women being cared for in 12 medical-school affiliated hospitals in different regions of the United States. The sample included 53,518 pregnancies in 10,699 women and examination of 31,494 placentas (59% of all pregnancies). Placenta data was available for 86% of late fetal deaths and infant deaths. Included in the data were information on placental pathology along with demographic, social, obstetric, medical and postmortem examinations. The outcomes of low birth weight (less than 2500 grams) and preterm delivery (less than 259 days) that repeated in both pregnancies were examined and compared to placenta pathology which also repeated in both pregnancies. The first two pregnancies during the data collection of all women of black and white races were used in the analysis. This provided as sample of 7653 women. A subsample 2935 women who had never been pregnant before entering the study was also analyzed separately.

Several analytical techniques were employed to explore this

relationship. These techniques included testing of the proposed model with a causal modelling computer algorithm, TETRAD II (Spirtes, et al, 1991), univariate cross-tabulations with construction of crude odds ratios and linear logistic regression modelling.

Three research questions were posed to evaluate this relationship:

Research Question 1: *Which factors represent significant risks of repeating a poor outcome*

Research Question 2: *Is there a significant risk of repeating a poor outcome if placental pathology repeats?*

Research Question 3: *Does the risk of recurrence of poor outcome if placental pathology repeats remain significant after controlling for other factors?*

A model was proposed which stated that measures of social class, education, expected education, marital status, per capita income, occupation and family social class, were causally related to gynecologic age and behavior which interacted with obstetric history and medical history to have an impact on placental development and finally fetal growth and outcome. A pathologic impact on placental development could be manifested in two ways. The first was a placental response to infection and the second was a placental response to hypoxia.

The model was tested and supported using TETRAD II BUILD. The TETRAD II BUILD algorithm is a structural modelling technique that provides a means to increase the ability to establish causality. It operates by examining sample data and providing a set of directed graphs as output. This research is the first to use this algorithm on actual sample data. All the testing of this algorithm was used on simulated data

constructed using Monte Carlo techniques.

Evaluation of the group of 2935 women who were never pregnant was conducted for the TETRAD II BUILD modelling. These models are presented in Appendix C. Univariate analyses were suggestive of similar results as the overall sample. The models were tested over a wide range of significance levels to evaluate robustness of the relationships. The strongest relationships were between marital status and other social class variables, especially gynecologic age. Marital status and recurrence of either low birth weight or preterm delivery also were robust. In addition, the relationship between poor outcome and recurrence of infection and recurrence of hypoxia were also robust This suggests that the phenomenon of poverty or poorer social class has a significant effect of repeating placental pathology and poor outcome.

Following the evaluation of causal relationships, an analysis of risk was conducted. This included univariate contingency table analyses and linear logistic regression modelling.

The first research question investigated those factors which represented a significant risk of repeating a low birth weight birth or a preterm delivery. A linear logistic regression analysis revealed two social class factors that represented significant risks of repeating a low birth weight birth and preterm delivery. There was a 1.6 (1.2-2.3) times greater risk of repeating a low birth weight or preterm delivery if the woman was unmarried. Educational incongruity was defined as (years education of the woman - the years education of the father of the baby) It was evaluated as a continuous variable in years of education. It too demonstrated a increased risk of poor outcome. There was a 10% greater

risk of repeating a low birth weight or preterm delivery for each year of greater incongruity. Therefore women who are highly educated and who have born children with men who are poorly educated are at the greatest risk of repeating a preterm delivery or low birth weight infant. Cigarette smoking in both pregnancies also represented a significantly higher risk of repeating a low birth weight birth (4.5, 3.9-5.2) or a preterm delivery (3.6, 3.0-4.4) before adjustment.

The second research question asked if there was a significant risk of repeating a low birth weight birth or preterm delivery if placental pathology repeats. Evaluation of two-by-two tables identified two key significant relationships between recurrence of placental pathology and recurrence of preterm delivery or low birth weight birth. First, an increased risk of preterm delivery when there was a recurrence of acute placental inflammation was demonstrated with a crude odds ratio of 1.6, (1.1-2.3). When analyzed alone, recurrence of chorionic vasculitis represented a 4.5 (4.3-4.6) times greater risk of repeating a preterm delivery and recurrence of placental chorionitis which represents a 16 times greater risk of repeating a preterm delivery.

Secondly, two of the hypoxia pathologies were significant. An increased risk of low birth weight was demonstrated with a recurrence of meconium filled macrophages and recurrent decidual necrosis examined together, crude odds ratio 2.6, (2.4-2.8). When analyzed alone, there as a 6.5 (1.4-31) times greater risk of repeating a low birth weight birth if there was recurrence of decidual necrosis. Recurrence of meconium filled macrophages represented a 6.5 (5.3-7.9) times greater risk of repeating a low birth weight birth.

The third research question asked if the risk of recurrence of poor outcome when placental pathology repeats remains significant after controlling for social class factors. This question was addressed by linear logistic modelling which included all the social class factors, cigarette smoking and the placental pathologies. Two of the placental pathologies remained significant after this adjustment. Recurrent chorionic vasculitis remained significant after adjustment with a 4.2 (1.4-12) greater risk of repeating a preterm delivery. Recurrent decidual necrosis also remained a significant risk (5.5, 1.1-27.6) of repeating a low birth weight birth after adjustment.

Cigarette smoking remained significant for low birth weight after adjustment (2.1, 1.5-2.9) but became nonsignificant for preterm birth (1.4, 0.8-2.4). This indicates that social class operates through cigarette smoking in the case of recurrence of preterm delivery. In addition, meconium filled macrophages became nonsignificant after adjustment. This suggests that cigarette smoking may operate through meconium filled macrophages. The findings of the logistic regression analysis are summarized in tables 8 and 9.

It should be noted that this research was an initial exploratory study to investigate if a relationship exists between recurrence of placental pathology and recurrence of poor outcome. Its focus was on main effects and it did not examine the effect of intricate variables such as race or medical history or interactions between variables because the models that resulted were too complex for a preliminary analysis. These results should serve as a pilot study for future research.

DISCUSSION

The findings of this study are compelling and provide an impetus to pursue future investigations. It is well known that preterm birth and LBW are highly associated with infant mortality. As noted earlier, Yankauer (1990) notes that questions asked over 20 years ago concerning factors that affect infant and perinatal mortality have remained unanswered. The goal of this research was to provide direction to answer some of these questions concerning the mediating channels and how the effects of both social and biologic factors operate on pregnancy outcome.

Regardless of the approach used, the results indicate a strong relationship between recurrence of placental pathology and recurrence of poor outcome. This relationship was independent of obstetric history since it also was demonstrated in a group of women who have no prior obstetric history as well. In addition, it remained when controlling for marital status as a proxy for social class.

The Collaborative Perinatal Project collected placenta data on 59% of all pregnancies including 86% of late fetal and infant deaths. Stringent guidelines for evaluation of placental pathology were established by an expert in the field. Four specially trained technicians evaluated the placentas and all nonroutine abnormalities were examined by a senior pathologist (Naeye and Peters, 1978). This increases the validity of the pathologic placental findings and support these results.

The weakness of this study lies is the sample. It is not representative of the population of the United States as a whole. This was easily demonstrated by per capita income which was severely skewed to the right with univariate analysis indicating a skewness of over -3. In

addition, the highest incomes were limited to two of the twelve centers. These centers also had a higher mean educational level and higher percentage of married women. Proportions of black and white women were also unevenly distributed among the centers.

Attributable risk is an important consideration when evaluating the findings of this study presented in tables 8 and 9. Attributable risk is the proportion of the outcome that is ascribed to the factor. It differs from relative risk which is the likelihood of the outcome in exposed individuals relative to those who are not exposed. In a rare disease the odds ratio is a close estimate of the relative risk. (Hennekens and Buring, 1987).

The results may represent an inflation of risk when evaluated in the context of the population of the study. As noted above, majority of the sample population were of lower socioeconomic classes. This especially evident in the per capita income where the variance was 600,000 and the skewness was -3. In addition, 27% of the women were unmarried and 94% were of non-professional occupation.

A large proportion of the attributable risk of preterm delivery and low birth weight birth was explained by the social class factors of marital status and educational incongruity. The attributable risk of cigarette smoking was higher for low birth weight births, but was not much different than the placental pathology for preterm delivery.

The findings demonstrate that there is a significant relative risk of repeating a poor pregnancy outcome if the woman is unmarried or there is high educational incongruity and non-professional occupation. Two of these social class variables remained significant after adjustment and one

became protective. The protective effect may be for being skilled compared to unskilled. The social class factors have the highest attributable risk. There is an intermediate attributable risk for cigarette smoking and low birth weight birth. There is a lower attributable risk for recurrence of the placental pathologies. The lower attributable risk of recurrence of the placental pathologies may be due to the rareness of the event.

TABLE 10
ATTRIBUTABLE RISK
RECURRENCE OF LOW BIRTH WEIGHT BIRTH OR PRETERM DELIVERY

	LOW BIRTH WEIGHT	PRETERM DELIVERY
MARITAL STATUS		
MARRIED	Reference	Reference
UNMARRIED	8%	8%
OCCUPATION		
PROFESSIONAL	Reference	Reference
SKILLED	21%	34%
UNSKILLED	35%	41%
CIGARETTE SMOKING	51%	38%
INFECTION		
PLACENTAL CHORIONITIS	N/A	9%
CHORIONIC VASCULITIS	N/A	7%
HYPOXIA		
DECIDUAL NECROSIS	4%	N/A

The remainder of this discussion addresses each research question separately and is followed by implications for future study.

RESEARCH QUESTIONS

1. *What social, demographic, medical, and past obstetric factors represent a significant risk of repeating a poor pregnancy outcome?*

The most consistent findings were the effect of marital status and educational incongruity. Causal relationships between expected education and actual education, and marital status and gynecologic age were robust at more than two significance levels in each model. The effect of incongruity was significant when tested with a Wald chi-square test ($p=.01$) for most models, but the adjusted odds ratio included 1. This indicates that the effects of educational incongruity are conditional on other social class factors, in particular marital status which has almost a two-fold risk of recurrence of prematurity when there is a recurrence of acute placental inflammation or any of the pathologies included in the syndrome.

Marital status and educational incongruity are both indicators of poverty. The results demonstrate that poverty produces more than a single poor outcome and that there is a common pathway by which there is attributable risk of recurrence due to the effects of poverty. This was also demonstrated by the TETRAD II modelling. The number of edges among the social class indicators drops dramatically when only a group of married women is considered. In a model with any placental recurrence and any preterm delivery, any low birth weight there were no edges produced. In addition, skilled occupation became a protective effect when controlling for marital status and educational incongruity. This may indicate that as social class increases, women in skilled occupations have a lower risk of repeating poor outcomes. This raises important questions

for future studies.

Analysis of the interaction between social class and recurrence of placental pathology and recurrence of poor outcome is beyond the scope of this exploratory study but is a necessary follow-up. It would be important to identify a sample with a less skewed per capita income and further assess the effect of per capita income to develop a more complete picture of the poverty status. Gynecologic age may be a more powerful predictor in a current population where there is a higher number of teenage and unwed pregnancies. Some of the effects observed may be nonlinear. Only linear logistic regression modelling was used for this study. The effects of non-linearity may be masked in this analysis.

2. *Is there a significant risk of repeating a poor pregnancy outcome when there is a recurrence of placental pathology?*

TETRAD II modelling identified a robust edge between recurrence of chronic hypoxia and recurrence of both low birth weight and preterm delivery. A weaker edge was identified for recurrence of any infection pathologies. The TETRAD II models were run to confirm the proposed model. The variables included in the five recurrence pathologies for the TETRAD II analysis are identified in the data analysis plan in Appendix C. Since this was the preliminary analysis, many pathologies include in each of the conditions (chronic hypoxia, acute placental inflammation, sub-acute hypoxia, acute hypoxia and inflammation) were not significant predictors or had very small sample sizes. In spite of this added "noise" the relationships were robust.

The next important step would be to take the most significant pathological conditions and enter them into the TETRAD II build program to verify the relationships. Cigarette smoking was not added into the models

since it is such a powerful predictor on its own. It was conceivable that it would shield very significant but less powerful relationships. TETRAD II also has a other features which can test a plausible model or a model where there may be latent variables which share edges with several observed variables. Finally, the model can be tested quantitatively using EQS (Bentler, 1985).

Linear logistic regression, univariate and bivariate analyses identified a significant risk of repeating low birth weight when there is a recurrence of decidual necrosis and a significant risk of repeating a preterm delivery when there is a recurrence of acute placental inflammation, in particular, chorionic vasculitis and placental chorionitis. These findings confirm that a relationship exists between recurrence of placental pathology and recurrence of poor outcome. The findings are biologically plausible. Decidual necrosis is indicative of chronic hypoxia, making its relationship with low birth weight logical since repeated hypoxic insult will impede growth. In addition, the relationship is moderated by cigarette smoking, also a cause of hypoxia.

Acute placental inflammation has been associated with preterm delivery (Herman, 1987, Berman, et al, 1987, McGregor, 1987, 1988a, 1988b). The finding that there is an increased risk of repeating a preterm delivery if there is recurrence of acute placental inflammation has many significant implications. It may be a preliminary answer to McGregor's question of how to identify women at risk for preterm delivery. The implications of these findings was discussed later in this chapter.

