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The Relationship Between Oral Contraceptives and Intraepithelial Neoplasia of the Uterine Cervix

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THE RELATIONSHIP BETWEEN ORAL CONTRACEPTIVE INTRAEPITHELIAL NEOPLASIA OF THE UTERINE C

A thesis submitted in partial fulfillment of the requirements for the Degree of Master of Science at Virginia Commonwealth University

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אם תרצו אין זאת אגדה

"If You Will It, It Is No Dream.."

Theodor Herzl

I would like to dedicate this thesis to my parents whose understanding, love, support and belief in my ability to come "shining through" the rigors of graduate school has sustained me and brought me to this educational milestone.

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ABSTRACT

THE RELATIONSHIP BETWEEN ORAL CONTRACEPTIVES AND INTRA-EPITHELIAL NEOPLASIA OF THE UTERINE CERVIX

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The purpose of this study was to determine the relationship between specific oral contraceptive use and cervical intraepithelial neoplasia (CIN), and to determine if duration of use and content of oral contraceptives were related to CIN. The hypotheses tested in this study were: (1) norgestrel-containing oral contraceptives are associated with more severe levels of CIN, and (2) longer duration of oral contraceptive use is associated with more severe CIN.

Data was collected from 52 clinical records of clients who attended a colposcopy clinic during a four month period. Clients included in the study were utilizing one of five specific oral contraceptives for a minimum of six continuous months. During their initial clinic visit, all clients were interviewed by the colposcopy clinic nurse who recorded information concerning duration and type of oral contraceptive use on part one of an investigator-designed data collection form. From the data collection forms completed

by the nurse, the investigator determined clinical record eligibility for inclusion in the study. The investigator utilized part two of the data collection form to record age, race and colposcopic diagnosis from the client clinical record.

The majority of study clients were black and younger than 26 years of age. The duration of oral contraceptive use ranged from six to 96 months. OrthoNovum 1/50 (ON 1/50) was the most frequently used, and LoOvral was the least frequently used, oral contraceptive. Mild/moderate dysplasia was the most frequent CIN diagnosis and carcinoma in situ (CIS) was the least frequent. Condyloma was the second most frequent CIN diagnosis.

OrthoNovum 1/35 (ON 1/35) users had the highest frequency of mild dysplasia, and the highest Estimate of Relative Risk (ERR) of mild/moderate dysplasia. Users of $\leq$ 35 mcg. estrogen oral contraceptives had a higher percentage and ERR of mild/moderate dysplasia than users of 50 mcg. estrogen oral contraceptives. ON 1/35 and Loestrin users had no severe dysplasia/CIS diagnoses.

ON 1/50 and Ovral users (50 mcg. estrogen oral contraceptives) had a higher percentage and ERR of severe dysplasia/CIS and condyloma than users of $\leq$ 35 mcg. estrogen oral contraceptives. Loestrin users had the highest overall percentage and ERR of condyloma, and LoOvral users had the lowest overall percentage and ERR of condyloma. Of those

clients with 12 or more months of oral contraceptive use, the 50 mcg. estrogen oral contraceptive users had the highest percentage of condyloma. Of the study clients with 12 months or less oral contraceptive use, the 50 mcg. estrogen oral contraceptive users had the lowest percentage of condyloma. For all durations of oral contraceptive use, 50 mcg. estrogen users had the highest percentage of severe dysplasia/CIS. Users of oral contraceptives for 12 months or less had a higher percentage and ERR of severe dysplasia/CIS and condyloma than users of oral contraceptives for more than 12 months.

Users of norgestrel-containing oral contraceptives had a higher percentage and ERR of severe dysplasia/CIS and a lower percentage of condyloma and mild/moderate dysplasia than other oral contraceptive users in the study.

Fisher's exact one-tail test and Analysis of Variance (ANOVA) showed a statistically significant difference in the incidence of dysplasia between $\leq$ 35 mcg. estrogen and 50 mcg. estrogen oral contraceptive users. Fisher's exact one-tail test also showed statistically significant differences in the incidence of dysplasia between ON 1/35 and Ovral users. Differences in the incidence of condyloma between norgestrel-containing oral contraceptives and other oral contraceptive users were not statistically significant with Fisher's exact one-tail test.

The investigator concluded that there were differences between specific oral contraceptives and the associated incidence of CIN. The investigator also concluded that these differences were not associated with duration of oral contraceptive use.

CHAPTER ONE

Introduction

Contraception is a conscious effort to prevent the probability of pregnancy (Stedman, 1976). To promote control of human fertility, new advances in reproductive knowledge in the 1950's led to the development of oral contraceptives composed of hormones and their analogs. Oral contraceptives are the most widely used drugs requiring a prescription. It is estimated that eight million women in the United States and 150 million women worldwide use the "pill" (Wrenn, 1979). As a hormonal preparation, the "pill" inhibits ovulation. Questions concerning the safety and possible side effects of ongoing hormonal therapy have resulted in considerable research, however, many questions remain unanswered.

Potentially serious side effects associated with oral contraceptives include hypertension, thromboembolitic disease, cerebral vascular accidents and endometrial hyperplasia. Research has shown that oral contraceptive agents may have direct effects on the genital tract by altering the status of the endometrium and the cervical mucus (Dallenbach-Hellweg, 1981). Considerable concern exists regarding the association of carcinomas of the uterus, cervix and vagina and the use of oral contraceptives.

Among these concerns is the association between intraepithelial neoplasia of the uterine cervix (CIN) and oral contraceptive use. Many studies involving the association between cancer of the cervix and oral contraceptives have been inconclusive (Robbins and Cotran, 1979). Although it is still uncertain whether oral contraceptive use significantly increases the incidence of cervical cancer, research has shown that oral contraceptive use is related to endometrial and cervical tissue changes. The possible association between oral contraceptive use and an increased risk of CIN has been the subject of more than 12 major epidemiologic studies (Swan and Petitti, 1982). The results of these studies are contradictory. Most of the studies conducted have been related to the association between cervical cancer and factors such as dysplasia, age of menarche, number of sexual partners, age of first coitus, race, economic status, and environmental influences (Meisels, et al., 1977; Stern, 1971; Miller, 1973; Rotkin, 1981).

A number of recent studies have been concerned with the relationship between CIN and condyloma. Condyloma acuminatum is caused by the Human Papilloma Virus and may mimic, precede or coexist with CIN (Koss, 1983). Malignant transformation of these genital warts has been documented (Meisels and Morin, 1981). Research concerning CIN and

condyloma has not investigated oral contraceptive use associated with condyloma.

Many studies have focused on users vs. nonusers of oral contraceptives. Few studies have been conducted on the effects of the individual drugs on the user. A number of studies have researched the effects of specific combinations of estrogen and progesterone. Reactions reported with these oral contraceptives have included breakthrough bleeding, changes in menstrual flow, spotting, changes in the cervical transformation zone, and viscosity of cervical mucous secretion (Dickey, 1979). A consistent outcome of these studies has been the need for further research related to associated effects of oral contraceptives.

The most significant way in which oral contraceptives may affect cervical cancer is by an alteration of the hormonal balance which affects the immune response and metabolism (Beral, 1980). This immune response effect may interact with individual hormonal and immune responses. Rather than being a direct carcinogenic agent, oral contraceptives may potentiate the susceptibility of the individual to carcinogenic influences.

Research has shown that the risk of cancer is related to the duration of exposure to a carcinogen. Several studies have reported a relationship between the length and the potency of oral contraceptive use and the

development of cervical cancer (Ory, et al., 1977; Peritz, et al., 1977; Melamed and Flehinger, 1973). It has been suggested that the longer the duration of use and the higher the potency of the oral contraceptive, the greater is the risk for cervical cancer.

Because of the risk of cervical cancer which may be associated with CIN and oral contraceptive use, health care providers prescribing these preparations need to be aware of the potential health risks that can be avoided by being attentive to the duration of use and strength of the oral contraceptive prescribed for clients. This study will provide additional information concerning the relationship between specific oral contraceptives, duration of use, and intraepithelial neoplasia of the uterine cervix (CIN).

Problem Statement

The purpose of this study was to determine the relationship between specific oral contraceptives and CIN, and to determine if duration of use and content of the oral contraceptive were related to CIN.

Hypotheses

The hypotheses to be tested in this study were:

1. Norgestrel-containing oral contraceptive use is associated with more severe levels of CIN.

2. Longer duration of oral contraceptive use is

associated with more severe levels of CIN.

Definition of Terms

Specific oral contraceptives included in this study were five drug preparations with estrogen and progestogen content (Appendix A). These five drug preparations represent two dosage strengths of estrogen and three progestogens.

Cervical Intraepithelial Neoplasia (CIN) is defined in this study as mild, moderate, and severe dysplasia, carcinoma in situ, and flat condyloma acuminatum as noted on the colposcopic examination reports in 52 client medical records from a colposcopy clinic in a large university teaching hospital located in a southeastern state.

Duration of oral contraceptive use is defined as the length of time the client reported having taken the specific oral contraceptive which was being taken at the time of the CIN diagnosis. All clients included in the study had been taking the specific oral contraceptive continuously for a minimum of six months.

Assumptions

1. All reports and information contained in the client's record were accurately recorded.

2. The five specific oral contraceptives studied

represented the most commonly prescribed oral contraceptives.

Limitations

1. Because the study did not include variables, such as social and medical history and certain demographic variables, other factors that may have influenced the study results were not controlled.

2. Because of geographic location and the limited population sample, the study results cannot be generalized.

3. Some clients may have been using another oral contraceptive prior to the one reported in the study which could have influenced study results.

Delimitations

1. A convenience sample of diagnostic reports from 52 client medical records were utilized in this study.

2. Only those medical records of clients which met defined criteria for specific oral contraceptives were included in the study.

3. Only those clinical records of clients seen in the colposcopy clinic site between October, 1983 and March 1984 were included in the study.

Conceptual Framework

The conceptual framework for this study includes epidemiological concepts for the investigation of disease and Chrisman and Fowler's Systems-in-Change model (1980).

Both nursing and epidemiology are concerned with demographic, biologic, social, psychological and cultural characteristics of clients and how these may influence the development of disease (Lilienfeld and Lilienfeld, 1980). Chrisman and Fowler's model (1980) was selected because it provides an organized approach to the assessment of change. Epidemiological concepts enable a systematic approach to the study of a characteristic, such as oral contraceptives, and disease. This study of the relationship between specific oral contraceptives and CIN utilizes epidemiological concepts for the investigation of disease.