3. *Does the risk of recurrence of poor outcome remain significant when the other identified risk factors are controlled for?*

Social class factors were added to the logistic model, which

included recurrence of low birth weight and recurrent decidual necrosis, with and without cigarette smoking. When only social class variables were added (education, incongruity, marital status and occupation), the risk changed slightly, remaining significant 6.5 (1.4-31) to 5.4 (1.1-28), adding adjusted the odds ratio 5.2 (1.0-28). The wide confidence intervals indicate that there may be collinearity and possible interactions with social class and cigarette smoking. The Wald Chi-Square statistic for the full model was 3.7 and marginally significant with p=0.05. This indicates that much of the effect of recurrent decidual necrosis is explained by cigarette smoking. It does indicate that there may be other factors that in decidual necrosis these include the effects of poverty.

The other pathologies indicative of hypoxia that were significant before adjustment became nonsignificant after adjustment. Recurrence of meconium filled macrophages became nonsignificant (4.9, 0.6-42) as well as the combination of meconium filled macrophages and decidual necrosis (1.5, 0.4-7.5). This suggests that cigarette smoking may operate through meconium filled macrophages.

Meconium in the macrophages is indicative of an acute hypoxic event that occurred at least a 6 hours prior to the birth (Benirschke, 1990). Decidual necrosis is indicative of a chronic hypoxic condition. The affects of adjustment indicate that there is a complex set of interactions present. It is conceivable that the effects of the chronic hypoxic event may disappear when further adjustment and examination of nonlinear relationships is conducted. It may well be that these factors are serving as a proxy for poverty and the stress that occurs due to poverty. In the context of poverty, acute hypoxia may be more severe in women who smoke

than those not in poverty. Further investigation, including nonlinear analysis into these findings is necessary to describe these interactions.

The relationship between recurrence of acute placental inflammation was significant for the crude odds at 1.6 (1.1-2.3) but became nonsignificant when adjusted for social class and cigarette smoking. One of the placental pathologies included in acute placental infection, recurrent chorionic vasculitis, remained highly significant with a 4.2 (1.4-12) greater risk of repeating preterm birth. Chorionic vasculitis indicates a very severe infection. This risk was stronger than cigarette smoking or any of the social class variables for predicting recurrence of preterm birth. An evaluation of this relationship in a group of women with no other risk factors is indicated.

IMPLICATIONS

The relationship between recurrent placental pathology and recurrent poor outcome has received little attention in the past. Reasons for this include the difficulty of data collection and consistent evaluation of placenta pathology. This study was exploratory in nature, seeking to identify if a relationship existed, using both predictive and causal analysis. The results of this study should provide a rationale for investment of time and money into future investigations. In addition it provides some implications for further study and clinical practice.

The implications of the findings presented in this research study are far reaching. As stated in the introduction to this thesis, the ultimate desired outcome of all pregnancies is a healthy woman and newborn infant. Failure to achieve this outcome can impact on the future of an entire society. The association of many factors to poor pregnancy outcome

has been examined in the past but the ability to determine causality is problematic because of the interdependence between the fetus and the woman. The ability to elucidate information about the relationships involved in this interdependence may provide further clues that will lead to the identification of biologic factors in the pregnancy history that can become part of risk assessment.

Remington, et al (1988) define the mission of public health as:

> *fulfilling society's interest in assuring conditions in which people can be healthy...Its aim is to generate organized community effort to address public concerns about health by applying scientific and technical knowledge (p.140).*

They note that sound decision-making about health requires an understanding of the determinants of health and the nature and extent of community need and recommend that every public health agency exercise its responsibility to serve the public interest in the development of comprehensive public health policies by promoting use of the scientific knowledge base in decision-making about public health.

Caplan (1974) discussed the importance of mobilizing the environment by acting as a bridge between the health care system and the patient. He stressed the necessity of conservation of manpower by increasing collaborative efforts and focusing these efforts on those patients of the highest need where remedy is possible by using minimal intelligent intervention. Minimal intelligent intervention involves the prudent use of available resources with consideration of the economic impact and effect on the quality of care.

Chiles, et al (1990) noted that low birth weight is a powerful

predictor of cost and that increasing the birth weight of just one low birth weight infant from two to two and one-half pounds would result in a cost savings of $17,000 in acute inpatient hospital costs alone. Gold, et al (1987) note that women who do not obtain sufficient prenatal care are about twice as likely as those who do to have a low birth weight birth and that they are also likely to have a preterm delivery. Identification of women with the greatest risk of preterm delivery or low birth weight birth will provide a focus for allocation of funds and resources. These recommendations point to the need to provide sufficient and efficient services to women in poverty.

This study evaluates recurrence of risk and therefore provides information on breaking the cycle of repetition of poor outcome. It points to the importance of the interconceptual period and the initial post partum visit as well as family planning. This is an area that receives less support and funding than prenatal care. It is possible that the effects of prenatal care are limited by not providing conceptual counselling to the women before her next pregnancy.

Historically, pregnancy has been surrounded with myths, taboos and cultural practices which identifies the pregnant woman as having unique needs. In the middle of the 18th century men entered the practice of delivery of infants and the medicalization of obstetrics began.

Organized prenatal care in the United States evolved out of a home delivery service of the Boston Lying-In Hospital started in 1901 by Mrs. William Lowell Putnam, nurse and leader of the Instructive District Nursing Association. The goal of the program was to promote healthier infants. Women received home visits every 10 days which included self-

care instruction and emotional support. The success of the program led to the establishment of an outpatient clinic in 1911. Other centers began opening throughout the country and research demonstrated effectiveness by a reduction in the infant mortality rate attributed to prenatal care. In 1922, Dr. Ralph W. Lobenstine made a recommendation in the American Journal of Public Health that educating the public regarding prenatal care was identified as one of three ways to reduce maternal mortality. He introduced the concept of the necessity of a competent physician in the care of pregnant women (Thompson, et al, 1990).

The effect of prenatal care and home visits on infant and maternal mortality had an economic impact as well. Insurance companies began to pay for nursing services during pregnancy and the post partum period. In addition, local initiatives supported assistance by the federal government. This led to the passage of the Sheppard-Towner Maternity and Infancy Protection Act which was the first federal initiative in maternal and child health. The mode of care changed from a self-care approach to one of physician supervision and physician control. The physician was now expected to provide the information on self-care, normal pregnancy changes and relief of minor discomforts that information once was obtained from respected older women in the community (Thompson, et al, 1990).

Thompson, et al (1990) stated that the current biomedical view of pregnancy, including prenatal visits with physicians and/or nurse-midwives in their offices dates only to the early 20th century. They note that the pattern of prenatal care in the United States has shown little change since the early 1900s apart from the addition of a few biochemical tests and the move from a broad support system for pregnancy care to a

physician-directed system of prenatal visits in institutions, often outside a woman's own culture and community In the many years of prior success with home visits as a dominant site of prenatal care has been lost to most.

The move away from home visits also moved away from three aspects of reproductive care and focused on prenatal care. There are four components to comprehensive reproductive care. These components are preconceptual care, prenatal (conceptual) care, postpartum care and interconceptual care. The effects of prenatal care have been well established, as discussed above, dating back to the turn of the century. The benefits of preconceptual and interconceptual care are not as well documented. This study indicates that the benefits of interconceptual care warrant further investigation.

There is an emphasis on prenatal care but the importance of interconceptual care, which includes family planning and post partum visits, have not received as much attention. Prior to the first pregnancy and in between pregnancies, there is diminished contact between the woman and the health care system. Increased emphasis in the importance of these periods to optimize pregnancy outcome requires further research to demonstrate its effectiveness. The risk of repeating a preterm delivery or low birth weight birth was significantly higher if placental pathology recurs, smoking is continued, or there are factors of social class indicative of poverty was demonstrated by this study. This provides support for the importance of maintaining contact with the woman after delivery and providing her with information on the results of placental pathology and the implications of these findings and the effects of her

behaviors on future pregnancies.

The woman must be provided information on her options of spacing pregnancies, her risk of repeating a poor outcome and the effects of behaviors such as cigarette smoking on pregnancy. All the options must be presented to the woman so that she can make informed decisions before she becomes pregnant again. The existence of a relationship between recurrence of placental pathology and recurrence of poor outcome provides important information to the practitioner in the detection of risk of low birth weight birth and preterm delivery. This information will facilitate the practitioner in helping the client to make an informed decision about her care.

The context of lower socioeconomic class must be considered when evaluating the results of this analysis. The biologic effects observed in the placenta may be the common pathway of the social and environmental effects of poverty. After controlling for the social class factors, recurrent chorionic vasculitis and recurrent decidual necrosis both remained significant but this was in the context of a sample of lower social class women. The risks observed may be expressed to a greater degree due to the effects of poverty. It may be that the environment predisposes women to experience placental pathology. There are other factors which were not considered in this model. Interpregnancy interval was not measured as well as gravidity and parity. These factors were considered in the TETRAD II analysis in the subsample of women who had no obstetric history and the relationships remained robust.

Marital status was one of the most significant social class findings, remaining significant in both models after adjustment. This

finding warrants further research in the very different social climate of the 1990's. Unmarried pregnant women in the current society may be children or even grandchildren of the unmarried women included in this study who are involved in a cycle of single parenthood. An intergenerational effect might be observed. The significant effect of educational incongruity contains the variable years of education and thus may modify the expression of the effect of education.

There are many factors in the environment of the woman which may not be mutable, including social class, obstetric and medical history. There are other factors such as behavior, receiving health care and social support which may be changed. Based on the results of this study, the effect of poverty on the outcome of pregnancy should be considered. It is of prime importance to provide the woman with the greatest amount of information in an understandable and usable form so that she can make informed choices about her own life. The problem lies in the decision making process. As researchers we can identify clues to the causes of the problems and recommend the "best" actions for optimum outcomes but this artificially places a value on the actions taken by another. These options may not represent the same value to the woman in her situation. Operating in this arena, it is the responsibility of the researcher to provide the woman with as much information as possible on the risks of behaviors and actions. In this way the social responsibility of choice is given to the woman and, with the greatest amount of information, she is in a position to take informed responsibility for her own actions.

In the context of poverty, there are many barriers to care as well as a loss of control over life events. As noted above, the broad support

system for pregnancy care has moved to a physician directed system in institutions that are often outside the woman's own culture and community. This adds another barrier to receiving adequate care. Jack and Culpepper (1990) note that patients at a social risk who have limited access to health services may also not have access to counseling and care before conception. Those that will benefit the most are least likely to have access. They also note that health during pregnancy depends on a woman's general health and habits before conception and that optimizing outcome must include health before conception. The health care system must act as a facilitator to provide the woman with greater control over some of these life events by providing information and devising ways to decrease the barriers to care. To facilitate this control, the health care system must include care to the women before the pregnancy begins.

Two key findings support the need for further research into the benefits of interconceptual care. The first finding identified a relationship between repeating a preterm delivery if placental pathology indicative of infection repeats and the second finding identified a relationship between recurrence of placental pathology indicative of hypoxia and recurrence of low birth weight births. This supports the notion that the placenta should be sent to pathology for analysis without hesitation if a poor outcome occurs. This is an ongoing debate in the medical community since pathological examination of the placenta is costly and there are not many pathologists who are highly skilled in analysis of the placenta.

Part of the evaluation of the effectiveness of interconceptual care in further reducing low birth weight births and preterm deliveries will

include the cost-efficiency of this practice. Applying the concept of minimal intelligent effective intervention, those who are in the greatest need of interconceptual care should be identified. In addition the importance of mobilizing the environment to maintain the bridge to the health care system open especially during the woman's childbearing years should be evaluated. Many times the women is lost to the system at delivery, only to present again with another poor pregnancy outcome.

The relationship between recurrence of a placental pathology which is indicative of infection and recurrence of preterm delivery supports the hypothesis presented by McGregor (1988a, 1988b) and others who suggest treatment during pregnancy will decrease the incidence of preterm delivery. This notion should be extended to the interconceptual period where treatment should be initiated after assessment and determination of the type of infection present. The most common organisms that result in infection are *Escherichia coli*, *Bacteroides fragilis* and streptococci, in addition, *Chlamydia trachomatis* and *Mycoplasma hominis* (Benirschke, 1990). All can be identified by endocervical culture. The effectiveness of this approach should be evaluated by a randomized double-blind placebo-controlled clinical trial. Women who experience a preterm delivery in an initial pregnancy should be entered into the study and followed through treatment and their next pregnancy. The effects of long-standing infection may be a confounder, so a third group of women who exhibit evidence of long-standing infection should be considered.

Similar implications can be drawn from the findings of decidual necrosis. If cigarette smoking is involved, interconceptual counselling on the risks of cigarette smoking may be better received. This is a less

stressful time to initiate intervention to help the women stop smoking. Here also, a randomized clinical trial can be conducted which assigns women to smoking intervention or placebo counseling. Women who experienced a low birth weight birth and decidual necrosis would be included in this trial.

Endpoints for both treatment of infection and the need for smoking intervention are clear. Other goals of interconceptual care may not have as clear endpoints. Research into the care needs of women at risk for poor pregnancy outcomes is recommended to determine these endpoints.

In conclusion, a relationship between recurrence of placental pathology and recurrence of poor outcome has been demonstrated. The relationship is robust when different approaches to analysis are used. A follow up study should focus on the nonlinear as well as the existing linear relationship. Many of the social class variables may be acting in a non linear fashion and have a greater effect that is apparent. This may also be true for those placental variables which did not prove to be significant.