Epidemiological Concepts

Ideas of epidemiology date back to Hippocrates who emphasized the importance of looking at environmental influences on disease (Lilienfeld and Lilienfeld, 1980). Epidemiology focuses on the patterns of disease that occur in human populations and the biological, chemical, physical and social factors that may influence these patterns (Lilienfeld and Lilienfeld, 1980). An epidemiological approach is useful for this study because it enables a systematic method to determine a statistical association of a characteristic (specific oral contraceptive) and disease (CIN). It also enables biological inferences from patterns of statistical associations, and it can provide a basis for preventative health care practices of primary

health care providers.

The major concepts of epidemiology include agent, host, environment, time, place, person and spectrum of disease. Patterns of disease depend on the interaction of agent, host and environment which may be affected by time and place. Host and person may be considered synonymous. The host is the susceptible person. Characteristics of the host include demographic, biological, socioeconomic, personal and genetic variables (Lilienfeld and Lilienfeld, 1980). The agent can be defined as the "infectious" material or a precipitating event (Lilienfeld and Lilienfeld, 1980), such as a "carcinogenic" agent. It is possible that both an initiating agent and a promoting agent may be involved in the development of disease.

The environment and place are inclusive of each other. Associations with different levels of disease have often been found in different geographic locations. The epidemiologist studying infectious disease is concerned with the specific place where contact is made. This knowledge is crucial in the study of epidemics. In the study of any disease entity, analysis of disease distribution can identify if some viral, environmental or cultural factor may be present in more than one place or more prevalent in one population than another. For example, the Epstein-Barr virus has been pinpointed as a likely

etiological agent in a number of disease conditions including tumors that have specific geographic distribution (Lilienfeld and Lilienfeld, 1980). Environmental factors include cultural factors, such as religion, socioeconomic milieu, and exposure to chemicals, occupational and personal lifestyle stressors. Environmental factors could also include the person's internal immunological and physiological condition.

Time indicates the incubation period from the time of contact with the agent to the onset of illness or the manifestation of disease. The length and extent of exposure are important elements of the time concept in the development of disease. In order to demonstrate a cause in an epidemiological study, a time sequence must be shown. Epidemiological investigations have shown that there is often a long latency period between causal exposure and clinical disease (Hutchison, 1975).

The spectrum of disease refers to the sequence of events occurring in a human organism from the time of contact with the etiological agent to death associated with the disease (Lilienfeld and Lilienfeld, 1980). This may also be considered the gradient of infection. Both subclinical and clinical stages are included in the disease spectrum even though only the clinical stage may be noted. Whether a person will go through the full spectrum of

disease is dependent upon the host/person's immunological status and the preventative measures initiated by the health care provider, such as screening, procedures, and treatments to inhibit further development of the disease.

In studying the prevalence and associated patterns of disease, epidemiology attempts to integrate and investigate the interactions of agent, host, environment, time, place, person and the spectrum of disease. Incorporation of these factors in health care practice enables the health care provider to assess and evaluate physical, psychological, and socioeconomic client data. This data gives the health care provider a better understanding of the possible explanations for this information, and it enables intervention in the progression and extension of disease in the client.

The Systems-in-Change Model

The Systems-in-Change model was developed by Chrisman and Fowler (1980) for utilization in their nursing practice. They developed the model in an attempt to incorporate both systems and developmental theories of stress and adaptation into their nursing practice. The model is comprehensive and flexible and it is applicable to clinical practice. Riehl and Roy (1980) classified the Systems-in-Change model as a developmental model for nursing practice.

Chrisman and Fowler (1980) include the following

concepts in their Systems-in-Change model for nursing practice: (1) professional nursing's functions and activities are directed by a therapeutic purpose, and (2) the nurse supports and promotes health and the quality of life. The Systems-in-Change model is based on the following assumptions: (1) man is viewed as three dynamic systems interacting with each other and the environment along a developmental continuum, (2) the status of each system and its interactions influences health, (3) the individual moves from one developmental stage to another with information and effects of the past being stored for incorporation into the present and for utilization in the future, and (4) change is inherent in life and growth.

The structure of the Systems-in-Change model provides an organized way to assess interdependent factors, such as physical development, physiological systems, health and socioeconomic milieu, in a client/patient situation. The Systems-in-Change model emphasizes structure composed of biological, social and personal systems and it states that these are in a continual process of change. The model also emphasizes the active process of change in individual development throughout life. The process identifies the changes that influence growth, and the equilibrium of each system involves those changes within systems, between systems, and changes that occur along a developmental

continuum. The two basic components of the Systems-in-Change model are the structure (systems) and the process (change).

The structure (systems) perceives man as a biological, social, and personal system that interacts and is open to the environment and to each system (Chrisman and Fowler, 1980). Each of these systems has its own internal organization and they are interdependent. They interact with each other as an "integrated whole" and there is feedback among the systems and with the environment. Changes that occur inside or outside of the systems may produce stress which can disturb the equilibrium of the systems. Assessment of the systems includes the state of equilibrium and the existence or absence of compensatory/regulatory mechanisms that help the individual system achieve, restore or maintain optimal function. Although the system may be studied in the present, the role of the past and the future potential are incorporated into the assessment.

The process (change) refers to the stages of human development which range from the prenatal period through maturation and death. The client's present status always consists of a past as well as a potential future. The client's development includes change which is influenced by his environment and genetics. This change affects all systems. In all stages of life, development is an active process that involves change.

In assessment of developmental change, a comparison is made of the factors observed, which indicate the developmental stage of the client's biological, social and personal systems, with the stages expected by the client's chronological age and sociocultural milieu (Chrisman and Fowler, 1980). The general developmental assessment that is established by gathering this information influences evaluation of the individual systems and guides the practitioner in therapeutic goal setting and intervention. The practitioner can identify the specific developmental problem and if a significant discrepancy exists between the observed and the expected data, the practitioner can use specific tools to further assess and focus on the problem. Changes of the systems are not only developmental, they are also continually occurring in response to input processing from the ever changing internal and external environment (Chrisman and Fowler, 1980).

Chrisman and Fowler's model attempts to enable the nurse to examine the many variables, such as lifestyle, occupational stress, genetics, past history, medication use, and immune system which may affect the client at any one point in time. Because the model is open and flexible, it permits incorporation of a variety of concepts and theories. The practitioner can then utilize appropriate epidemiological concepts and emphasize aspects of the model

that apply to the specific client situation.

Chrisman and Fowler (1980) identify the implications of their model for different levels of nursing personnel and its utilization in the nursing process. Their model presents a very specific assessment tool that the practitioner can utilize with the individual client. The model also provides guidelines for establishment of diagnosis, goals, intervention and evaluation. The model can be applied to a variety of settings within the hospital and in public health by the nurse practitioner. The nurse practitioner is concerned with the interaction of the systems with the environment, the client's developmental stage, and the client's past, present and future.

The nurse practitioner's assessment includes an evaluation of the current functioning of each client system (biological, social and personal), the signs and symptoms of dysfunctional changes within each system, and the environmental variables that influence each system. The nursing diagnosis is then based on the actual or potential dysfunction of one or more of the systems. Goals for intervention and evaluation are developed from the diagnosis.

Chrisman and Fowler's model is particularly useful in this study of the relationship between oral contraceptives and CIN. The model addresses the importance of change which is inherent in life and growth. Change may

occur within a normal cycle and it may be affected by man's biology and environment. Normal tissue changes occur cyclically within a woman's menstrual cycle. The etiology of abnormal cytology and cervical tissue change is still uncertain; it may be due to a combination of factors that exist within the dynamic interaction of man's biology and the environment. Among these factors are oral contraceptives, their associated hormonal influences, duration of exposure to contraceptives, and sociodemographic factors of the client.

Utilizing the Systems-in-Change model, the nurse practitioner assesses past and present biological, social, and personal systems of the client along with the state of equilibrium of the systems. She then identifies both the expected point along the developmental continuum and the actual observed point of development. Identification of a deviation from the expected and observed point of development, combined with informatiom from the data base, enables the establishment of a diagnosis. Intervention could consist of counseling, appropriate referral, education and/or adjustment of the client's medication. The nursing goal is to enable the client to return to an equilibrium of systems. Follow-up evaluation would determine if this goal had been met. A continued disequilibrium would indicate a reassessment for more appropriate nursing intervention to alter

the existence of the disease or the factors affecting the disease process.

Observation by the practitioner of CIN and oral contraceptive (agent) use is considered with the interaction of all systems including the past, present and future medical history of the client. The nurse practitioner must also observe and consider the epidemiological process that exists with host, environment, and agent interaction in the development of disease. The practitioner assesses the interaction of the client/host's biological and immunological, personal and social systems (environment) by utilizing the Systems-in-Change model and notes that the expected normal cytological smear is different from the observed changes in cervical tissue. With an understanding of the interaction of the client's systems, and the epidemiological process of CIN, the practitioner may be able to assess the client's risk for developing cervical cancer.

The nurse practitioner can set goals for the promotion of optimal health by utilizing the Systems-in-Change model. She may recommend a different oral contraceptive with less risk for CIN. In addition, she may counsel the client about increased CIN risks based on the client's environmental factors, such as duration of oral contraceptive use, client immunological system (infection susceptibility) and client lifestyle. Included with counseling, is the importance

for the nurse practitioner to provide the client with contraceptive alternatives and support in her compliance with regular health care follow-up.

The nurse practitioner must practice with a knowledge of epidemiological and systems factors that may inhibit the client's achievement of optimal functioning. She must have an awareness of the active process of change and the spectrum of disease in relation to normal and abnormal pathology of cervical tissue. She must also have an awareness of the interaction of man's personal, biological and social systems along the developmental continuum.

The nurse practitioner in her expanded role provides primary health care for the gynecology client. She is responsible for performing a thorough history and physical examination, prescribing the appropriate oral contraceptive, obtaining cytological smears, and reviewing laboratory reports. To promote the well-being and provide for the needs of her clients, the nurse practitioner needs an understanding of the differential effects of the estrogen and progestogen components of oral contraceptives. The nurse practitioner also needs to be able to take into account how the interaction of agent (oral contraceptive), host (client) and the environment (the client's biopsychosocial and cultural environment) influence health outcomes.

In summary, nursing and epidemiology share in the goal

to understand the relationship between factors that affect disease occurrence. Both consider time, place, person, host, agent, environment, and the spectrum of disease in order to plan health promotion strategies for clients. The Systems-in-Change model provides an approach to assess the client's systems and alterations in equilibrium. Epidemiological concepts provide tools for evaluation of the factors involved in the development of disease. Nursing research concerning the relationship between CIN and oral contraceptives utilizes an epidemiological approach. This information provides a basis for the development and evaluation of preventive procedures and public health practice, such as counseling and cytological screening. An understanding of potentially serious effects of estrogen and progesterone provides information that can assist the nurse practitioner in her delivery of optimum care to clients with gynecological needs.

CHAPTER TWO

Literature Review

The study of intraepithelial neoplasia of the uterine cervix (CIN) and oral contraceptive use necessitates an understanding of the literature concerning CIN, the influence of estrogens and progestogens on cervical tissue changes, and an understanding of the risk factors that are associated with cervical cancer. The literature review includes information on these three topics. Section one contains information on CIN and screening methods, section two addresses oral contraceptives and the influence of estrogens and progestogens on cervical tissue change, and section three contains information on the factors which have been shown to be associated with CIN.

CIN and Screening Methods

Cervical cancer is considered a major malignant neoplasm of the female genital tract and it ranks sixth as the cause of cancer deaths in women. The frequency of cervical cancer in young women has risen significantly which suggests an increase in early exposure to carcinogenic influences (Robbins and Cotran, 1979). The incidence of cervical cancer increases sharply to approximately 30 years of age, and it peaks at approximately 40 to 50 years of

age (Cramer, 1982).

Meisels, et al. (1977) found that the prevalence rate for CIN was highest in women between the ages of 15 to 44 years, with a mean of 30.5 years followed by a gradual decline with age. The prevalence rate of CIN in women who have had cytological smears during screening is 1.1 to 1.6 cases per 100 women. The rate for carcinoma in situ of the cervix is 0.2 to 0.4 cases per 100 women screened (Stern, 1969). The decrease in deaths from cervical cancer is due to the early detection of curable lesions. During the 1960's only 20 percent (20.0%) of cervical cancers were detected in the in situ stage. Currently, 50 percent (50.0%) of cervical cancers are detected at an early stage of development.

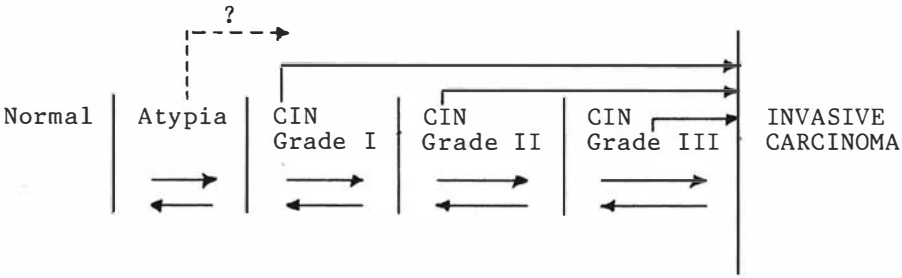
The increase in early detection is primarily due to the development of the cytological screening test. Cytological smears are recommended for all women beginning at 20 years of age and earlier if women are sexually active. Cytological smears are routinely performed on all women who request, and are using oral contraceptive prescriptions. Although there are a certain number of false positive and false negative cytological smear reports, they have been found to be at least 90 percent (90.0%) effective in detecting cervical carcinomas and CIN (Hoffkin and Soost, 1981). The squamocolumnar junction at the cervix is the

site where most cervical carcinomas arise. This is the area where the cytological smear is taken (Robbins and Cotran, 1979) and where special attention is given during colposcopic examination.

The colposcopic examination is performed on women who have an abnormal cytological smear. This examination increases the accuracy of diagnosis, decreases the need for biopsy, and it can lead to more focused CIN treatments for the patient/client. Colposcopy was first introduced in 1925. The colposcope is a stereoscopic binocular microscope with 10 levels of magnification that utilizes special direct and indirect coloring procedures to detect and identify cell changes on the cervix and vaginal mucosa (Fogel and Woods, 1981).

The development of CIN and cancer of the cervix occurs on a continuum of morphological abnormalities. These abnormalities progress from normal tissue to reactive changes and inflammation, squamous metaplasia, then mild, moderate and severe dysplasia, ending in carcinoma in situ. Condylomas are also included as another entity in the continuum of CIN (Robbins and Cotran, 1979; Figure 1). Invasive cervical carcinomas arise almost exclusively from CIN lesions.

Natural History of Precancerous Lesions
of the Uterine Cervix



CIN = Cervical intraepithelial neoplasia used for the entire morphological spectrum of precursor lesions
Grade I = mild dysplasia
Grade II = intermediate lesions (moderate dysplasia)
Grade III = classical carcinoma in situ and severe dysplasia

Figure 1

Diagrammatic Representation of Several Possible Pathways of Progression or Regression of Intraepithelial Cancerous Events in the Uterine Cervix (Koss, 1978)

It is important to note that there are a variety of alterations of the cervical epithelium which are benign. These benign alterations include repair following trauma which results in regeneration and proliferation of cells (hyperplasia). Benign changes also include chronic cervicitis and squamous metaplasia of the endocervical glands that are not associated with dysplasia. When an epithelial alteration develops on the external cervical surface due to an erosion of the vulnerable columnar epithelium that may have grown at that site, estrogenic stimulation initiates reepithelialization by the stratified squamous epithelium (ectocervical epithelium). The alteration is covered by regenerative epithelium which grows over it from the outside and upward. With progestogenic stimulation, the reserve cells beneath the columnar epithelium of the endocervix proliferate in the form of reserve cell hyperplasia. Reserve cell hyperplasia precedes the regeneration of the squamous epithelium which constitutes the epithelium of the ectocervix (Dallenbach-Hellweg, 1981). Reserve cell hyperplasia spreading over the defect undergoes maturation through the process of squamous metaplasia. Up to this point the repair processes have been benign. However, in the last stage of maturation, a percentage of the cases do not proceed smoothly from reepithelialization to normal maturation.

In these situations, precancerous lesions of various grades develop. These include a variety of levels of dysplasia, carcinoma in situ and condyloma.

Condyloma (Human Papilloma Virus-HPV) are included in the continuum of CIN (Koss, 1983). They are flat papillar lesions of the genitalia that have been known for centuries. Viral etiology of these warts, which are usually sexually transmitted, has been well documented (Meisels, et al., 1983). These lesions are an important factor considered to be responsible for at least some of the precancerous changes of cervical tissue (Koss, 1983). Though not all condylomas progress to more advanced lesions, malignant transformations of genital warts have been documented (Meisels and Morin, 1981).

Cervical condylomas have often been mistaken for dysplasia (Meisels, Fortin and Roy, 1977). In a review of previously diagnosed dysplasias, more than 70 percent (70.0%) were found to be condylomas (Meisels, et al., 1977). Syrjanen (1979) reported that condylomatous lesions were present in 49.4 percent (49.4%) of patients with dysplasia and neoplastic lesions. Of these condylomas, 88.1 percent (88.1%) were present in women who were less than 40 years of age. Of the four types of condylomas, the flat type is the most common one found on the cervix and it is the most common lesion of the cervical epithelium of the teenage

woman (Koss, 1983).

Oral Contraceptives and the Influence of Estrogens and Progestogens on CIN

Dallenbach-Hellweg (1981) found that oral contraceptives may cause alterations of the cervical epithelium. Therefore, it is important to consider the estrogen and progestogen influence on CIN. Although estrogens and progestogens were first isolated and synthesized during the 1940's, they were not used therapeutically until five years later. Initially, estrogens and progestogens were used for the treatment of reproductive disorders and for disseminated cancer. Since the 1960's, the primary use of estrogens and progestogens has been for contraception (Beral, 1980).

The most commonly used oral contraceptives include both estrogen and progestogen. Progestogen is an "agent capable of producing biological effects similar to those of progesterone" (Stedman's, 1976). The combination of estrogen and progestogen in oral contraceptives inhibit ovulation by suppression of gonadotropins follicle stimulating hormone (FSH) and luteinizing hormone (LH). They also stimulate alterations in the cervical mucus and endometrium (Kastrup, 1983). There are many brands of oral contraceptives which are composed of different dosages and types of estrogens and progestogens.

Estrogens and progestogens in oral contraceptives act specifically on the menstrual cycle. Estrogens suppress FSH, block follicular development for ovulation, and they stimulate the proliferation of the stratified squamous epithelium of the ectocervix. Progestogen suppresses LH secretion to inhibit ovulation. Progestogens stimulate the columnar epithelium and the reserve cells beneath it (Dallenbach-Hellweg, 1981). Ober (1977) reports that stimulation of glandular hypersecretion is the most commonly found effect of progestogen. In addition, he has noted that progestogen alters the cervical mucus by modifying the normal protein pattern which causes it to thicken, and it stimulates clumping and folding of epithelial cells. Progestogens cause a disturbance in the endometrium which makes it unsuitable for implantation of a fertilized ovum (Dong and Eoff, 1978).

The effect of the exogenous estrogens and progestogens depends greatly on the maturity of the cervical epithelium at the time they are ingested. Estrogen may induce cellular maturation. Progestogen may inhibit cellular maturation and/or induce an increase in desquamation of the cervical epithelium (Wied, et al., 1983). The endocrinologic condition of the client and the dosage and structure of the estrogen and progestogen preparation, determine whether the hormones will act antagonistically

or synergistically (Wied, et al., 1983).

Kamal (1966) studied the effects of different combinations of estrogen and progestogen on the endometrium and cervical mucosa. He found that pills with a higher content of progestogen had a weak estrogen and strong progestogen effect which could lead to breakthrough bleeding, weight gain, and scanty menses. Pills with a lower content of progestogen tended to increase the amount and length of menstrual flow. Other side effects associated with a higher content of estrogen in pills include nausea, fluid retention, breast tenderness, headache, hypertension, dysmenorrhea, fibroid growth, and leukorrhea (Wrenn, 1979). Higher content of progestogen is also associated with irritability, headache, depression, and occasionally hypertension (Wrenn, 1979). Because estrogens used alone can often cause irregular, prolonged, and unpredictable menstrual bleeding patterns, it is necessary to use a combination of progestogen with the estrogen (Wrenn, 1979).

Variables Associated with CIN

Beginning in the early 1950's and extending through the 1960's, considerable research was conducted which helped to clarify risk factors and demographic variables associated with cervical cancer. The age of first coitus and multiple sexual partners were two important variables found to be associated with CIN. Rotkin (1981) stated that these two

variables showed the strongest epidemiological relationship found with cervical cancer. Rotkin also stated that in all populations where early coitus is widespread, there is a high degree of cervical cancer. It is believed that a high degree of cellular activity exists during adolescence which provides maximal opportunity for the oncogenic transformation of cervical cells (Rotkin, 1972). Rotkin reported that the increased risk of cervical cancer may be related to a combination of demographic, epidemiological, etiological and pathological interactions.