Further research into this area is warranted by this exploratory study. The interactions which are apparent by the effect of adding social class to the model and by the difference in the TETRAD II models of married only versus the whole nulligravid population raise questions about the latent variables which might be at work. This study can also serve as a comparison to evaluate whether these effects remain significant in the very different economic and social climate of the 1990's.

The results of this study indicate a need to consider preconceptual and interconceptual care as a necessary part of comprehensive reproductive

care. In 1986, the Public Health Service convened 19 experts from a variety of disciplines to examine the scientific basis of the content of prenatal care (Merkatz and Thompson, 1990). Klerman (1990) summarized these findings and stated that although preconception care had been mentioned before by expert groups, this report was the first to identify its importance. This presents a change in the 90 year-old thinking about the approach to reproductive care. Prior to the medicalization of care of the pregnant women, the nurse was the key to her care, mobilizing the environment and serving as a bridge to the health care system. Home visit by nurses were the norm. The primary problem that may be encountered in providing preconceptual care may be the ability of maintaining contact with the woman. Consideration of going back to basics by again providing a home visit approach may be a means to decrease the barriers and reach those women who are in the greatest need but have the least access to the health care system.

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APPENDIX A
CHARACTERISTICS OF THE SAMPLE

TABLE 1
SOCIO-DEMOGRAPHIC CHARACTERISTICS
NCPP DATASET 1ST AND 2ND PREGNANCIES BY RACE AND TOTAL

	WHITE		BLACK		TOTAL	
	1st	2nd	1st	2nd	1st	2nd
MARITAL STATUS						
Single/Div/Sep	278 (7)	253 (6)	1328 (37)	989 (27)	1606 (44)	1242 (16)
Married	3772 (93)	3797 (94)	2275 (63)	2614 (73)	6047(156)	6411 (84)
Total	4050	4050	3603	3603	7653	7653
Missing						
HUSBAND LIVING AT HOME						
Yes	316 (8)	297 (7)	1277 (37)	985 (28)	1593 (22)	1282 (17)
No	3553 (92)	3622 (92)	2205 (63)	2559 (72)	5758 (78)	6181 (83)
Total	3869	3919	3482	3544	7351	7463
Missing	181	131	121	59	302	190
AGE OF THE WOMAN						
< 16	42 (1)	5 (1)	234 (6)	30 (<1)	276 (4)	35 (<1)
16-19	919 (23)	418 (10)	1089 (30)	742 (21)	2008 (26)	1160 (15)
20-24	1649 (41)	1672 (41)	1220 (34)	1367 (38)	2869 (37)	3039 (40)
25-34	1274 (31)	1644 (41)	926 (26)	1219 (34)	2200 (29)	2863 (37)
> 34	166 (4)	311 (8)	134 (4)	245 (7)	300 (4)	556 (7)
Total	4050	4050	3603	3603	7653	7653
Missing	0	0	0	0	0	0

	WHITE		BLACK		TOTAL	
GYNECOLOGIC AGE	1st	2nd	1st	2nd	1st	2nd
< 4	219 (5)	105 (4)	452 (12)	132 (5)	671 (9)	237 (5)
4-6	718 (18)	334 (13)	834 (23)	596 (24)	1552 (20)	930 (18)
7-9	1053 (26)	912 (35)	807 (22)	850 (34)	1860 (24)	1762 (35)
10-14	1047 (26)	235 (48)	728 (20)	922 (37)	1775 (23)	1157 (23)
> 14	1013 (25)	1000 (38)	782 (22)	0	1795 (24)	1000 (20)
Total	4050	2586	3603	2500	7653	5086
Missing	0	1464	0	1103		
AGE OF FATHER						
< 16	194 (5)	131 (3)	138 (4)	62 (2)	332 (4)	193 (2)
16-19	181 (4)	65 (2)	132 (4)	85 (2)	313 (4)	150 (2)
20-34	3675 (90)	2935 (73)	1765 (49)	2046 (57)	7008 (92)	4981 (65)
> 34	0	919 (23)	1568 (43)	1410 (39)	0	2329 (30)
Total	4050	4050	3603	3603	7653	7653
Missing						
NUMBER OF CIGARETTES SMOKED PER DAY						
0	1848 (46)	1847 (46)	2015 (57)	1948 (54)	3863 (51)	3795 (50)
1-10	564 (14)	442 (11)	867 (24)	790 (22)	189 (2)	156 (2)
10-20	684 (17)	547 (14)	357 (10)	409 (11)	220 (3)	173 (2)
> 20	869 (22)	1118 (28)	280 (8)	391 (11)	256 (3)	178 (2)
< 1/month	29 (<1)	29 (<1)	40 (1)	35 (1)	170 (2)	131 (2)
Total	3994	3983	3559	3573	4698	4433
Missing	56	67	44	30	100	97

	WHITE		BLACK		TOTAL	
EDUCATION OF WOMAN	1st	2nd	1st	2nd	1st	2nd
1-6	175 (5)	160 (4)	99 (3)	125 (3)	274 (4)	285 (4)
7-8	455 (13)	427 (12)	357 (9)	347 (9)	812 (11)	774 (10)
9-12	2742 (79)	2838 (80)	2729 (71)	2769 (76)	5471 (75)	5607 (78)
> 12	114 (4)	11 (3)	666 (7)	419 (11)	780 (11)	465 (6)
Total	3486	3536	3851	3660	7337	7131
Missing	117	67	199	390	316	457
EDUCATION OF FATHER						
1-6	654 (16)	192 (7)	1639 (45)	138 (4)	2293 (30)	330 (5)
7-8	321 (8)	311 (11)	250 (7)	331 (9)	571 (7)	821 (11)
9-12	1096 (27)	2163 (77)	930 (26)	2261 (6)	2026 (26)	2956 (38)
> 12	1979 (49)	155 (5)	784 (22)	938 (26)	2763 (36)	1722 (23)
Total	4050	3603	3603	4050	7653	7653
Missing	0	0	0	0	0	0
EDUCATIONAL INCONGRUITY						
< - 2 yrs	847 (26)	613 (19)	984 (41)	320 (13)	1831 (32)	933 (17)
-1-2 yrs	377 (12)	420 (13)	210 (9)	305 (13)	587 (10)	725 (13)
0 yrs	1015 (31)	1128 (35)	488 (20)	716 (30)	1503 (26)	1844 (33)
1-4 yrs	853 (26)	839 (26)	589 (24)	837 (35)	1442 (25)	1676 (30)
> 4 yrs	171 (5)	202 (6)	144 (6)	211 (9)	315 (5)	413 (7)
Total	3263	3202	2415	2389	5678	5591
Missing	787	848	1188	1214	1975	2062

	WHITE		BLACK		TOTAL	
MOTHERS OCCUPATION	1st	2nd	1st	2nd	1st	2nd
Never Worked	328 (8)		1020 (29)		1348 (18)	
Professional	368 (9)	382 (10)	32 (<1)	30 (1)	400 (5)	412 (6)
Clerical/Sales	1676 (43)	1672 (45)	321 (9)	406 (14)	1997 (27)	2078 (32)
Craftsmen/Operat	885 (23)	949 (26)	705 (20)	881 (30)	1590 (22)	1830 (28)
Private Househol	591 (15)	648 (18)	1378 (39)	1538 (53)	1969 (27)	2187 (33)
Laborers	29 (<1)	23 (<1)	28 (<1)	24 (<1)	57 (<1)	47 (<1)
Students		3 (<1)		6 (<1)		9 (<1)
Total	3877	3678	3484	2885	7361	6563
Missing	173	372	119	718	292	1090
FATHERS OCCUPATION						
Never Worked	2 (<1)	1 (<1)	8 (<1)	2 (<1)	10 (<1)	3 (<1)
Professional	841 (23)	924 (25)	69 (3)	109 (4)	910 (15)	1033 (15)
Clerical/Sales	445 (12)	451 (12)	207 (9)	266 (9)	652 (11)	717 (11)
Craftsmen/Operat	1705 (47)	1808 (48)	1085 (47)	1482 (50)	2790 (47)	3290 (49)
Private Househol	258 (7)	257 (7)	436 (19)	563 (19)	694 (12)	820 (12)
Laborers	340 (9)	307 (8)	492 (21)	535 (18)	832 (14)	842 (12)
Students	9 (<1)	8 (<1)	21 (<1)	13 (<1)	30 (<1)	21 (<1)
Total	3600	3756	2318	2970	5918	6726
Missing	450	294	1285	633	1735	927

GRANDFATHERS OCCUPATION	WHITE 1st	WHITE 2nd	BLACK 1st	BLACK 2nd	TOTAL 1st	TOTAL 2nd
Never Worked	71 (11)	171 (8)	92 (21)	316 (18)	163 (15)	487 (13)
Professional	166 (27)	479 (23)	61 (14)	215 (12)	227 (21)	694 (18)
Clerical/Sales	63 (10)	180 (9)	12 (3)	59 (3)	75 (7)	239 (6)
Craftsmen/Operat	254 (41)	877 (43)	142 (32)	550 (31)	396 (37)	1427 (38)
Private Househol	40 (6)	206 (10)	87 (20)	404 (23)	127 (12)	610 (16)
Laborers	31 (5)	122 (6)	48 (11)	217 (12)	79 (7)	339 (9)
Total	625	2035	442	1761	1067	3796
Missing	3425	2015	3161	1842	6586	3857
PER CAPITA INCOME						
< 500	615 (15)	423 (10)	1326 (37)	1051 (29)	1941 (25)	1474 (19)
500-999	884 (22)	1237 (30)	1329 (37)	1736 (48)	2213 (29)	2973 (39)
1000-1999	1324 (33)	1832 (45)	703 (19)	705 (20)	2027 (26)	2537 (33)
2000-3999	982 (24)	497 (12)	219 (6)	107 (3)	1201 (16)	604 (8)
> 3999	245 (6)	61 (<1)	26 (<1)	4 (<1)	271 (3)	65 (<1)
Total	4050	4050	3603	3603	7653	7653

TABLE 2
CHARACTERISTICS OF THE INFANT
NCPP DATASET 1ST AND 2ND PREGNANCIES BY RACE AND TOTAL

	WHITE		BLACK		TOTAL	
BIRTHWEIGHT (GRAMS)	1st	2nd	1st	2nd	1st	2nd
< 500	197 (5)	158 (4)	93 (3)	84 (2)	290 (4)	242 (3)
500-1499	28 (<1)	22 (<1)	37 (1)	31 (<1)	65 (<1)	53 (<1)
1500-1999	30 (<1)	22 (<1)	60 (2)	41 (1)	90 (1)	63 (<1)
2000-2499	222 (6)	268 (7)	408 (11)	431 (12)	630 (8)	699 (9)
> 2499	3573 (88)	3580 (88)	3005 (83)	3016 (84)	6578 (86)	6596 (86)
Total	4050	4050	3603	3603	7653	7653
Missing	0	0	0	0	0	0
GESTATIONAL AGE						
< 140 Days	1018 (25)	114 (3)	991 (27)	46 (1)	1018 (25)	114 (3)
140-209 Days	33 (1)	71 (2)	89 (2)	165 (5)	33	71 (2)
210-279 Days	1344 (33)	1820 (45)	1497 (41)	2101 (58)	1344 (33)	1820 (45)
280-350 Days	1633 (40)	2021 (50)	1005 (28)	1270 (35)	1633 (40)	2021 (50)
> 2499	22 (<1)	24 (1)	21 (1)	21 (1)	22 (<1)	24 (<1)
Total	4050	4050	3603	3603	4050	4050
Missing	0	0	0	0	0	0
CROWN-HEEL LENGTH (CMS)						
< 40	342 (8)	360 (9)	297 (8)	233 (6)	639 (8)	593 (8)
40-44	55 (1)	72 (2)	125 (3)	132 (4)	180 (2)	204 (3)
45-49	1114 (27)	1120 (28)	1488 (41)	1430 (40)	2602 (34)	2550 (33)
50-54	2381 (59)	2290 (56)	1646 (46)	1751 (49)	4027 (53)	4041 (53)
> 54	158 (4)	208 (5)	47 (1)	57 (2)	205 (3)	265 (3)
Total	4050	4050	3603	3603	7653	7653
Missing	0	0	0	0	0	0

	WHITE		BLACK		TOTAL	
GENDER OF NEONATE	1st	2nd	1st	2nd	1st	2nd
Male	2039 (51)	1972 (49)	1810 (50)	1784 (50)	3849 (51)	3756 (49)
Female	1866 (46)	1963 (48)	1736 (48)	1779 (49)	3602 (47)	3742 (49)
Undetermined	114 (3)	101 (2)	44 (1)	29 (1)	158 (2)	130 (2)
Total	4019	4036	3590	3592	7609	7618
Missing	31	14	13	11	44	35
HEAD CIRCUMFERENCE(CMS)						
< 25	329 (8)	314 (8)	259 (7)	203 (6)	588 (8)	517 (7)
25-29	34 (1)	72 (1)	77 (2)	72 (2)	111 (1)	106 (1)
30-34	2309 (57)	2336 (58)	2541 (70)	2565 (71)	4850 (63)	4901 (64)
35-36	859 (21)	868 (21)	514 (14)	517 (14)	1373 (18)	1385 (18)
> 36	519 (13)	498 (12)	212 (6)	246 (7)	731 (10)	744 (10)
Total	4050	4050	3603	3603	7653	7653
Missing	0	0	0	0	0	0
MECONIUM AT BIRTH						
Yes	3091 (80)	3136 (82)	2761 (80)	2649 (78)	5852 (80)	5785 (80)
No	747 (19)	699 (18)	672 (20)	739 (22)	1419 (19)	1438 (20)
Total	3838	3835	3433	3388	7271	7223
Missing	212	215	170	215	382	430
EARLY FETAL DEATH (Less then 20 Weeks)						
No	3896 (96)	3932 (97)	3555 (99)	3567 (99)	7451 (97)	7499 (98)
Yes	154 (4)	118 (3)	48 (1)	36 (1)	202 (3)	154 (2)
Total	4050	4050	3603	3603	7653	7653
Missing						