Research indicates that carcinogenesis requires a combination of available vulnerable tissue, the application of a carcinogen, and a latent period (Rotkin, 1981). The nature of the carcinogenic component is not fully understood. Rotkin provided an extensive list of proposed variables that have been studied for their relationship to the risk of cervical cancer (Rotkin, 1981; Appendix B). Kessler (1981) stated that there are several well accepted variables in cervical cancer epidemiology. These variables include a "nonwhite" mortality risk which is twice that of the white population, and a mortality risk for the total population which is one half of that which existed in 1960 for cervical cancer. This decrease in mortality can be explained by the increase in early detection and treatment of cervical cancer.

Among the many risk factors associated with CIN and cervical cancer is condyloma. Koss (1983) stated that there is "excellent evidence" that flat condylomas may persist in a significant proportion of women and become associated with intraepithelial neoplasms or invasive cancer. Many cases of condyloma have been found to coexist with an adjacent dysplasia or carcinoma in situ. Meisels and Morin (1981) found that 25.6 percent (25.6%) of the condylomas were associated with dysplasia and neoplastic lesions. Meisels and Morin (1981) stated that condylomas precede dysplasia by 3.3 years, carcinoma in situ by 9.3 years and invasive cancer by 27 years. Therefore, condyloma may act as an initiating or promoting agent of abnormal cervical tissue changes.

Not all condylomas progress to more advanced lesions and many regress which indicates the possibility of other promoting factors that may be necessary for malignant transformation. Host resistance may play an important role in the development of malignant transformations. The presence and persistence of the Human Papilloma Virus in the genital tract of immunosuppressed women over many years has been cited and associated with precancerous lesions that led to invasive carcinoma (Tabibzadeh, et al., 1981). Oral contraceptives may also be promoting factors of condyloma in CIN, although this has not been investigated.

The role of oral contraceptives in cervical cancer is still unclear, however they have been associated with CIN. Most of the research involving oral contraceptives has focused on a comparison of oral contraceptive users and nonusers rather than on the effects of the individual oral contraceptive preparations. A number of factors have affected and complicated the user versus nonuser studies, such as the finding that oral contraceptive users tend to be more sexually active than nonusers (Lilienfeld, 1980). The more sexually active population is frequently correlated with a higher risk and incidence of cervical dysplasia which complicates evaluation of the relationship between oral contraceptives and cervical tissue changes (Rotkin, 1981). Oral contraceptive users also have a higher frequency of yearly cytological smears, therefore, they are more likely to have early recognition of cervical tissue changes (Swan and Petitti, 1982). Different progestogen and estrogen strengths may also have different cytological effects on the contraceptive user, which are not accounted for in studies comparing users of different contraceptive methods.

Sandmire, et al. (1976) stated that studies of CIN are often based on cytology alone and conclusions are drawn without tissue examination. Duration of oral contraceptive usage and the follow-up period is often inadequately studied when one considers the latent period involved in

carcinogenesis. Lilienfeld (1980) stated that methodological problems are present in studies of oral contraceptives and cervical cancer because prior to beginning the use of contraceptives, women may have different risk factors for cervical cancer. Therefore, results of the studies may be totally unrelated to the contraceptive method utilized. Stern, et al. (1970) found that even before they started taking oral contraceptives, women who chose the "pill" in the early 1960's were more likely than intrauterine device (IUD) users to have abnormal cytological smears. Factors such as the number of sexual partners and the amount of sexual activity may have influenced the choice of contraceptive.

Meisels, et al. (1977) studied the age at first coitus and its relationship to oral contraceptive use. He found highly significant correlations between early onset of sexual activity and dysplasia, oral contraceptive use and dysplasia, and early age of coitus and oral contraceptive use. After correcting for the age at first coitus, the researchers noted an excess of dysplasias among oral contraceptive users.

Swan and Brown (1981) in their study of the interaction of oral contraceptive use, sexual activity and cervical cancer, attempted to match oral contraceptive users with nonusers. Although no significant relative risk of cervical

cancer was found among oral contraceptive users, their study was somewhat biased because the cytological smear interval was longer for nonusers, and the oral contraceptive clients had twice as many sexual partners as the control group. Swan and Brown (1981) found that the most increased risk of cervical cancer occurred among women who were more sexually active and who had been using oral contraceptives from four to six years.

Ory, et al. (1976) compared the risk of cervical cancer in oral contraceptive users to the risk in IUD users. Although they did not report cervical carcinoma more frequently in the oral contraceptive users, they did find that at the time of choosing oral contraceptives, women with one cytologic smear had fewer carcinoma in situ findings than IUD users. However, in established oral contraceptive users with one cytologic smear in which the duration of oral contraceptive use was not reported, there was a 40 percent (40.0%) higher risk of dysplasia as compared to IUD users. In contraceptive users with two cytologic smears, there was a 50 percent (50.0%) increased risk of dysplasia among oral contraceptive users as compared with IUD users. The two cytologic smears are indicative of a longer duration of contraceptive use.

Dallenbach-Hellweg (1981) stated that prolonged increase in proliferative activity provides an opportunity for the manifestation of the effects of carcinogenic

substances. The potential effects of risk factors associated with estrogen and progestogen use, and multiple sexual partners, may be increased during the proliferation of cervical epithelium which is associated with specific hormonal properties in contraceptives.

Singer and Jordan (1977) reported that the combined estrogen and progestogen pill may be directly associated with cervical neoplasms because the pill can lead to an increase in squamous metaplasia. An eversion of the endocervical columnar epithelium, when exposed to the vaginal environment and pH, induces the metaplastic transformation which is sometimes associated with cervical precancerous changes. Mingeot and Fievez (1974) compared biopsies of patients who were taking three different estrogen and progestogen combinations. They found that endocervical epithelium does appear to undergo important changes when it is under synthetic estrogen and progestogen influence. They also cite an increase in the frequency of metaplasia.

Rubio (1977) reported an increased maturation of squamous cells which are associated with circulating estrogen. He emphasized the need for further investigation of possible associations between oral contraceptives and cervical atypias.

Studies have been conducted on the relationship between exogenous estrogen and cervical cancer. Use of

the estrogen diethylstilbestrol (DES) in utero has been associated with increased frequency of abnormal cytological smears and an increased risk of cervical cancer (Lilienfeld, 1980). Bibbo, et al. (1977) studied women exposed to DES during pregnancy. The drug was randomly assigned to one group and a placebo was given to the other group. A 25 year follow-up study showed that cervical cancer occurred in one percent (1.0%) of the exposed group as compared to 0.4 percent (0.4%) of the unexposed group. The prevalence rate for cervical cancer for the general population is 0.2 to 0.4 per 100 women screened (Stern, 1969). Although Boyce, et al. (1977) in their study of the estrogen component of the "pill" and its relationship to cervical cancer found no association, other research findings indicate the potential increased risk of cervical cancer in premenopausal women using estrogen (Rubio, 1977; Lilienfeld, 1980; Bibbo, et al., 1977).

Progestogen is also involved in cervical tissue changes and it has been studied for its association with the risk of cervical cancer. Szontagn's (1966) study of progestogen cited the differences in endometrial and cervical mucus effects between dosages of 2.5 to 2.0 mg. and 1.0 to 1.5 mg. of progestogen. His study showed that the combination of estrogen with progestogen tends to negate the potent effect of progestogen on the cervical mucus. A number of studies

have shown an increased risk of cervical cancer in women using the injectable progesterone medroxyprogesterone acetate (Depo-Provera or DMPA) (IARC Working Group, 1974; Powell, 1971). In countries where DMPA is frequently used, the incidence of cervical cancer is high (Lilienfeld, 1980).

Dallenbach-Hellweg (1981) made the observation that among young girls who had taken oral contraceptives for the treatment of skin disease, and who had never had intercourse, the incidence of preneoplastic lesions was higher than normal with the lesions tending to occur earlier in life than would normally be expected. Dallenbach-Hellweg (1981) also found that the incidence of adenomatous hyperplasia of the cervical mucosa was four times higher in women taking high progestogen pills and pure progestogen products. Although in 1981 Dallenbach-Hellweg reported that adenocarcinoma was somewhat uncommon, Ng reported in 1983 that the two types of carcinoma of the uterine cervix are squamous cell carcinoma (estrogen responsive squamous epithelial cells) and adenocarcinoma (from progesterone responsive endocervical columnar epithelium). Ng (1983) reported that during the period 1940 to 1974, there was a decrease in the incidence of squamous cell carcinoma and an increase in adenocarcinoma. A definite correlation between adenomatous hyperplasia and adenocarcinoma in situ and the intake of oral contraceptives has been found by

a number of other researchers (Maqueo, et al., 1966; Taylor, et al., 1967; Candy and Abell, 1968; Mingeot and Fievez, 1974). Dallenbach-Hellweg (1981) reported that between 80 to 100 percent (80.0 to 100.0%) of the women with adenohyperplasia of the endocervical mucosa had been taking oral contraceptives.

According to the Dallenbach-Hellweg study (1981) there may be evidence to suspect an etiological link between progestogen administration and adenocarcinoma of the endocervix. The progestogen produced implicated in the "pill" is the highly potent hormone norgestrel. This study showed that all of the clients with adenocarcinoma of the endocervix had taken oral contraceptives containing norgestrel.

Following several years of study of the effects of oral contraceptives, Dallenbach-Hellweg (1981) found an apparent predominance of cervical intraepithelial neoplasia which was derived from stratified squamous epithelium among those women who had taken high estrogen pills. Cervical neoplasias, derived from reserve cells which are stimulated by progesterone, were more prominent among clients who had taken high progestogen products. Dallenbach-Hellweg's statistical analysis of a large series of women revealed an increased incidence of CIN among women who used oral contraceptives and in the younger age groups. Dallenbach-Hellweg found that precancerous changes in women who used

oral contraceptives occurred 10 years earlier than in those who were not using them. According to the Dallenbach-Hellweg study (1981), oral contraceptives affected maturation and accelerated the appearance of precancerous cervical tissue changes.