	WHITE		BLACK		TOTAL	
LATE FETAL DEATH (> 20 Weeks)	1st	2nd	1st	2nd	1st	2nd
No	3822 (98)	3876 (98)	3460 (97)	3501 (98)	7282 (98)	7377 (98)
Yes	74 (2)	56 (1)	95 (3)	66 (2)	169 (2)	122 (2)
Total	3896	3932	3555	3567	7451	7499
Missing	154	118	48	36	202	154
NEONATAL DEATH (Up to 27 Days of Life)						
No	3768 (97)	3936 (98)	3389 (98)	3474 (98)	7157 (98)	7410 (98)
Yes	54 (1)	58 (1)	71 (2)	63 (2)	125 (2)	121 (2)
Total	3822	3994	3460	3537	7282	7531
Missing	228	56	143	66	371	122
INFANT DEATH (28 Days to 1 Year)						
No	25 (1)	25 (1)	39 (1)	42 (1)	64 (<1)	67 (1)
Yes	3728 (99)	3790 (99)	3337 (99)	3387 (99)	7065 (99)	7177 (99)
Total	3753	3815	3376	3429	7128	7244
Missing	297	235	227	174	524	409

TABLE 3
OBSTETRIC HISTORY
NCPP DATASET 1ST AND 2ND PREGNANCIES BY RACE AND TOTAL

NUMBER OF PREGNANCIES	WHITE 1st	WHITE 2nd	BLACK 1st	BLACK 2nd	TOTAL 1st	TOTAL 2nd
No Previous	1713 (43)	0	1240 (35)	2 (<1)	2953 (39)	2 0
1	1360 (34)	2444 (61)	1159 (32)	1753 (49)	2519 (33)	4197 (56)
2	890 (22)	1476 (37)	1108 (31)	1651 (46)	1998 (26)	3127 (41)
3	32 (<1)	61 (1)	61 (2)	122 (3)	93 (1)	183 (2)
4 or more	2 (<1)	11 (<1)	16 (<1)	35 (1)	18 (<1)	46 (<1)
Total	3997	3992	3584	3563	7581	7555
Missing	53	58	19	40	72	98
NUMBER OF PREVIOUS DELIVERIES						
0	1825 (45)	0	1319 (37)	2 (<1)	3144 (41)	2 (<1)
1	1400 (35)	2658 (66)	1208 (34)	1907 (53)	2608 (34)	4565 (60)
2	779 (19)	1304 (33)	1017 (28)	1567 (44)	1796 (24)	2871 (38)
3	13 (<1)	28 (<1)	40 (1)	83 (2)	53 (<1)	111 (1)
4 or more	1 (0)	4 (<1)	8 (<1)	19 (<1)	9 (<1)	23 (<1)
Total	4018	3994	3592	3578	7610	7572
Missing	32	56	11	25	43	1019
LAST PRIOR OUTCOME						
No Poor Outcome	1697 (44)		1238 (35)	2 (<1)	2935 (39)	2 0
Still Living	1748 (35)	3435 (88)	1858 (53)	2906 (86)	4402 (10)	7181 (11)
Fetal Death	404 (10)	408 (10)	340 (10)	370 (11)	53 (<1)	75 (1)
Neonatal Death	28 (<1)	41 (1)	47 (1)	51 (1)	45 (<1)	54 (<1)
Infant Death	12 (<1)	20 (<1)	19 (<1)	34 (1)	19 (<1)	17 (<1)
Total	3889	3904	3502	3363	7454	7329
Missing	161	146	101	240	199	324

LAST PRIOR OUTCOME BIRTH WEIGHT GRAMS	WHITE 1st	WHITE 2nd	BLACK 1st	BLACK 2nd	TOTAL 1st	TOTAL 2nd
No Prior	1697 (48)	0	1238 (39)	2 (<1)	2935 (44)	2 (<1)
< 500 gms	0	9 (<1)	0	28 (<1)	0	37 (<1)
500-1499 gms	31 (<1)	48 (1)	39 (1)	73 (2)	70 (1)	121 (2)
1500-2500 gms	137 (4)	236 (6)	269 (8)	403 (13)	406 (6)	639 (10)
> 2500 gms	1675 (47)	3279 (92)	1644 (51)	2560 (83)	3319 (49)	5839 (88)
Total	3540	3572	3190	3066	6730	6638
Missing	510	478	413	537	923	1015
NUMBER PRIOR PERINATAL LOSS						
No Previous	1625 (41)	3060 (78)	1615 (46)	2612 (74)	5672 (76)	2612 (74)
1	403 (10)	558 (14)	434 (12)	561 (16)	1119 (15)	561 (16)
2	133 (3)	199 (5)	140 (4)	195 (6)	394 (5)	195 (6)
3	29 (<1)	65 (<1)	48 (1)	78 (2)	143 (2)	78 (2)
4 or more	1752 (44)	45 (1)	1277 (36)	67 (2)	112 (1)	67 (2)
Total	3942	3927	3514	3513	7440	
Missing	108	123	89	90	213	
NUMBER PRIOR VIABLE BIRTHS						
No Previous	108 (3)	38 (1)	73 (2)	13 (<1)	181 (2)	51 (<1)
1	845 (21)	1728 (44)	677 (19)	1102 (32)	1522 (20)	2830 (38)
2	499 (13)	875 (22)	506 (14)	687 (20)	1005 (13)	1562 (21)
3	345 (9)	526 (13)	399 (11)	477 (14)	744 (10)	1003 (14)
4 or more	2151 (54)	780 (20)	1910 (54)	1120 (33)	4061 (54)	1900 (26)
Total	3948	3947	3565	3399	7531	7346
Missing	102	103	38	204	140	307

	WHITE		BLACK		TOTAL	
PRIOR ABORTION	1st	2nd	1st	2nd	1st	2nd
No Previous	1660 (73)	3110 (78)	1782 (76)	2768 (78)	3442 (74)	5878 (78)
1	450 (20)	624 (16)	413 (18)	564 (16)	863 (19)	1188 (16)
2	120 (5)	171 (4)	105 (4)	134 (4)	225 (5)	305 (4)
3	32 (1)	60 (1)	24 (1)	65 (2)	56 (1)	125 (2)
4 or more	22 (1)	27 (<1)	20 (<1)	30 (<1)	42 (<1)	57 (<1)
Total	2284	3992	2344	3561	4628	7553
Missing	1766	58		42	3025	100
PRIOR PREMATURE						
No Previous	1921 (47)	3387 (84)	1684 (47)	2548 (71)	3605 (47)	5935 (78)
1	286 (7)	481 (12)	447 (12)	675 (19)	733 (10)	1156 (15)
2	59 (1)	102 (2)	143 (4)	205 (6)	202 (3)	307 (4)
3	16 (<1)	22 (<1)	43 (1)	80 (2)	59 (<1)	102 (1)
4 or more	1753 (43)	41 (1)	1279 (36)	87 (2)	3032 (40)	128 (2)
Total	4035	4033	3596	3595	7631	7628
Missing	15	17	7	8	22	25
PRIOR MULTIPLE BIRTHS						
No Previous	2227 (97)	3918 (98)	2273 (97)	3485 (98)	4500 (97)	7403 (98)
1	56 (2)	70 (2)	70 (3)	71 (2)	126 (3)	141 (2)
2	1 (0)	2 (<1)	0	5 (<1)	1 (<1)	7 (<1)
3	0	1 (<1)	0	0	0	1 (<1)
4 or more	0	1 (<1)	1 (<1)	0	1 (<1)	1 (<1)
Total	2284	3992	2344	3561	4628	7553
Missing	1766	58	1259	42	3025	100

LAST PRIOR WKS GESTATION	WHITE 1st	WHITE 2nd	BLACK 1st	BLACK 2nd	TOTAL 1st	TOTAL 2nd
< 10 Weeks	162 (7)	0	107 (5)	0	269 (6)	0
10-19	184 (8)	193 (5)	202 (9)	169 (5)	386 (9)	362 (5)
20-36	213 (10)	837 (22)	261 (11)	649 (20)	474 (11)	1486 (21)
> 36	1664 (75)	2769 (73)	1741 (75)	2454 (75)	3405 (75)	5223 (74)
Total	2223	3799	2311	3272	4534	7071
Missing	1827	251	1292	331	3119	582
PRIOR FETAL DEATHS (> 20 WKS GESTATION)						
No Previous	2124 (93)	3751 (94)	2116 (90)	3246 (91)	4240 (92)	6997 (93)
1	133 (6)	214 (5)	193 (8)	266 (7)	326 (7)	480 (6)
2	20 (<1)	23 (<1)	26 (1)	34 (1)	46 (1)	57 (<1)
3	3 (<1)	4 (<1)	4 (<1)	9 (<1)	7 (<1)	13 (<1)
4 or more	1 (<1)	0	2 (<1)	6 (<1)	3 (<1)	6 (<1)
Total	2281	3992	2341	3561	4622	7553
Missing	1769	58	1262	42	3031	100
PRIOR STILLBIRTH OR NEONATAL DEATHS						
No Previous	2016 (88)	3565 (89)	1946 (83)	3018 (85)	3962 (86)	6583 (87)
1	216 (9)	356 (9)	314 (13)	436 (12)	530 (11)	792 (10)
2	41 (2)	58 (1)	58 (2)	76 (2)	99 (2)	134 (2)
3	6 (<1)	6 (<1)	16 (<1)	20 (<1)	22 (<1)	26 (<1)
4 or more	3 (<1)	6 (<1)	7 (<1)	11 (<1)	10 (<1)	17 (<1)
Total	2282	3991	1262	3561	4623	7552
Missing	1768	59	1262	42	3030	101

TABLE 4
PLACENTAL PATHOLOGY
NCPP DATASET 1ST AND 2ND PREGNANCIES BY RACE AND TOTAL

	WHITE		BLACK		TOTAL	
	1st	2nd	1st	2nd	1st	2nd
PLACENTAL WEIGHT (GRAMS)						
< 350 gms	1264 (31)	807 (20)	1390 (38)	948 (26)	2654 (35)	1755 (23)
350-399 gms	577 (14)	612 (15)	556 (15)	671 (18)	1133 (15)	1283 (17)
400-449 gms	735 (18)	821 (20)	635 (17)	698 (19)	1370 (18)	1519 (20)
450-499 gms	604 (15)	699 (17)	501 (14)	582 (16)	1105 (14)	1291 (17)
> 499 gms	870 (21)	1111 (27)	521 (14)	694 (19)	1391 (18)	1805 (24)
Total	4050	4050	3603	3603	7653	7653
Missing	0	0	0	0	0	
CORD VASCULITIS--VEIN						
NOT SEEN	2503 (84)	2557 (85)	2498 (92)	2511 (92)	5001 (88)	5068 (89)
SLIGHT	365 (12)	333 (11)	149 (5)	137 (5)	514 (9)	470 (8)
MARKED	96 (3)	93 (3)	78 (3)	73 (3)	174 (3)	166 (3)
COMBO/MODERATE	9 (<1)	5 (<1)	0	0	9 (<1)	5 (<1)
Total	2973	2988	2725	2721	5698	5709
Missing	1077	1062	878	882	1955	1944
CORD VASCULITIS--ARTERY						
NOT SEEN	2895 (97)	2910 (97)	2596 (95)	2585 (95)	5491 (96)	5495 (96)
SLIGHT	45 (1)	46 (1)	68 (2)	74 (3)	113 (2)	120 (2)
MARKED	31 (1)	31 (1)	62 (2)	62 (2)	93 (2)	93 (2)
COMBO/MODERATE	2 (<1)	1 (0)	0	0	2 0	1 0
Total	2973	2988	2726	2721	5699	5709
Missing	1077	1062	877	882	1954	1944