Stern, et al. (1977) reported that 30 percent (30.0%) of the oral contraceptive users with dysplasia progressed to cervical carcinoma in situ as compared with five percent (5.0%) of those not using the "pill." The researchers indicated that oral contraceptives may accelerate the rate of progression from dysplasia to carcinoma in situ. Rather than a direct etiological link to cervical dysplasia, this progression may be associated with an alteration of the woman's immunological system. Beral (1980) states that it is possible that certain estrogen-progestogen combinations in the combined "pill" may induce cancer where other combinations might suppress it. Because the endogenous hormonal status of the client is considered important in all cancer risk, reproductive tract cancers are more likely to be associated with complex hormonal relationships. Endogenous hormonal influences may vary in nullipara, multipara, and menopausal women, and women with an early age of menarche. Beral (1980) stated that the most important way in which the exogenous estrogens and progestogens may affect cancer risk is by altering the hormonal balance which affects the

metabolism, immune response and the entire homeostatic mechanism.

Although studies have not been able to consider all of the variables involved in the relationship between oral contraceptive use and cervical carcinoma, research findings suggest that oral contraceptive use, especially long-term use, may increase the risk of cervical carcinoma. Ory, et al. (1977) and Peritz, et al. (1977) have found an increased cervical cancer risk in long-term oral contraceptive usage. In studies of duration of oral contraceptive use, other confounding variables have fewer indirect effects (Lilienfeld, 1980).

Ory, et al. (1977) studied a black population of 6,663 IUD users and 14,447 oral contraceptive users. The researchers found that the relative risk for carcinoma in situ increased from 2.5 for one to two years of oral contraceptive use to 4.7 for three or more years of oral contraceptive usage. Worth, et al. (1972) and Boyce, et al. (1977) also reported that a larger number of long duration oral contraceptive users were associated with cervical carcinoma in situ. Melamed and Flehinger (1973) found that the relative risk for cervical cancer was increased 1.5 in oral contraceptive users as compared with diaphragm users, and 0.8 as compared with IUD users. Peritz, et al. (1977) studied 18,000 women and adjusted study findings for age, education,

marital status, number of cytological smears and religion. He compared duration of oral contraceptive users of less than two years with users of other contraceptive methods of less than two years. He found a relative risk for oral contraceptive users of 2.4. For two to four years of oral contraceptive use, he found a relative risk of 3.0, and for four or more years of oral contraceptive use, he found a relative risk of 4.1.

Swan and Brown (1981) studied 69 patients with cervical cancer and 216 matched control subjects. They found a trend in the risk of cervical cancer which was associated with the duration of oral contraceptive use. Short-term oral contraceptive users had a slight increase in relative risk of cervical cancer which gradually increased with a maximum of four to six years of oral contraceptive use. The cervical cancer risk gradually declined in over six years duration of oral contraceptive use. Swan and Brown (1981) concluded that oral contraceptive users with a median duration of four to six years usage were at the highest risk for cervical cancer (significance $p < 0.05$). Sandmire, et al. (1976) also cited risks with the duration of oral contraceptive use. They studied 76 subjects with cervical carcinoma and compared them with 780 control subjects. They also compared IUD users with oral contraceptive users for risks of cervical cancer. They found no increased risk between the two groups

with the exception of an increased risk for cervical cancer in the oral contraceptive users of three to six years duration. No other associations for cervical cancer risk were found in their study.

In one of the most recent studies of the relationship between oral contraceptives, duration of use, and cervical cancer (Vessey, et al., 1983), both carcinoma in situ and dysplasia occurred more frequently in the oral contraceptive group than in the IUD group. Of 13 cases of invasive cancer, nine cases had more than 13 years use of oral contraceptives. Duration of oral contraceptive use was significantly correlated with the risk of cervical cancer. The incidence for cervical dysplasia, carcinoma in situ, and invasive cervical cancer combined rose from 0.9 per 1000 woman years in those with up to nine years of oral contraceptive use to 2.2 per 1000 woman years in those with more than eight years of oral contraceptive use. No such trend in incidence with duration of use was noted among the IUD users. Although Vessey, et al. (1983) found no significant associations with specific estrogens or progestogens or with any particular dose or brand of oral contraceptive, a high proportion of the oral contraceptive use in the study was related to products containing 50 mg. or more of estrogen.

Summary

In summary, the development of CIN and carcinoma of the cervix occurs on a continuum of morphological abnormalities. Early detection of curable lesions with the cytological smear, and accuracy of diagnosis and improvement of treatment with colposcopy have been associated with a decreased mortality risk from cervical cancer. The significant rise in the risk of cervical cancer in younger women suggests an increase in early exposure to carcinogenic influences. Many variables have been studied to examine the carcinogenic influences and their relationship to the risk of cervical cancer (Rotkin, 1981). Among these variables are oral contraceptives composed of estrogens and progestogens. Studies have found that these hormones may influence the processes of regeneration and reepithelialization of cervical erosions (Dallenbach-Hellweg, 1981: Wied, et al., 1983). Stern, et al. (1977) and Beral (1980) indicated that oral contraceptives may increase the rate of progression from cervical dysplasia to carcinoma in situ by affecting the woman's hormonal balance. The specific oral contraceptive and the duration of oral contraceptive use may also have a significant effect on the development of CIN. A number of studies have shown that exogenous estrogens may be associated with an increased risk of cervical cancer (Lilienfeld, 1980; Rubio, 1977;

Bibbo, et al., 1977; Stern, 1970). Cervical cancer risk, especially adenocarcinoma risk, has also been associated with progestogen use (Dallenbach-Hellweg, 1981; IARC Working Group, 1974; Powell, 1971). Many of these studies found significant associations between oral contraceptives and CIN.

Most of the research involving oral contraceptives and cervical cancer has focused on a comparison of oral contraceptive users with nonusers, rather than on the effects of the individual oral contraceptive preparations. These comparison studies have been complicated by other factors such as differences in levels of sexual activity or oral contraceptive users as compared with users of other contraceptive methods. In addition, most studies have been based on cytological smear reports rather than on more specific colposcopy tissue examination.

Most cancer risk is related to dose and duration of exposure to the carcinogen. Malignancy is not expected until a certain latency period has elapsed. A number of studies have noted a relationship between longer duration of exogenous estrogen and progestogen use and cervical cancer (Melamed and Flehinger, 1973; Sandmire, et al., 1976; Ory, et al., 1977; Peritz, et al., 1977; Swan and Brown, 1981; and Vessey, et al., 1983). The association between oral contraceptives and condyloma of the uterine

cervix has not been examined in these studies, however it may be an important variable in the progression of CIN. Lilienfeld (1980) stated that confounding variables have fewer indirect effects on the findings in studies of duration of oral contraceptive use and CIN.

Further research on specific oral contraceptive preparations and their duration of use is needed. Research in this area should include CIN and condyloma which have been diagnosed by colposcopy. Studies of specific oral contraceptive preparations and their duration of use could help to confirm and clarify previous trends in studies which have focused on oral contraceptive users and nonusers.

CHAPTER THREE

Methodology

The purpose of this study was to determine the relationship between specific oral contraceptives and CIN, and to determine if the duration of use and content of the oral contraceptive were related to CIN. Most of the research that has been conducted compared oral contraceptive users with nonusers. These studies were concerned with the level of sexual activity of the contraceptive user, the duration of contraceptive use, and other variables associated with the risk of cervical cancer. Only a few of these studies were concerned with specific oral contraceptive preparations, duration of use, and cervical tissue changes. Condyloma, which is a form of precursor cervical tissue change, and oral contraceptive use have not received sufficient attention in studies related to the risk of cervical cancer.

In an effort to obtain additional information concerning the risk of cervical cancer, this study investigated specific oral contraceptive preparations, duration of use, and their relationship to CIN.

Research Design

The research design for this study was a retrospective correlational design. Polit and Hungler (1978) stated that

retrospective and correlational research are effective in examining present health problems and their link with events or phenomena from the past. Lilienfeld (1980) stated that retrospective correlational studies allow for the examination of associations between the characteristics of interest and the condition or disease being studied. The retrospective correlational study design was appropriate for this study which investigated oral contraceptives and duration of usage, and their relationship to CIN.

Information for this study was obtained from clinical records of clients who attended a colposcopy clinic in a large university medical center located in a southeastern, metropolitan area of the United States. Client records were examined to obtain information on current diagnosis of CIN, the clients' past history of specific oral contraceptive use, and duration of usage. Because of study location and sample size, study results cannot be generalized.

Population and Sample

The study population included a convenience sample of 52 clinical records of clients who attended a colposcopy clinic from October 24, 1983 through March 6, 1984. The clients had been referred to the colposcopy clinical because of abnormal findings on their cytological smears. Only those clinical records of clients who met the following

study criteria were included: (1) the client had been using one of the five oral contraceptives specified in the definition of terms, (2) the client had been using the specific oral contraceptive continuously for a minimum of six months prior to the first clinic visit, and (3) the oral contraceptive user was a newly referred client.

Sampling began on October 24, 1983 and continued through March 6, 1984. The colposcopy clinic nurse recorded the specific oral contraceptive, the duration of use, and the client's name on an investigator-designed data collection form during the client's initial attendance at the colposcopy clinic (Appendix C). Nurses assisted client recall of specific oral contraceptives by utilizing a picture chart. Sampling was limited to the specified time period for data collection. During this time period a total of 52 client clinical records met the criteria for inclusion in the study.

Study Setting

The study took place in a colposcopy clinic located in a large university medical center. The clinic served one major city and many surrounding counties and it was staffed by hospital staff. Clients seen in this clinic were referred from gynecology clinics and private physicians in the metropolitan city and surrounding areas. The study population included both private and public clinic clients from rural and urban areas. Clinics were conducted each

Monday morning and Tuesday afternoon. All clients received a colposcopic examination with a biopsy being performed when necessary.

Data was collected by the colposcopy clinic nurse while interviewing the client to obtain the medical history. Interviews were conducted in a semiprivate interviewing area prior to the colposcopic examination performed by the physician.

Data Collection Instrument

The data collection instrument utilized in this study was an investigator-designed, two-part data collection form. The investigator developed the necessary form based on review of the literature, past clinical work experience, and a pilot study. Part one of the form was completed by the colposcopy clinic nurse and part two was completed by the investigator.

The data collection form was designed to identify the clinical records to be included in the study and to provide for individual observations of specific oral contraceptives and diagnoses. Part one consisted of items to obtain the clinical record identification of the client, the specific oral contraceptive used, and the duration of oral contraceptive use. Part two of the data collection form consisted of four items constructed to obtain information related to client race, age, and colposcopy diagnosis.