FUNISITIS	WHITE 1st	WHITE 2nd	BLACK 1st	BLACK 2nd	TOTAL 1st	TOTAL 2nd
NOT SEEN	2811 (95)	2849 (95)	2557 (94)	2568 (94)	5368 (95)	5417 (94)
SLIGHT	121 (4)	103 (3)	106 (4)	105 (4)	227 (4)	208 (4)
MARKED	31 (1)	35 (1)	43 (2)	47 (2)	74 (1)	82 (1)
COMBO/MODERATE	6 (<1)	1 (<1)		20 (<1)	6 (<1)	1 (<1)
Total	2969	2992	2706	2740	5675	5732
Missing	1081	1062	897	863	1978	1945
NECROSIS OF EPITHELIUM OF AMNION						
NOT SEEN	2644 (91)	2612 (91)	2250 (86)	2265 (88)	4894 (88)	4877 (89)
PRESENT	247 (8)	243 (8)	369 (14)	289 (11)	616 (11)	532 (10)
PRESENT-SLIGHT	9 (<1)	15 (<1)	4 (<1)	9 (<1)	13 (<1)	24 (<1)
PRESENT-MARKED	6 (<1)	14 (<1)	2 (<1)	4 (<1)	8 (<1)	18 (<1)
Total	2906	2884	2625	2567	5531	5451
Missing	1144	1166	978	1036	2122	2202
SQUAMOUS METAPLASIA OF AMNION						
NOT SEEN	2827 (97)	2787 (97)	2480 (94)	2372 (92)	5307 (96)	5159 (95)
PRESENT	79 (3)	99 (3)	146 (6)	194 (8)	225 (4)	293 (5)
TOTAL	2906	2886	2626	2566	5532	5452
MISSING	1144	1164	977	1037	2121	2201
AEPM AMNIONITIS						
NOT SEEN	2612 (91)	2618 (91)	2376 (91)	2299 (90)	4988 (91)	4917 (91)
SLIGHT	206 (7)	178 (6)	170 (6)	186 (7)	376 (7)	364 (7)
MARKED	58 (2)	62 (2)	58 (2)	58 (2)	116 (2)	120 (2)
COMBO/MODERATE	3 (<1)	3 (<1)	0	1 (<1)	3 (<1)	4 (<1)
Total	2879	2861	2604	2544	5483	5405
Missing	1171	1189	999	1059	2170	2248

	WHITE		BLACK		TOTAL	
AEPM CHORIONITIS	1st	2nd	1st	2nd	1st	2nd
NOT SEEN	2606 (87)	2591 (87)	2282 (84)	2297 (84)	4888 (86)	4888 (86)
SLIGHT	282 (9)	289 (10)	287 (10)	237 (9)	569 (10)	526 (9)
MARKED	83 (3)	95 (3)	155 (6)	187 (7)	238 (4)	282 (5)
COMBO/MODERATE	6 (<1)	6 (<1)	0	4 (<1)	6 (<1)	10 (<1)
Total	2977	2981	2724	2725	5701	5706
Missing	1073	1069	879	878	1952	1847
PLACENTAL AMNIONITIS						
NOT SEEN	2310 (94)	2324 (94)	2310 (94)	2324 (94)	4975 (94)	4954 (93)
SLIGHT	100 (4)	114 (5)	100 (4)	114 (5)	214 (4)	240 (4)
MARKED	46 (2)	41 (2)	46 (2)	41 (2)	90 (2)	89 (2)
COMBO/MODERATE	0	1 (<1)	0	1 (<1)	2 (<1)	2 (<1)
Total	2456	2861	2456	2480	5281	5285
Missing	1147	1123	1147	1123	2372	2368
PLACENTAL CHORIONITIS						
NOT SEEN	2731 (91)	2655 (89)	2418 (88)	2399 (88)	5149 (90)	5054 (88)
SLIGHT	191 (6)	256 (9)	217 (8)	217 (8)	408 (7)	473 (8)
MARKED	60 (2)	72 (2)	96 (3)	115 (4)	156 (3)	187 (3)
COMBO/MODERATE	2 (<1)	4 (<1)	0	3 (<1)	2 0	7 (<1)
Total	2456	2861	2731	2734	5715	5721
Missing	1147	1123	872	869	1938	1932

	WHITE		BLACK		TOTAL	
MARGINAL DECIDUITIS	1st	2nd	1st	2nd	1st	2nd
NOT SEEN	2660 (94)	2587 (87)	2380 (87)	2303 (84)	5040 (88)	4890 (86)
SLIGHT	250 (4)	293 (10)	253 (9)	305 (11)	503 (9)	598 (10)
MARKED	71 (1)	97 (3)	99 (4)	121 (4)	170 (3)	218 (4)
COMBO/MODERATE	5 (<1)	6 (<1)	0	2 (<1)	5 (<1)	8 (<1)
Total	2986	2983	2732	2731	5718	5714
Missing	1064	1067	871	872	1935	1939
CHORIONIC VASCULITIS						
NOT SEEN	2819 (94)	2755 (92)	2539 (93)	2518 (92)	5358 (94)	5273 (92)
SLIGHT	115 (4)	156 (5)	128 (5)	140 (5)	244 (4)	296 (5)
MARKED	44 (1)	67 (2)	64 (2)	75 (3)	108 (2)	142 (2)
COMBO/MODERATE	4 (<1)	3 (<1)	1 (<1)	0 0	5 (<1)	3 (<1)
Total	2982	2981	2733	2733	5715	5714
Missing	1068	1069	870	870	1938	1939
CAPSULARIS DECIDUITIS						
NOT SEEN	2429 (82)	2254 (76)	2161 (79)	2036 (75)	4590 (80)	4290 (75)
SLIGHT	392 (13)	513 (17)	382 (14)	471 (17)	774 (14)	984 (17)
MARKED	145 (5)	197 (7)	180 (7)	213 (8)	325 (6)	410 (7)
COMBO/MODERATE	11 (<1)	16 (<1)	3 (<1)	1 (<1)	14 (<1)	17 (<1)
Total	2977	2980	2726	2721	5703	5701
Missing	1073	1070	877	882	1950	1952
BASALIS DECIDUITIS						
NOT SEEN	2929 (98)	2880 (96)	2591 (95)	2530 (92)	5520 (97)	5410 (95)
SLIGHT	45 (1)	96 (3)	121 (4)	180 (7)	166 (3)	276 (5)
MARKED	6 (<1)	9 (<1)	16 (<1)	25 (<1)	22 (<1)	34 (<1)
COMBO/MODERATE	1 (<1)	0	0	1 (<1)	1 (<1)	1 (<1)
Total	2981	2985	2728	2736	5709	5721
Missing	1069	1065	875	867	1944	1932

BASALIS LYMPHOCYTIC DECIDUITIS	WHITE		BLACK		TOTAL	
	1st	2nd	1st	2nd	1st	2nd
NOT SEEN	2587 (87)	2473 (83)	1632 (60)	1589 (58)	4219 (74)	4062 (71)
SLIGHT	381 (13)	486 (16)	1078 (39)	1123 (41)	1459 (26)	1609 (28)
MARKED	10 (<1)	7 (<1)	19 (<1)	13 (<1)	29 (<1)	20 (<1)
COMBO/MODERATE	3 (<1)	6 (<1)	0	0	3 (<1)	6 (<1)
Total	2981	2972	2729	2725	5710	5697
Missing	1069	1078	874	878	1943	1956
MARGINAL LYMPHOCYTIC DECIDUITIS						
NOT SEEN	2503 (84)	2517 (84)	1565 (57)	1536 (56)	4068 (71)	4053 (71)
SLIGHT	475 (16)	455 (15)	1144 (42)	1164 (43)	1619 (28)	1619 (28)
MARKED	8 (<1)	12 (<1)	23 (<1)	31 (1)	31 (<1)	43 (<1)
Total	2986	2984	2732	2731	5718	5715
Missing	1064	1066	871	872	1935	1938
CAPSULARIS LYMPHOCYTIC DECIDUITIS						
NOT SEEN	2417 (81)	2407 (81)	1590 (58)	1546 (57)	4007 (70)	3953 (69)
SLIGHT	550 (18)	561 (19)	1106 (41)	1153 (42)	1656 (29)	1714 (30)
MARKED	9 (<1)	12 (<1)	29 (1)	21 (<1)	38 (<1)	33 (<1)
COMBO/MODERATE	1 0	0	0	1 (<1)	1 (<1)	0
Total	2977	2980	2725	2720	5702	5700
Missing	1073	1070	878	883	1951	1953
MELANIN						
NOT SEEN	2982(100)	2966(100)	2689 (98)	2667 (97)	5671 (99)	5633 (98)
SLIGHT	7 (<1)	9 (<1)	44 (1)	48 (2)	51 (<1)	57 (1)
MARKED	0	17 (<1)	7 (<1)	14 (<1)	7 (<1)	14 (<1)
COMBO/MODERATE	0	0	0	11 (<1)	0	28 (<1)
Total	2989	2992	2740	2740	5729	5732
Missing	1061	1058	863	863	1924	1921

THROMBOSIS OF CORD VESSELS	WHITE 1st	WHITE 2nd	BLACK 1st	BLACK 2nd	TOTAL 1st	TOTAL 2nd
NOT SEEN	2964(100)	2965(100)	2698(100)	2705(100)	5662 (99)	5670 (99)
PRESENT	9 (<1)	23 (<1)	28 (<1)	15 (<1)	37 (<1)	38 (<1)
Total	2973	2988	2726	2720	5698	5708
Missing	1077	1062	877	883	1954	1945
LANGHANS LAYER						
NOT SEEN	2933 (98)	2953 (99)	2708 (99)	2706 (99)	5641 (98)	5659 (99)
PRESENT	55 (2)	36 (1)	32 (1)	34 (1)	87 (1)	70 (1)
Total	2988	2989	2740	2740	5728	5729
Missing	1062	1061	863	863	1925	1924
HOFBAUER CELLS						
FEW	2903 (97)	2929 (98)	2667 (97)	2671 (97)	5570 (97)	5600 (98)
MANY	85 (3)	60 (2)	73 (3)	68 (2)	158 (3)	128 (2)
Total	2988	2989	2740	2739	5728	5728
Missing	1062	1061	863	864	1925	1925

	WHITE		BLACK		TOTAL	
STROMAL FIBROSIS	1st	2nd	1st	2nd	1st	2nd
NOT SEEN	2774 (93)	2861 (96)	2662 (97)	2647 (97)	5436 (95)	5508 (96)
NORMAL	23 (<1)	24 (<1)	17 (<1)	19 (<1)	40 (<1)	43 (<1)
LESS THAN NORMAL	147 (5)	75 (2)	41 (1)	56 (2)	188 (3)	131 (2)
EXCESSIVE FOR TE	46 (1)	29 (1)	19 (<1)	17 (<1)	65 (1)	46 (<1)
Total	2990	2989	2739	2739	5729	5728
Missing	1060	1061	864	864	1924	1925
MECONIUM FILLED MACROPHAGES IN AMNION/CHORION						
NOT SEEN	2899 (97)	2885 (96)	2488 (91)	2529 (92)	5387 (94)	5414 (94)
PRESENT	90 (3)	105 (3)	248 (9)	207 (8)	338 (6)	312 (5)
Total	1061	1060	867	867	5725	5726
Missing	2989	2990	2736	2736	1926	1927
MECONIUM FILLED MACROPHAGES IN DECIDUA						
NOT SEEN	2973 (99)	2975 (100)	2623 (96)	2641 (97)	5596 (97)	5616 (98)
PRESENT	17 (<1)	13 (<1)	108 (4)	92 (3)	125 (2)	105 (2)
Total	1060	1062	2731	2733	5721	5721
Missing	2990	2988	872	870	1932	1932
DECIDUAL VESSEL THROMBOSIS						
NOT SEEN	2951 (99)	2915 (98)	2639 (97)	2561 (93)	5590 (98)	5476 (96)
PRESENT	28 (<1)	41 (1)	37 (1)	43 (1)	65 (1)	84 (1)
UNABLE TO DETERM	11 (<1)	32 (1)	56 (2)	136 (5)	67 (1)	168 (3)
Total	2990	2988	2732	2740	5722	5728
Missing	1060	1062	871	863	1931	1925

ATHEROMA OF DECIDUAL VESSELS	WHITE 1st	WHITE 2nd	BLACK 1st	BLACK 2nd	TOTAL 1st	TOTAL 2nd
NOT SEEN	2966 (99)	2934 (88)	2657 (97)	2524 (92)	5623 (98)	5458 (95)
PRESENT	10 (<1)	12 (<1)	16 (<1)	27 (1)	26 (<1)	39 (<1)
UNABLE TO DETERM	13 (<1)	41 (1)	57 (2)	189 (7)	70 (1)	230 (4)
Total	2989	2987	2730	2740	5719	5727
Missing	1061	1063	873	863	1934	1926
FIBRINOID DECIDUAL VESSELS						
NOT SEEN	2917 (98)	2890 (97)	2606 (92)	2519 (92)	5523 (96)	5409 (94)
PRESENT	60 (2)	63 (2)	83 (3)	83 (3)	146 (3)	146 (2)
UNABLE TO DETERM	13 (<1)	35 (1)	138 (5)	138 (5)	53 (<1)	173 (3)
Total	2990	2988	2740	2740	5722	5728
Missing	1060	1062	863	863	1931	1925
MARGINAL DECIDUAL NECROSIS						
NOT MARKED	2835 (95)	2775 (93)	2527 (92)	2407	5362 (94)	5182 (91)
MARKED	150 (5)	189 (6)	171 (6)	241	321 (6)	430 (7)
UNABLE TO DETERM	2 (<1)	18 (<1)	34 (1)	85	36 (<1)	103 (2)
Total	2987	2982	2732	2733	5719	5715
Missing	1063	1068	871	870	1934	1938
CAPSULARIS DECIDUAL NECROSIS						
NOT MARKED	2848 (96)	2805 (94)	2593 (95)	2540 (93)	5441 (95)	5345 (94)
MARKED	124 (4)	169 (6)	116 (4)	163 (6)	240 (4)	332 (6)
UNABLE TO DETERM	8 (<1)	5 (<1)	17 (<1)	22 (<1)	25 (<1)	27 (<1)
Total	2980	2979	2726	2725	5706	5704
Missing	1070	1071	877	878	1947	1949