Pilot Study

Prior to data collection, a pilot study was conducted in February, 1983 by the investigator. The study was conducted because of the investigator's interest in oral contraceptives and CIN as an area for further research. The pilot study included clinical records of clients who attended a donation and grant supported gynecology clinic located in the same metropolitan area. The results of the pilot study prompted further investigation to determine the relationship between CIN and oral contraceptives. Information for the pilot study was obtained from a convenience sample of cytological smear reports taken from 86 clinical records of clients who used six specific oral contraceptives.

Results of the pilot study showed that five-sixths of the mild dysplasia noted on cytological smear reports were associated with a specific oral contraceptive. It was also noted that squamous metaplasia and reactive changes tended to be more frequently associated with lower estrogen dosages of 35 mcg. or less. The average age of the pilot study sample was 22 years.

Data Collection Procedure

This study was conducted between October, 1983 and March, 1984. Prior to data collection, permission to review client clinical records was obtained from the study

organization (Appendix D). The investigator met with appropriate nursing personnel to inform them of the study being conducted and to answer any questions pertaining to the study. The nursing supervisor in the colposcopy clinic was responsible for informing the staff members about the study being conducted.

The colposcopy clinic nurse utilized part one of the data collection form on Monday between 9:00 a.m. and 11:00 a.m. and Tuesday between 12:30 p.m. and 3:30 p.m. All clients attending the clinic for the first time were interviewed by the nurse and information concerning duration and type of oral contraceptive use was hand recorded on part one of the data collection form. The nurse retained the data collection form for the investigator to collect each week from the clinic.

From the data collection forms completed by the nurse, the investigator determined clinical record eligibility for inclusion in the study. Eligibility criteria included the use of one of the five specific oral contraceptives with a minimum of six months usage. The investigator utilized part two of the data collection form to record age, race, and colposcopic diagnosis from the client's clinical record. A total of 52 clinical records of clients were identified, examined and included in the study.

CHAPTER FOUR

Data Analysis and Interpretation

The purpose of this study was to determine the relationship between specific oral contraceptives and cervical intraepithelial neoplasia (CIN), and to determine if duration of use and content of the oral contraceptives were related to CIN. The design for this study was a retrospective, correlational design which allowed for examination of the associations between oral contraceptives and CIN. Data was collected from 52 clinical records of clients who attended a colposcopy clinic during a four-month period. The analysis of data includes three sections: section one includes a description of study population characteristics; section two includes an analysis of specific oral contraceptives and CIN; and section three includes a description of duration of oral contraceptive use and CIN. A discussion of study results is also included in this chapter.

Data was analyzed by frequency and percent of oral contraceptive use, diagnoses, age and race. Data analysis also included Estimates of Relative Risk (ERR) of specific diagnoses. Chi-square analysis was utilized to determine the differences in frequency of specific diagnoses. Fisher's exact one-tail probability test was used to determine

proportional differences with a small sample size (Siegal, 1956). Analysis of variance (ANOVA) was used to evaluate the significance of the association of oral contraceptive duration of use with CIN as compared with oral contraceptive estrogen dosage and CIN. The level of significance for all statistical tests was placed at $p < 0.05$ with $df = 1$.

Study Population Characteristics

Table 1

Age of Study Clients by Frequency and Percent, 1984

Age (years)	Frequency	Percent
17-20	17	32.7
21-25	19	36.5
26-30	14	26.9
31-33	2	3.8
Total	52	100.0
Mean age = 23.3 years	Age range = 17-33 years	

Table 1 shows the age distribution of the study population. The age range was between 17 and 33 years of age with a mean age of 23.3 years. Approximately 69 percent (69.0%) of the sample population was younger than 26 years

of age and 96 percent (96.0%) were 30 years of age or younger. Information from the clinical records showed that only 3.8 percent (3.8%), or two clients, were over 30 years of age. Figure 2 shows the age distribution graphically.

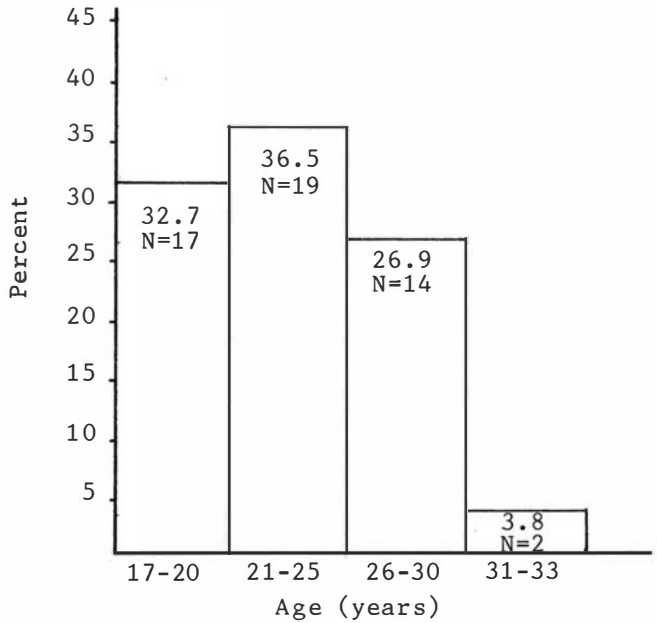


Figure 2

Age of Study Population by Frequency and Percent

Of the total 52 clinical records of clients examined, 32 (61.5%) clients were black and 20 (38.5%) of the clients were white. Although the university hospital colposcopy clinic referrals were from a wide range of private practices and public clinics, the larger number of black clients may have been due to the university hospital clinic being a state institution which serves a large percentage of the black population.

Table 2

Specific Oral Contraceptive Use of Study Clients by Frequency and Percent, 1984

Oral Contraceptive	Number	Percent
Group One (35 mcg. of estrogen or less)		
Loestrin	7	13.5
LoOvral	3	5.8
OrthoNovum 1/35	13	25.0
Subtotal	23	44.3
Group Two (50 mcg. of estrogen)		
OrthoNovum 1/50	22	42.3
Ovral	7	13.5
Subtotal	29	55.8
TOTAL	52	100.0

Table 2 shows the distribution of specific oral contraceptive use by study clients. Client oral contraceptive use ranged from three clients who used LoOvral to 22 clients

who used OrthoNovum 1/50 (ON 1/50). The oral contraceptive usage by clients was divided into two subgroups based upon the estrogen content of the oral contraceptive. This grouping allowed for more comparable sample sizes and comparison of estrogen dosage associated with CIN diagnosis. Oral contraceptives included in group one contained 35 mcg. or less of estrogen. Oral contraceptives in group two contained 50 mcg. of estrogen.

Forty-four and three-tenths (44.3%) of the study clients used oral contraceptives containing $\leq$ 35 mcg. of estrogen and 55.8 percent (55.8%) used oral contraceptives with 50 mcg. of estrogen. A total of 67.3 percent (67.3%) of the study clients used OrthoNovum products. Of these, 22 (42.3%) used ON 1/50 and 13 (25.0%) used ON 1/35. Ovral products were used by 19.3 percent (19.3%) and Loestrin was used by 13.5 percent (13.5%) of the study clients. The larger percentage of ON products used by study clients, reportedly, could be due to the lower cost of ON products a number of years ago.

Table 3

Duration of Study Client Oral Contraceptive Use by Frequency and Percent, 1984

Months	Number	Percent
6-12	22	42.3
13-36	12	23.1
37-60	9	17.3
61-96	9	17.3
Subtotal > 12	30	57.7
TOTAL	52	100.0

Mean use = 34.8 months
Usage range = 6 mos. - 96 mos.

Table 3 shows the duration of oral contraceptive use by the study clients. The mean duration of use was 34.8 months and the range of usage was from six to 96 months. Oral contraceptives were used by 57.7 percent (57.7%) of the study clients for 13 to 96 months, and 42.3 percent (42.3%) of the study clients used oral contraceptives for 12 months or less. Seventeen percent (17.0%) of study clients used oral contraceptives for more than five years (60 months). For further analysis, duration of oral contraceptive use was divided into two subgroups based on specific time frames. One group included 12 months or less of oral contraceptive use, and the other group included more than 12 months of

oral contraceptive use. Duration of oral contraceptive use was divided into these two groups because physiological balance of the oral contraceptive occurs during the first 12 months of use. Conceivably, cervical tissue changes during this 12 month period would be less likely to be associated with oral contraceptive use than changes that would occur after 12 months of use.

Table 4

Colposcopic Diagnoses of Study Clients by Frequency and Percent, 1984*

Diagnosis	Number (N=52)	Percent
Mild dysplasia	31	59.6
Moderate dysplasia	6	11.5
Mild/moderate dysplasia Subgroup total	37	71.1
Severe dysplasia	9	17.3
Carcinoma-in-situ (CIS)	3	5.8
Severe dysplasia/CIS Subgroup total	12	23.1
Condyloma as only diagnosis	3	5.8
Condyloma coexisting with CIN	26	50.0
Condyloma Subgroup total	29	55.8
TOTAL	78	100.0

*Total percent not = 100 due to coexisting condyloma with dysplasia.

Table 4 shows the distribution of colposcopic diagnoses of the study clients. There were 78 diagnoses for the 52 clients in the study because a client may have had both dysplasia and condyloma. Mild dysplasia was the most common diagnosis of the study clients. Thirty-one (59.6%) had mild dysplasia, 29 (55.8%) had condyloma, and three (5.8%) had CIS. Levels of dysplasia were divided into two subgroups: mild/moderate dysplasia and severe dysplasia/CIS. Mild/moderate dysplasia accounted for 71.1 percent (71.1%) of the diagnoses and severe dysplasia/CIS accounted for 23.1 percent (23.1%) of the study client diagnoses. Condyloma coexisting with dysplasia was found in 50 percent (50.0%) of the study clients. Condyloma as a single diagnosis accounted for 5.3 percent (5.3%) of the study client diagnoses.