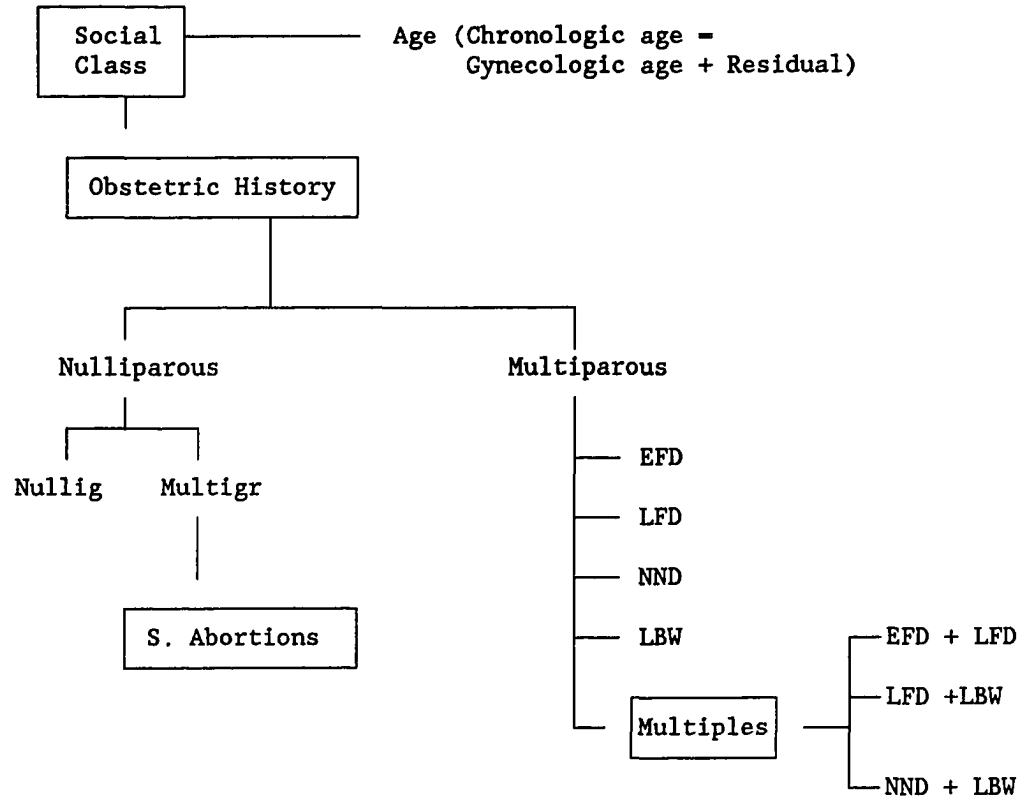
PATHOLOGICAL EDEMA OF THE VILLI	WHITE 1st	WHITE 2nd	BLACK 1st	BLACK 2nd	TOTAL 1st	TOTAL 2nd
NOT SEEN	2744 (92)	2818 (94)	2654 (98)	2682 (98)	5398 (94)	5500 (96)
PRESENT-NOT	17 (<1)	30 (1)	9 (<1)	6 (<1)	26 (<1)	36 (<1)
PRESENT-RARE	120 (4)	104 (3)	39 (1)	41 (1)	159 (3)	145 (2)
PRESENT-MANY	109 (4)	38 (1)	38 (1)	11 (<1)	147 (3)	49 <1)
Total	2990	2990	2740	2740	5730	5730
Missing	1060	1060	863	863	1923	1923
BASILIS DECIDUAL NECROSIS						
NOT MARKED	2949 (99)	2928 (98)	2602 (95)	2523 (93)	5551 (97)	5451 (95)
MARKED	18 (<1)	32 (1)	46 (2)	96 (6)	64 (1)	128 (2)
UNABLE TO DETERM	17 (<1)	25 (<1)	79 (3)	118 (<1)	96 (2)	143 (2)
Total	2984	2985	2727	2737	5711	5722
Missing	1066	1065	876	866	1942	1931
FIBRIN DISPOSITION-CYTOTROPHOBLAST						
NOT SEEN	2 (<1)	3 (<1)	0	2 (<1)	2 (<1)	5 (<1)
AVERAGE	2921 (98)	2906 (97)	2630 (96)	2591 (95)	5551 (97)	5497 (96)
EXCESSIVE	62 (2)	69 (2)	109 (4)	138 (5)	109 (2)	207 (4)
AVERAGE & EXCESSIVE	4 (<1)	8 (<1)	0	7 (<1)	4 (<1)	15 (<1)
Total	2989	2987	2739	2739	5728	5726
Missing	1061	1063	864	865	1925	1928
CYSTIC CHANGE-CYTOTROPHOBLAST						
NOT SEEN	2642 (88)	2642 (89)	1908 (70)	1787 (65)	4550 (79)	4429 (78)
PRESENT	347 (11)	330 (11)	831 (30)	940 (34)	1178 (21)	1270 (22)
Total	2989	2973	2739	2727	5728	5700
Missing	1061	1077	864	876	1925	1954

MARGINAL SINUS THROMBI	WHITE 1st	WHITE 2nd	BLACK 1st	BLACK 2nd	TOTAL 1st	TOTAL 2nd
NOT SEEN	2966 (99)	2968 (99)	2673 (98)	2671 (98)	5639 (98)	5639 (98)
RBC INTACT	10 (<1)	5 (<1)	26 (<1)	14 (<1)	36 (<1)	19 (<1)
RBC HEMOLYZED	13 (<1)	13 (<1)	38 (1)	44 (1)	51 (<1)	57 (1)
Combo-intact/ HEMOLYZED	0	0	1	4 (<1)	1	4 (<1)
Total	2989	2986	2738	2733	5727	5719
Missing	1061	1064	865	870	1926	1934
MICRO INFARCTS						
NOT SEEN	2651 (89)	2685 (90)	2417 (88)	2363 (86)	5068 (88)	5048 (88)
PRESENT-NOT	334 (11)	298 (10)	318 (12)	373 (14)	652 (11)	671 (12)
PRESENT-RARE	5 (<1)	4 (<1)	3 (<1)	2 (<1)	8 (<1)	6 (<1)
PRESENT-MANY		2 (<1)	2 (<1)	2 (<1)	2 0	4 (<1)
Total	2990	2989	2740	2740	5730	5729
Missing	1060	1061	863	863	1923	1924
NUCLEATED RED BLOOD CELLS						
NOT SEEN	2848 (95)	2876 (96)	2710 (99)	2710 (99)	5558 (97)	5586 (97)
PRESENT	142 (5)	113 (4)	30 (1)	29 (1)	172 (3)	142 (2)
Total	2990	2990	2740	2740	5730	5730
Missing	1060	1061	863	861	1923	1925

IVT AND ADJACENT VILLOUS INFARCTION	WHITE 1st	WHITE 2nd	BLACK 1st	BLACK 2nd	TOTAL 1st	TOTAL 2nd
NOT SEEN	2722 (91)	2714 (91)	2569 (94)	2556 (93)	5291 (92)	5270 (92)
RBC INTACT	84 (3)	103 (3)	75 (3)	68 (2)	159 (3)	171 (3)
RBC HEMOLYZED	166 (6)	158 (5)	75 (3)	95 (3)	241 (4)	253 (4)
Combo-intact/ HEMOLYZED	18 (<1)	14 (<1)	15 (<1)	19 (<1)	33 0	33 (<1)
Total	2990	2989	2734	2738	5724	5727
Missing	1060	1061	869	865	1929	1926
NUCLEAR CLUMPING-SYNCYTIOTROPHOBLAST						
NORMAL	2511 (84)	2627 (88)	2456 (90)	2311 (84)	4967 (87)	4938 (86)
LESS THAN NORMAL	392 (13)	246 (8)	234 (8)	381 (14)	626 (11)	627 (11)
EXCESSIVE FOR TERM	66 (2)	93 (3)	49 (2)	44 (1)	115 (2)	137 (2)
EXCESSIVE IN PARTS	21 (<1)	19 (<1)	0	1 0	21 (<1)	20 (<1)
Total	2990	2987	2739	2737	5729	5724
Missing	1060	1065	864	866	1924	1931

APPENDIX B
DATA ANALYSIS PLAN

Each of these 4 groups will consider the effects of social class as follows:



Gynecologic age is calculated as follows:

(Age at pregnancy event) - (Age at menarche)

Obstetric history of multigravid groups was analyzed in Comparison groups:

00000 (No deaths)
10000 (EFD)
01000 (LFD)
00100 (NND)
00010 (LBW)
11000 (EFD and LFD)
01010 (LFD and LBW)
00110 (NND and LBW)

Analysis of Comparison groups was accomplished by looking at obstetric history variables and:

1. Subsetting the group into:
   Nullipara (no deliveries greater than 20 weeks)
   Multipara (one or more deliveries greater than 20 weeks)

2. Dividing the Nulliparas into:

Early fetal loss
No previous pregnancies

3. Dividing the Multiparas into:
   Prev EFD
   Prev LFD
   Prev LBW
   Prev PTB
   Prev EFD and LFD
   Prev LBW with PTB
   Prev LBW without PTB

4. Dividing the Multiparas into:
   EFD 2nd pregnancy event in the study
   LFD 2nd pregnancy event in the study
   NND 2nd pregnancy event in the study
   PTB 2nd pregnancy event in the study
   NPO 2nd pregnancy event in the study

Each outcome group was considered as an exact replication of the event from the first pregnancy event in the study to the second, a non-exact replication or a single poor outcome in either pregnancy as follows:

P_1 = first pregnancy event in study
P_2 = second pregnancy event in study
O_1 = Poor outcome (1)
O_2 = Poor outcome (2)
O_N = No poor outcome

P_1 $[O_1]$	P_2 $[O_1]$	(Exact replication)
P_1 $[O_1]$	P_2 $[O_2]$	(Non-exact replication)
P_1 $[O_1]$	P_2 $[O_N]$	(Single poor outcome first pregnancy event)
P_1 $[O_N]$	P_2 $[O_1]$	(Single poor outcome second pregnancy event)
P_1 $[O_N]$	P_2 $[O_N]$	(Reference group--no poor outcome)

The outcomes that were be considered are:

1. Early Fetal Death (EFD) (less than 20 weeks gestation)

2. Late fetal death (LFD) (greater than 20 weeks and before delivery)

3. Neonatal death (NND) (from delivery to the first 7 days of life)

4. Preterm birth (PTB)

5. Intrauterine growth retardation (IUGR)

6. No poor outcome (NPO)

First Pregnancy	Second Pregnancy
EFD	EFD, LFD, NND, ID, IUGR, LBW, PTB
LFD	LFD
LFD	LBW, IUGR, PTB
LFD	EFD, LFD, NND, ID, IUGR, LBW, PTB

NND	LBW, IUGR, PTB
IUGR	EFD, LFD, NND, ID, IUGR, LBW, PTB
LBW	EFD, LFD, NND, ID, IUGR, LBW, PTB
LBW	LBW WITH PTB, LBW WITHOUT PTB
PTB	EFD, LFD, NND, ID, IUGR, LBW, PTB
PTB	PTB WITH LBW, PTB WITHOUT LBW

Logistic analysis

This will involve testing a series of models. The predicted outcome is RECURRENCE OF POOR OUTCOME. There are 2 types of recurrence, exact replication and non-exact replication and 7 groups. These are described in the data analysis plan (page 6).

The predicted outcome was compared to no poor outcome either pregnancy. The predicted outcome was coded 1 for recurrence and 0 for no recurrence.

To account for recurrence, medical variables and placental variables was coded in 4 levels as a string of the two outcomes:

1st pregnancy	2nd pregnancy	
1	1	(Exact replication)
1	0	(Single experience, 1st pregnancy)
0	1	(Single experience, 2nd pregnancy)
0	0	(No recurrence)

Because there is a correlation between previous placental weight and current placental weight, the placental weight in the 2nd pregnancy event and the difference in placental weight was used.

Placental development was divided into 2 major categories, infection and hypoxia/ischemic events.

ACUTE PLACENTAL INFLAMMATION
Cord Vasculitis--artery and vein
Funisitis
Chorionic vasculitis
Acute Epithelial Placental Membranitis (AEPM) of Amnion and Chorion
Placental Amnionitis and Chorionitis

HYPOXIA
Squamous metaplasia of the amnion
Amnion Nodosum
Macrophages in Amnion/Chorion and Decidua
Decidual vessel thrombosis
Fibrinoid decidual vessels

Atheroma of decidual vessels
Fibrin deposition-cytotrophoblast
Cystic changes-cytotrophoblast
Intervillous thrombi and adjacent villous infarction
Marginal sinus thrombi
Nucleated Red Blood Cells
Marginal decidual necrosis
Capsularis decidual necrosis
Basalis decidual necrosis
Marginal deciduitis
Capsularis deciduitis
Basalis deciduitis
Nuclear clumping--syncytiotrophoblast
Micro infarcts
Pathologic edema of the villi

The placenta variables were recoded as follows:

1. ACUTE PLACENTAL INFECTION

Level 1: AEPM of amnion or chorion
Level 1: Placental amnionitis or chorionitis
Level 2: Vasculitis of the umbilical vein
Level 2: Vasculitis of the umbilical artery or chorionic vasculitis
Level 3: Funisitis

2. ACUTE HYPOXIA:

Level 1: Squamous metaplasia of the amnion or Amnion Nodosum
Level 2: Macrophages in amnion, chorion or decidua, decidual vessel thrombosis, fibrinoid decidual vessels, atheroma of decidual vessels, fibrin deposition or cystic changes in the cytotrophoblast, intervillous thrombi and adjacent villous infarction, marginal sinus thrombi.

4. Chronic Hypoxia:

Decidual Necrosis: Level 1: None
Level 2: Marginal
Level 3: Capsularis
Level 4: Basalis

Nuclear Clumping of the syncytiotrophoblast

Micro infarcts

Pathologic edema of the villi

5. Inflammation

Deciduitis: Level 1: None
Level 2: Marginal
Level 3: Capsularis
Level 4: Basalis

TETRAD II MODELS

TIME ORDER:
1 Education
2 Occupation
3 Family social class, marital status
4 Gynecologic age
5 Per capita income
6 Medical history
7 Placental pathology
8 Growth
9 Outcome

Model 1: Social class (education, expected education, occupation, per capita income, family social class), gynecologic age and outcome (early fetal death, late fetal death, neonatal death, infant death, intrauterine growth retardation, low birth weight).

The group was subsetted to contain only those women who entered the study as nulligravidas (never pregnant)

Model 2: Social class, gynecologic age and growth (recurrence of low birth weight, prematurity)

Model 3: Social class, gynecologic age, medical history and growth and outcome (early fetal death, late fetal death, neonatal death, infant death, intrauterine growth retardation, low birth weight).

Model 4: Social class, gynecologic age, acute placental inflammation and growth and outcome.

Model 5: Social class, gynecologic age, acute placental hypoxia and growth and outcome.

Model 6: Social class, gynecologic age, chronic placental hypoxia and growth and outcome.

Model 7: Social class, gynecologic age, all placental effects and growth and outcome.

LOGISTIC REGRESSION ANALYSIS MODELS

Social class variables do not differ greatly from one pregnancy to the next, so the variables from the second pregnancy event was used. Variables was added to the model based on time order:

Model 1: recurrence = social class (occupation, education, expected education, per capita income, educational incongruity)

Model 2: recurrence = social class + gynecologic age

Model 3: recurrence = social class + gynecologic age + cigarette smoking

Model 4: recurrence = social class + gynecologic age + cigarette smoking + obstetric history

Model 5: recurrence = social class + gynecologic age + cigarette smoking + obstetric history + medical history

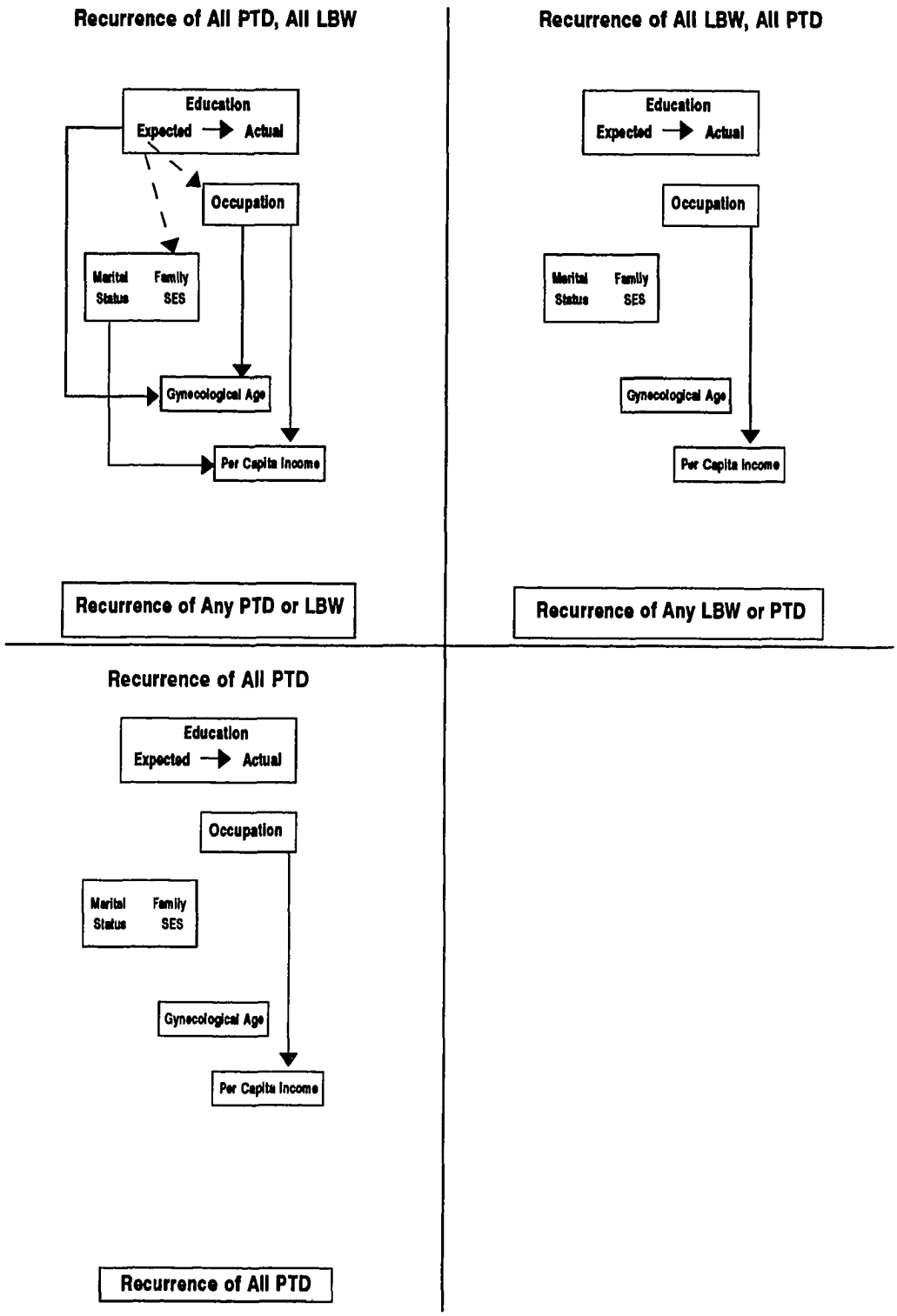
Model 6: recurrence = social class + gynecologic age + cigarette smoking + obstetric history + medical history + placental development

Model 7: recurrence = social class + gynecologic age + cigarette smoking + obstetric history + medical history + placental development + fetal development

APPENDIX C
TETRAD II MODELS

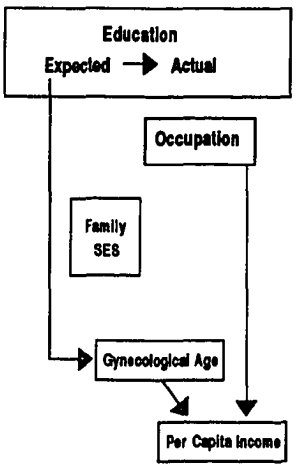
The following pages contain pictorial representations of the TETRAD II graphs. Solid lines indicate that the edge occurred at more than one significance level. Dotted lines indicate that the edge occurred at only one significance level.

Full Nulligravid Data Set (N=2935)
Social Class, Gynecologic Age
Recurrence of Low Birth Weight (LBW), and Preterm Delivery (PTD)

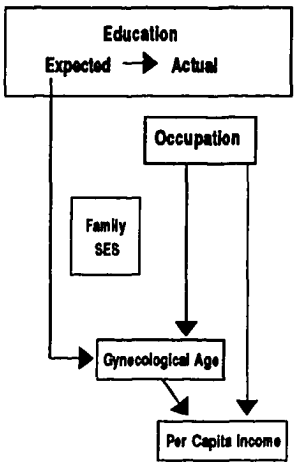


NULLIGRAVID Data Set Married Only (N=2462)
Social Class, Gynecologic Age
Recurrence of Low Birth Weight (LBW), and Preterm Delivery (PTD)