Table 5

Oral Contraceptive Usage and Associated Diagnosis by Frequency, Percent and ERR, 1984

Oral Contraceptive	DIAGNOSIS AND ERR													
	Mild/moderate dysplasia					Severe dysplasia/CIS					Condyloma			
	Mild		Mod.		Mild/ Mod. ERR	Severe		CIS		Severe/ CIS ERR	Condy-loma		Condy-loma ERR	Total
	F	P	F	P		F	P	F	P		F	P		F P
Loestin (N=7)	3	42.9	2	28.6	1.02	1	14.3	0	0	0.52	6	85.7	5.74	12 15.4
LoOvral (N=3)	2	66.7	0	0	0.80	0	0	1	33.3	1.73	0	0	0	3 3.8
*ON 1/35 (N=13)	11	84.6	2	15.4	195.0	0	0	0	0	0	6	46.2	0.60	19 24.4
ON 1/50 (N=22)	13	59.1	1	4.6	0.53	6	27.3	1	4.5	3.27	14	63.6	1.75	35 44.9
*Ovral (N=7)	2	28.6	1	14.3	0.24	2	28.6	1	14.3	3.00	3	42.9	0.50	9 11.5
TOTAL	31	59.6	6	11.5		9	17.3	3	5.8		29	55.8		78 100.0

*Fisher's Exact One-Tail Test:
incidence of dysplasia p = 0.02 significant at the p < 0.05 level
incidence of condyloma p = 0.49 not significant at the p < 0.05 level

Table 5 shows the oral contraceptives and associated CIN diagnoses for the study clients. Percentages of CIN diagnoses were determined from the number of diagnoses for each specific oral contraceptive used by the study clients. Loestrin users had the highest percent of condyloma. Of the seven Loestrin users, 85.7 percent (85.7%) had condyloma. The 22 ON 1/50 users had the second highest percent of condyloma. Of the ON 1/50 users, 14 (63.6%) had condyloma. Condyloma was diagnosed for 46.2 percent (46.2%) of the ON 1/35 users. All of the ON 1/35 users also had either mild or moderate dysplasia. Mild dysplasia was diagnosed for 84.6 percent (84.6%) of the ON 1/35 users and moderate dysplasia was diagnosed for 15.4 percent (15.4%) of the ON 1/35 users. There were no diagnoses of severe dysplasia/CIS for ON 1/35 users.

The percentage of severe dysplasia and CIS was highest for users of oral contraceptives containing 50 mcg. of estrogen. Severe dysplasia was diagnosed for 27.3 percent (27.3%) of the ON 1/50 users and 28.6 percent (28.6%) of the Ovral users.

Table 5 also shows the Estimates of Relative Risk (ERR) for the specific diagnoses. ERR was calculated for the combined number of mild and moderate dysplasia diagnoses, and for the combined number of severe dysplasia and CIS diagnoses.

The ERR (5.74) of condyloma was nearly six-fold for

Loestrin users as compared with an ERR of zero (0.0) for LoOvral users. The ERR of condyloma was 1.75 for ON 1/50 users. For all other oral contraceptives used by the study clients, the ERR of condyloma was less than one.

The ERR of severe dysplasia/CIS was at least three-fold for both oral contraceptives containing 50 mcg. of estrogen. The ERR of severe dysplasia/CIS was 3.27 for ON 1/50 users and 3.0 for Ovral users. ON 1/35 users had an ERR of mild/moderate dysplasia of 195.0 and no risk for severe dysplasia/CIS.

Fisher's exact one-tail test was used to compare the frequencies of dysplasia and condyloma for ON 1/35 and Ovral users. These two oral contraceptives were used to compare 35 mcg. and 50 mcg. dosages of the estrogen ethinyl estradiol. The difference in incidence of dysplasia between the ON 1/35 and the Ovral users was significant with Fisher's exact one-tail test at the $p < 0.05$ level. The incidence of condyloma was not significantly different between ON 1/35 and Ovral users. Figure 3 shows the percentage of dysplasia for ON 1/35 and Ovral users by study clients in graphic form.

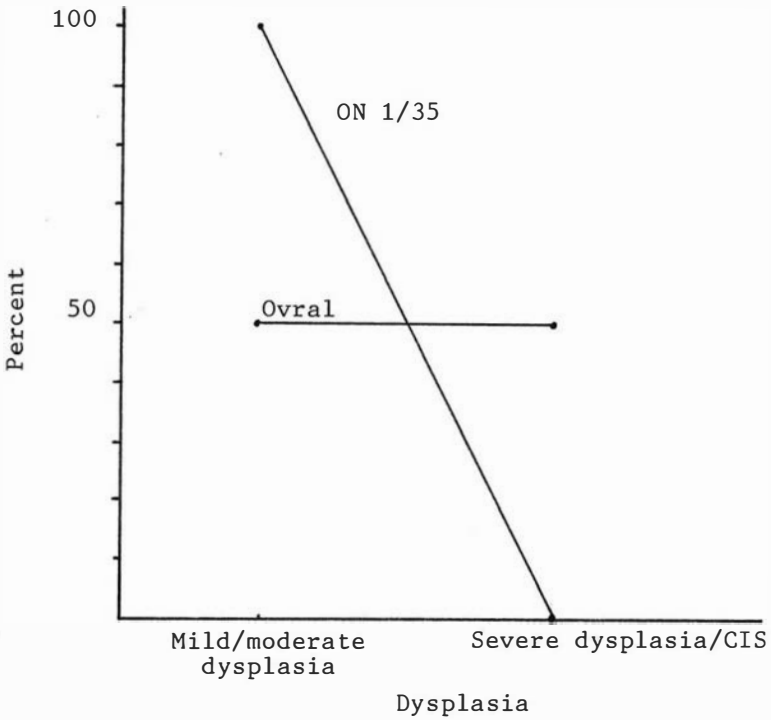


Figure 3

Percentage of Dysplasia Diagnoses for ON 1/35 and Ovral Users

Table 6

Levels of Dysplasia Associated with Dosages of Estrogen
by Frequency, Percent and ERR, 1984

Oral Contraceptive Dosage	Mild/Moderate Dysplasia			Severe Dysplasia/ CIS			Total	
	F	P	ERR	F	P	ERR	F	P
* ≤ 35 mcg.	20	90.9	4.71	2	9.0	0.18	22	44.9
* 50 mcg.	17	63.0	0.21	10	37.0	5.52	27	55.1
TOTAL	37	75.5		12	24.5		49	100.0

*Fisher's exact one-tail test: p = .024
Significant at p < 0.05 level

ANOVA F value = 5.93. pr > F = 0.0188
Significant p < 0.05 level (R square = 0.12)

Table 6 shows dysplasia by frequency, percent and ERR associated with the two dosages of estrogen used by study clients. The percent of mild/moderate dysplasia for users of oral contraceptives with $\leq$ 35 mcg. of estrogen was 90.9 percent (90.9%) with an ERR of 4.71. The percent of severe dysplasia/CIS for this oral contraceptive group was 9.0 percent (9.0%) with an ERR of 0.18. Users of 50 mcg. estrogen oral contraceptives had a 37.0 percent incidence (37.0%) of severe dysplasia/CIS and an ERR of 5.52. The incidence of mild/moderate dysplasia for 50 mcg. estrogen oral contraceptive users was 63.0 percent (63.0%) with an ERR of 0.21.

The difference between the two groups of oral contraceptive estrogen dosages and levels of dysplasia was statistically significant with Fisher's exact one-tail test. ANOVA showed that estrogen dosage and level of dysplasia was significant at the $p < 0.05$ level of significance. Figure 4 shows the percentage of dysplasia diagnoses for users of $\leq$ 35 mcg. estrogen and 50 mcg. estrogen oral contraceptives.

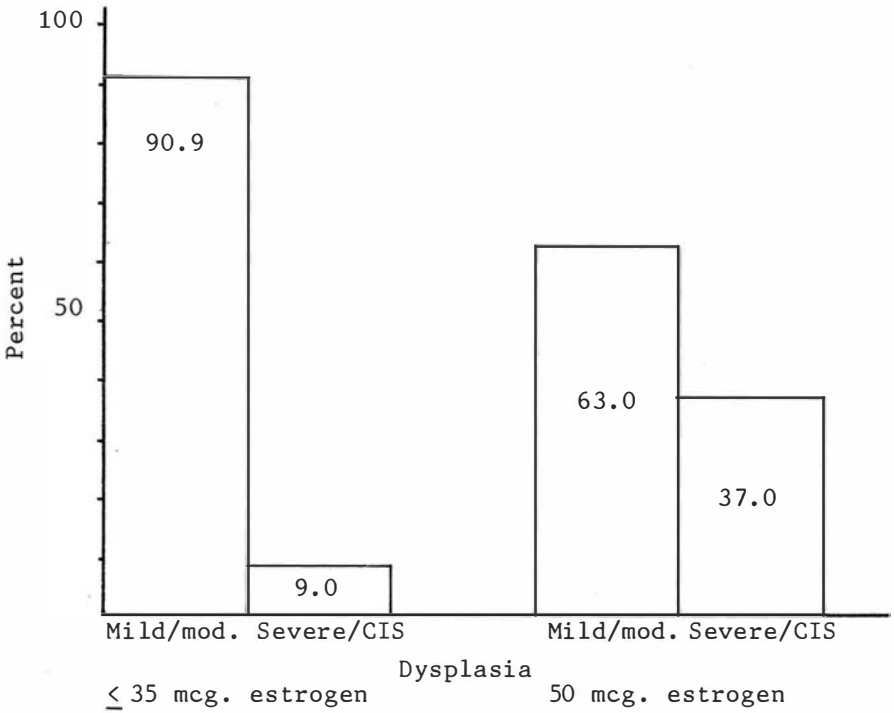


Figure 4

Percentage of Dysplasia Diagnoses for Users of ≤ 35 mcg. Estrogen and 50 mcg. Estrogen Oral Contraceptives

Table 7

Condyloma Associated with Oral Contraceptive Estrogen Dosages by Frequency, Percent and ERR, 1984

Oral Contraceptive Estrogen Dosage	Condyloma F	Condyloma P	Condyloma ERR
* ≤ 35 mcg. (N=23)	12	52.2	0.77
* 50 mcg. (N=29)	17	58.6	1.30
TOTAL (N=52)	29	55.8	

*Chi-square value = 0.216 Probability = 0.64
Not significant at the $p < 0.05$ level

Table 7 shows the frequency, percent and ERR of condyloma associated with dosages of estrogen used by study clients. The 50 mcg. estrogen oral contraceptive users had 58.6 percent incidence (58.6%) of condyloma and an ERR of 1.30. Users of oral contraceptives containing ≤ 35 mcg. of estrogen had a 52.2 percent incidence (52.2%) of condyloma and an ERR of 0.77.