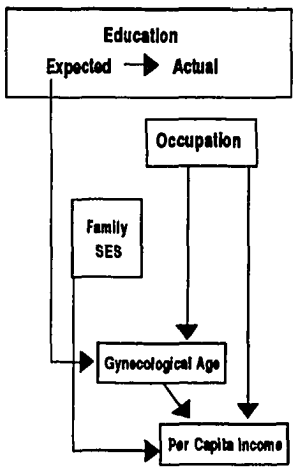
Recurrence of Any PTD, Any LBW

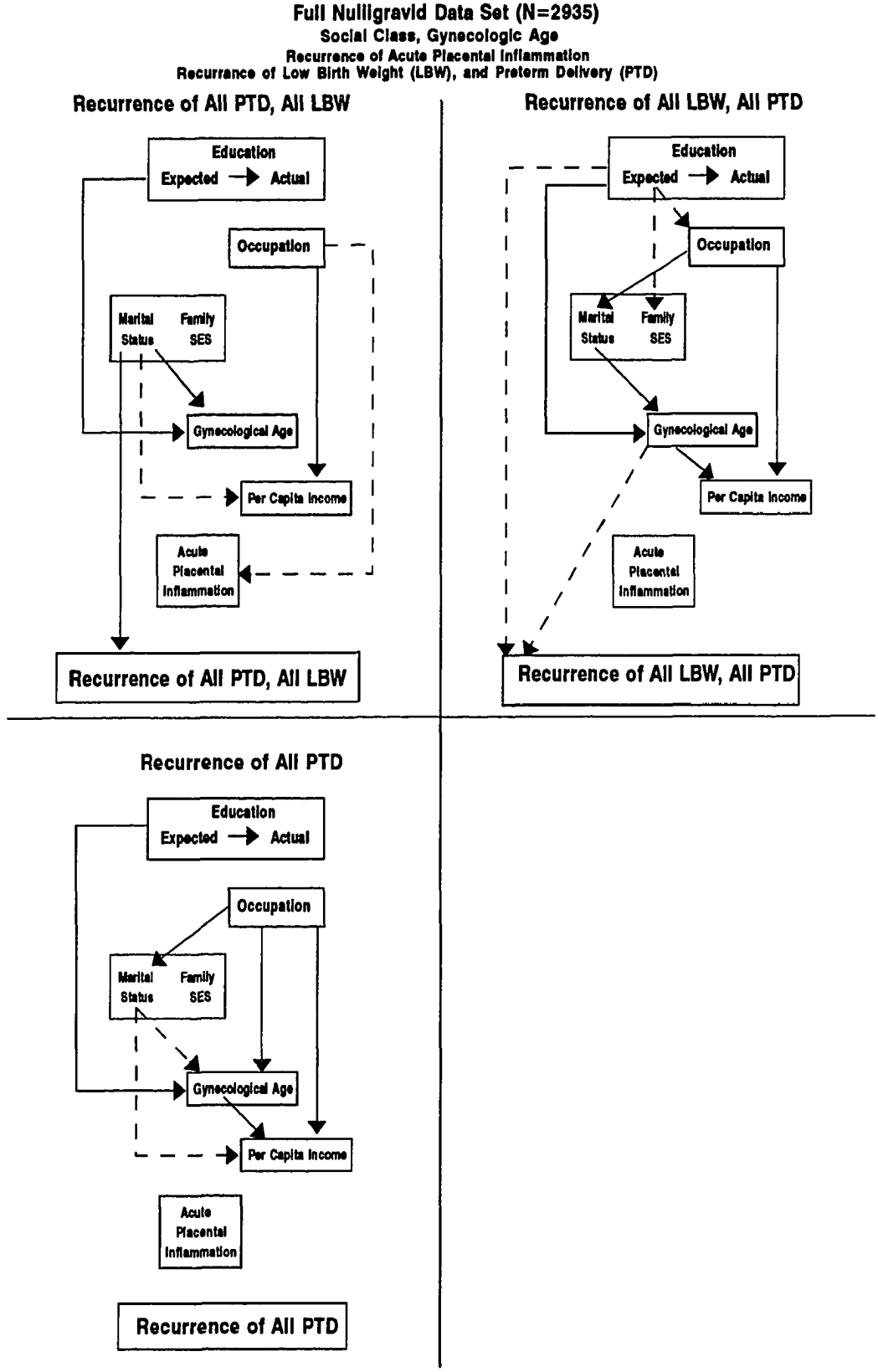


Recurrence of Any LBW, Any PTD



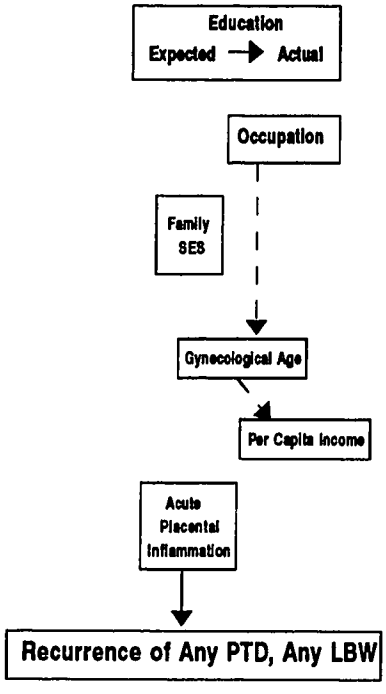
Recurrence of Any PTD with LBW



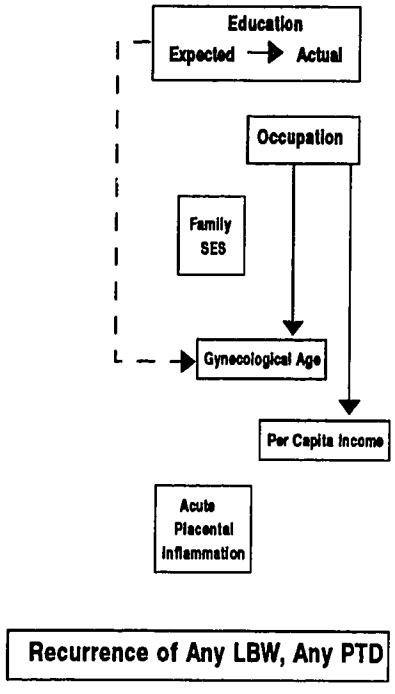


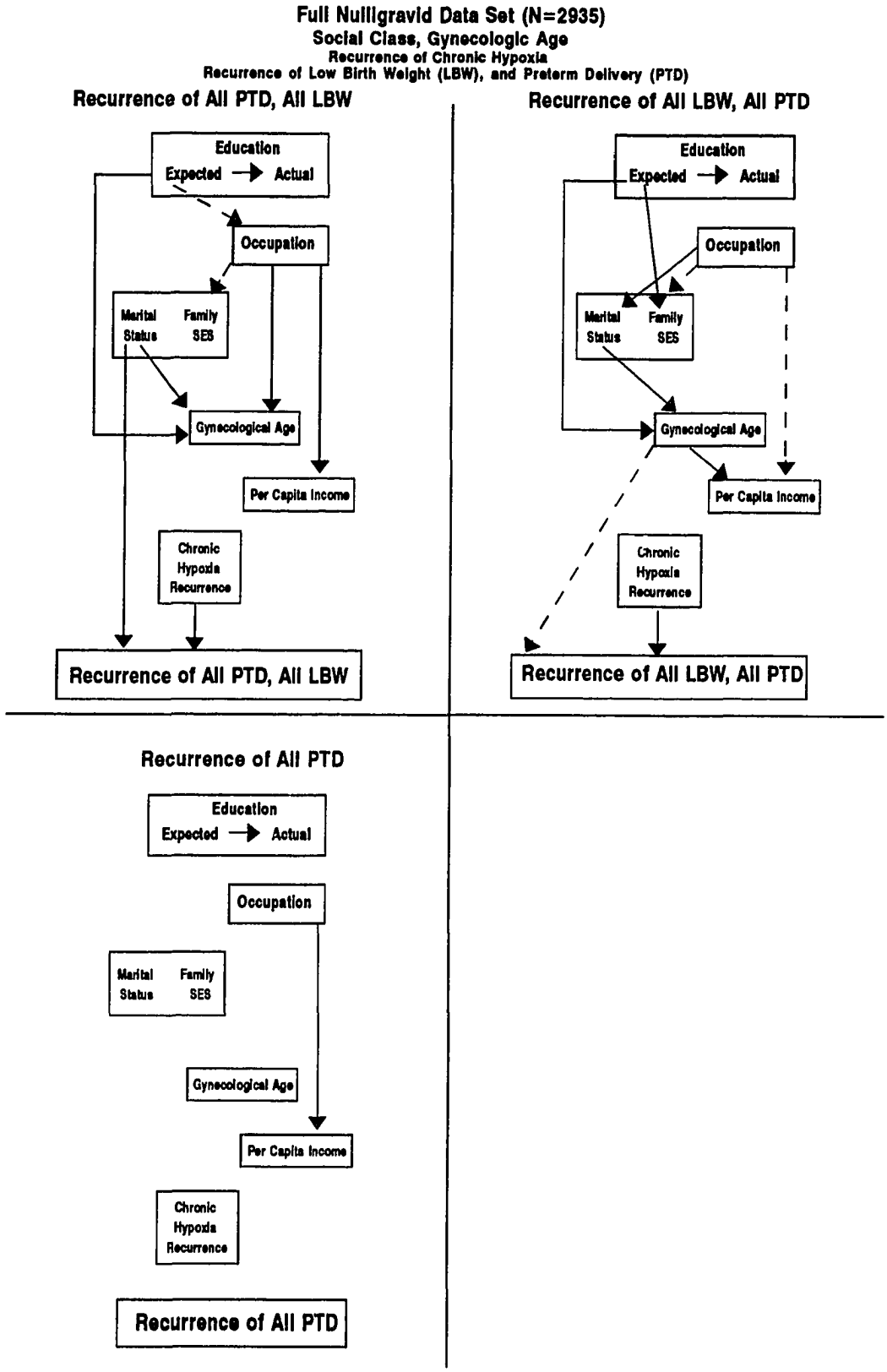
NULLIGRAVID Data Set Married Only (N=2462)
Social Class, Gynecologic Age
Recurrence of Acute Placental Inflammation
Recurrence of Low Birth Weight (LBW), and Preterm Delivery (PTD)

Recurrence of Any PTD, Any LBW

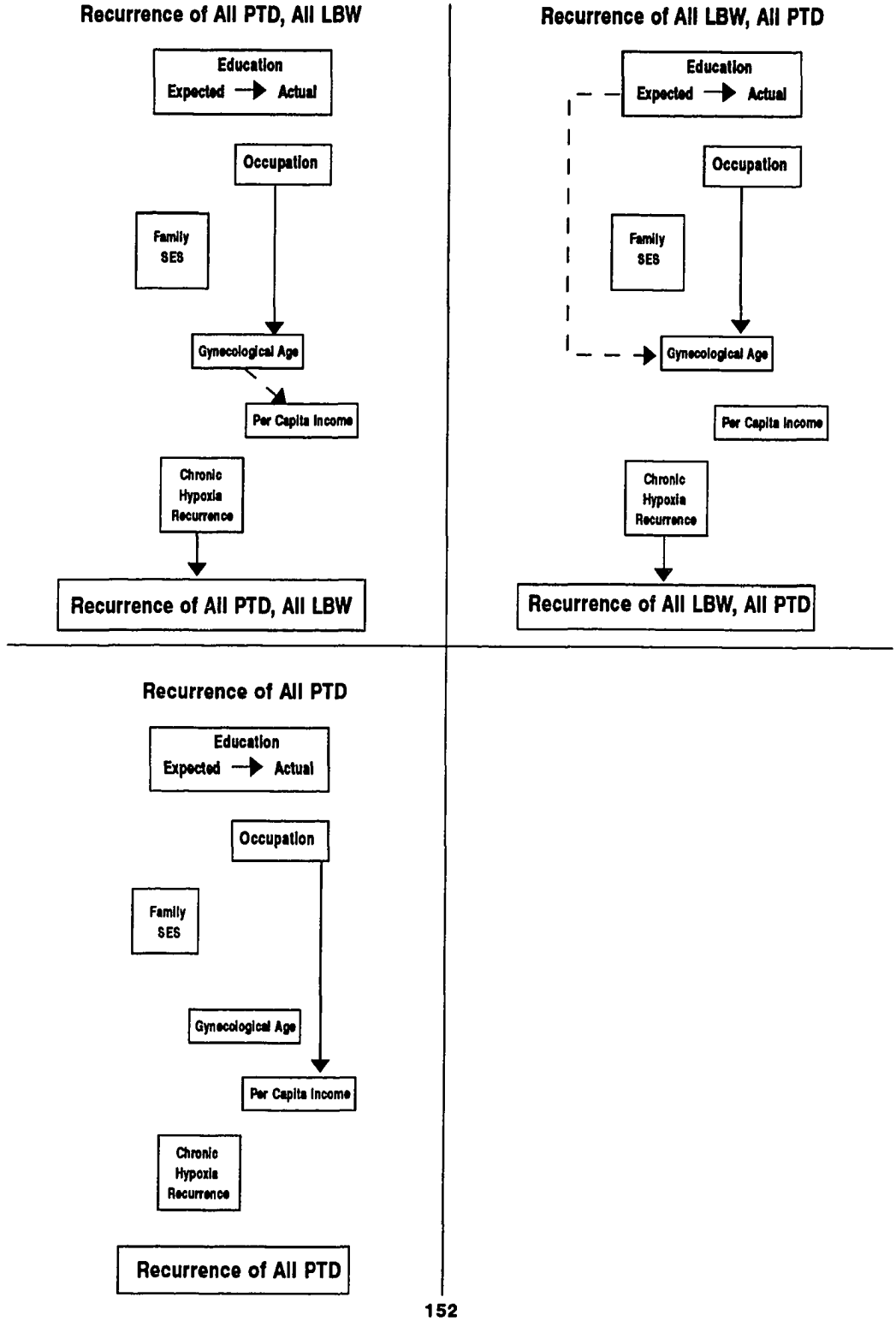


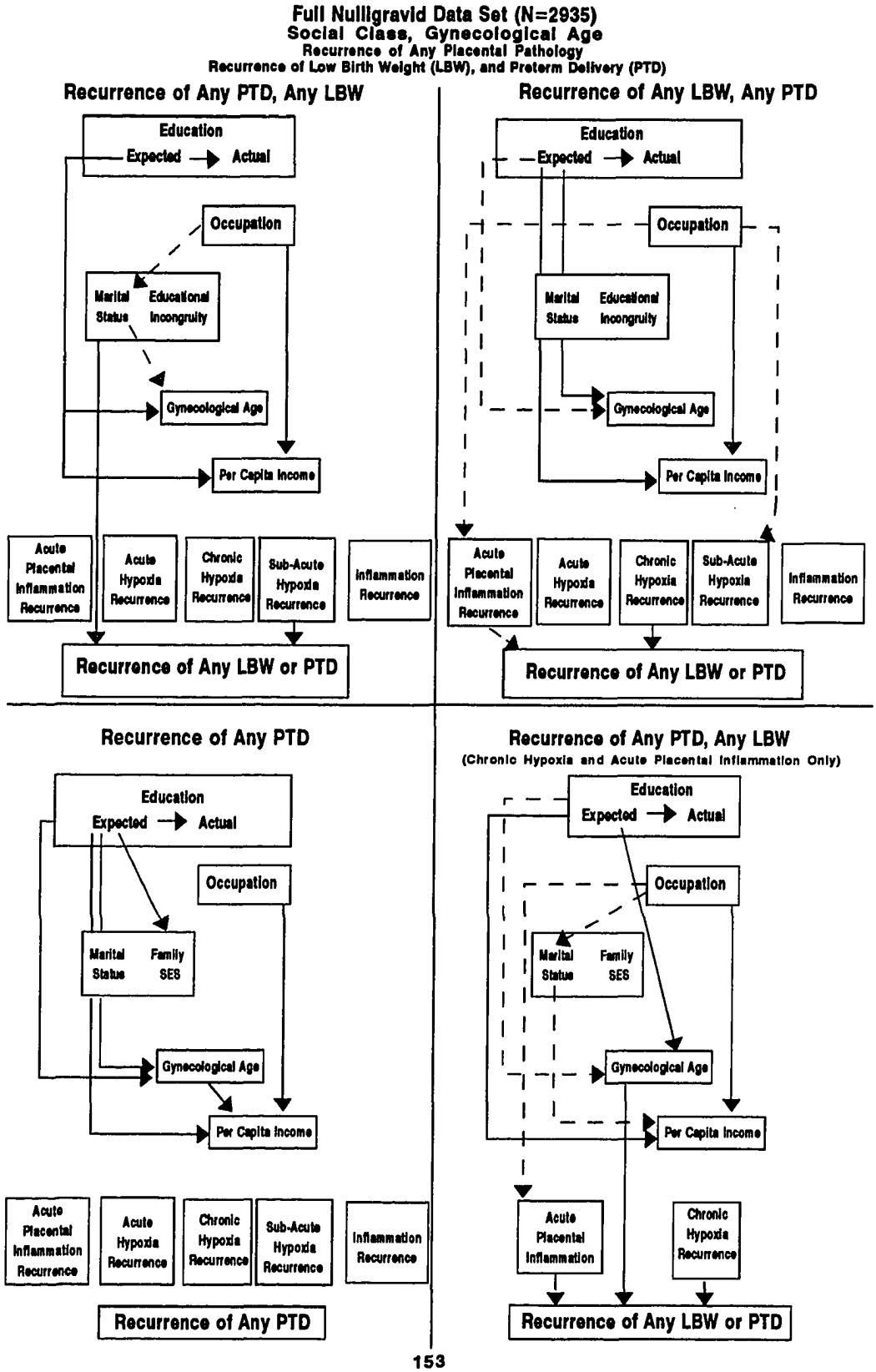
Recurrence of Any LBW, Any PTD





NULLIGRAVID Data Set Married Only (N=2462)
Social Class, Gynecologic Age
Recurrence of Chronic Hypoxia
Recurrence of Low Birth Weight (LBW), and Preterm Delivery (PTD)





NULLIGRAVID Data Set Married Only (N=2462)
Social Class, Gynecologic Age
Any Placental Recurrence Outcome
Recurrence of Low Birth Weight (LBW), and Preterm Delivery (PTD)