Table 8

Comparison of Norgestrel-Containing and Other Contraceptives Associated with Dysplasia Diagnoses by Frequency, Percent and ERR, 1984

Oral Contraceptive	Mild/Moderate Dysplasia			Severe/CIS Dysplasia			Total	
	F	P	EER	F	P	EER	F	P
*Norgestrel OC (N=9)	5	55.6	0.31	4	44.4	3.20	9	18.37
*Other OC (N=40)	32	80.0	3.20	8	20.0	0.31	40	81.63
TOTAL	37	75.5		12	24.5		49	100.0

*Fisher's exact one-tail test p = 0.1342
Not significant at the p < 0.05 level

Table 8 shows the dysplasia diagnoses by frequency, percent and ERR of users of oral contraceptives containing norgestrel (Ovral and LoOvral) and other contraceptives used by study clients. This comparison was done in order to determine if there was a difference in CIN associated with norgestrel-containing oral contraceptives. Of the norgestrel-containing oral contraceptive users, 44.4 percent (44.4%) had severe dysplasia/CIS with an ERR of 3.20, and 55.6 percent (55.6%) had mild/moderate dysplasia with an ERR of 0.31. The other oral contraceptive users had a 20.0 percent (20.0%) incidence of severe dysplasia/CIS with an ERR of 0.31 and an 80 percent (80.0%) incidence of mild/moderate dysplasia with an ERR of 3.20. Fisher's exact one-tail test did not show a significant difference between these two oral contraceptive user groups.

Table 9

Comparison of Norgestrel-Containing and Other Oral Contraceptive Users Associated with Condyloma by Frequency, Percent and ERR, 1984

Oral Contraceptive	Condyloma F	Condyloma P	ERR
*Norgestrel (N=9)	3	33.3	0.27
*Other Oral Contraceptives (N=40)	26	65.0	3.70
TOTAL (N=52)	29	55.8	

*Fisher's exact one-tail test p = 0.045
Significant at the p < 0.05 level

Table 9 shows the frequency, percent and ERR of condyloma diagnoses associated with users of norgestrel-containing oral contraceptives as compared with condyloma diagnosis associated with other oral contraceptives. Norgestrel-containing oral contraceptive use was associated with a 33.3 percent (33.3%) incidence of condyloma and an ERR of 0.27. The other oral contraceptives used by study clients were associated with 65.0 percent (65.0%) incidence of condyloma and an ERR of 3.7. Results were significant when Fisher's exact one-tail test was applied to this data.

Table 10

Dysplasia Associated with Duration of Oral Contraceptive use by Frequency, Percent and ERR, 1984

Duration of Oral Contraceptive Use (in months)	Mild/Moderate Dysplasia		Severe Dysplasia/ CIS			Total	
	F	P	F	P	ERR	F	P
* ≤ 12	15	71.4	6	28.6	1.47	21	42.9
* > 12	22	78.6	6	21.4	0.68	28	57.1
TOTAL	37	75.5	12	24.5		49	100.0

*Chi-square 0.332; p = 0.56.
Not significant at the p < 0.05 level

ANOVA F value = 0.82; pr > 0.3693; (R square = 0.12)
Not significant at p < 0.05 level

Table 10 shows dysplasia associated with duration of client oral contraceptive use by frequency, percent and ERR of severe dysplasia. The percent of mild/moderate dysplasia was slightly higher among users of oral contraceptives for more than 12 months as compared with users for 12 months or less. Of the oral contraceptive users for more than 12 months, 78.6 percent (78.6%) had mild/moderate dysplasia. Users of oral contraceptives for 12 months or less had a 71.4 percent (71.4%) incidence of mild/moderate dysplasia. The percent of severe dyaplasia/CIS was slightly higher for users with 12 months or less of oral contraceptive use. Users of oral contraceptives for more than 12 months had a 21.4 percent incidence (21.4%) of severe dysplasia/CIS with an ERR of 0.68, as compared with 28.6 percent (28.6%) and ERR of 1.47 for users of oral contraceptives less than 12 months. Chi-square and ANOVA analysis did not show significance when applied to this data.

Table 11

Duration of Oral Contraceptive Use Associated with Condyloma by Frequency, Percent and ERR, 1984

Duration of Oral Contraceptive Use	Condyloma F	P	ERR
* ≤ 12 months (N=22)	10	45.5	0.48
* > 12 months (N=30)	19	63.3	2.07
TOTAL (N=52)	29	55.8	

*Chi-square value 1.645
probability = 0.1997
not significant at $p < 0.05$ level

Table 11 shows the duration of oral contraceptive use associated with condyloma by frequency, percent and ERR. A higher percent of condyloma was noted for clients who used oral contraceptives for more than 12 months as compared with users for 12 months or less. Oral contraceptive users of more than 12 months had a condyloma incidence of 63.3 percent (63.3%) with an ERR of 2.07. Users of oral contraceptives for 12 months or less had a condyloma incidence of 45.5 percent (45.5%) with an ERR of 0.47. Condyloma incidence was calculated as a percentage of all other CIN diagnoses for each duration of oral contraceptive use.

Table 12

Duration of Oral Contraceptive Use Associated with Estrogen Dosage and Dysplasia by Frequency and Percent, 1984

Diagnosis	Duration of Oral Contraceptive Use							
	< 12 months				> 12 months			
	≤ 35 mcg. Estrogen		50 mcg. Estrogen		≤ 35 mcg. Estrogen		50 mcg. Estrogen	
	F	P	F	P	F	P	F	P
Mild/ Moderate Dysplasia	10	90.9	5	50.0	10	90.9	12	70.6
Severe Dysplasia/ CIS	1	9.0	5	50.0	1	9.0	5	29.4
TOTAL	11	100.0	10	100.0	11	100.0	17	100.0

Table 12 shows the duration of oral contraceptive use associated with estrogen dosage and dysplasia by frequency and percent. Of the oral contraceptive users for 12 months or less, users of 50 mcg. estrogen oral contraceptives had the highest incidence of severe dysplasia/CIS as compared with $\leq$ 35 mcg. estrogen oral contraceptive users. Fifty percent (50.0%) of 50 mcg. estrogen oral contraceptive users had severe dysplasia/CIS diagnoses as compared with nine percent (9.0%) of the $\leq$ 35 mcg. estrogen oral contraceptive users. The incidence of mild/moderate dysplasia for oral contraceptive users of less than 12 months was 90.9 percent (90.9%) for $\leq$ 35 mcg. estrogen oral contraceptive users as compared with 50 percent (50.0%) for 50 mcg. estrogen oral contraceptive users.

Of the oral contraceptive users for more than 12 months, users of 50 mcg. estrogen oral contraceptives also had the highest incidence of severe dysplasia/CIS as compared with $\leq$ 35 mcg. estrogen oral contraceptive users. Users of 50 mcg. estrogen oral contraceptives had a 29.4 percent (29.4%) incidence of severe dysplasia/CIS as compared with a nine percent (9.0%) incidence for $\leq$ 35 mcg. estrogen oral contraceptive users. The incidence of mild/moderate dysplasia for oral contraceptive users of more than 12 months was 90.9 percent (90.9%) for $\leq$ 35 mcg. estrogen oral contraceptive users as compared with 70.6 percent (70.6%) for 50 mcg. estrogen oral contraceptive

users.

Chi-square analysis could not be used with this data because cell counts were less than five for 20 percent of the cells.

Table 13

Condyloma Diagnoses Associated with Duration of Oral Contraceptive Use and Estrogen Dosage by Frequency and Percent, 1984

Duration	Estrogen Dosage	F	P
* ≤ 12 mo.	≤ 35 mcg. (N=11)	5	45.5
	50 mcg. (N=11)	5	50.0
Subtotal	(N=22)	10	45.5
* > 12 mo.	≤ 35 mcg. (N=12)	7	63.6
	50 mcg. (N=18)	12	70.6
Subtotal	(N=30)	19	67.9
TOTAL	(N=52)	29	55.8

*Chi-square value = 1.876 $p < 0.59$
Not significant at the $p < 0.05$ level

Table 13 shows the condyloma diagnoses associated with duration of oral contraceptive use and oral contraceptive estrogen dosage. Users of ≤ 35 mcg. estrogen oral

contraceptives for 12 months or less had frequencies of condyloma equal to the frequencies of 50 mcg. estrogen oral contraceptive users. Clients using 50 mcg. oral contraceptives for more than 12 months had a 70.6 percent (70.6%) incidence of condyloma as compared with a 63.6 percent (63.6%) incidence for users of $\leq$ 35 mcg. estrogen oral contraceptives. Chi-square analysis was not significant for this data.

Data Interpretation

The majority of the study clients were black and younger than 26 years of age. ON 1/50 was the most frequently used oral contraceptive and LoOvral the least frequently used. There were fewer users of $\leq$ 35 mcg. estrogen oral contraceptives than users of 50 mcg. oral contraceptives. Mild/moderate dysplasia was the most frequent CIN diagnosis. Carcinoma-in-situ was the least frequent CIN diagnosis for oral contraceptive users. Condyloma was the second most frequent CIN diagnosis for oral contraceptive users.

More of the study clients used oral contraceptives for more than 12 months than users for 12 months or less. ON 1/35 users had the highest frequency of mild dysplasia and Ovral users had the lowest frequency of mild dysplasia. Users of Loestrin had the highest frequency of moderate dysplasia. ON 1/35 users had the highest ERR of mild/moderate dysplasia. Ovral users had the highest percentage

of severe dysplasia. LoOvral and ON 1/35 had no severe dysplasia diagnoses. Although LoOvral users had the highest percentage of CIS, ON 1/50 and Ovral had the highest ERR of severe dysplasia/CIS. Loestrin users had the highest percentage and ERR of condyloma and LoOvral had the lowest percentage and ERR of condyloma.

Users of 50 mcg. estrogen oral contraceptives had a higher percentage and ERR of severe dysplasia/CIS than users of $\leq$ 35 mcg. estrogen oral contraceptives. Users of $\leq$ 35 mcg. estrogen oral contraceptives had a higher percentage and ERR of mild/moderate dysplasia than users of $\leq$ 50 mcg. estrogen oral contraceptives. Users of 50 mcg. estrogen oral contraceptives also had a higher percentage and ERR of condyloma than users of $\leq$ 35 mcg. estrogen oral contraceptives. Users of norgestrel-containing oral contraceptives had a higher percentage and ERR of severe dysplasia/CIS than the other oral contraceptive users in the study. Users of norgestrel-containing oral contraceptives also had a lower percentage and ERR of mild/moderate dysplasia and condyloma than the other oral contraceptive users in the study.

Users of oral contraceptives for 12 months or less had a somewhat higher percentage and ERR of severe dysplasia/CIS as compared with oral contraceptive users of more than 12 months. The percentage of mild/moderate

dysplasia was highest for users of oral contraceptives for more than 12 months. The percentage of condyloma was highest for users of oral contraceptives for less than 12 months.

Users of 50 mcg. estrogen oral contraceptives had the highest percentage of severe dysplasia/CIS for oral contraceptive users of both 12 months or less and more than 12 months. Users of $\leq$ 35 mcg. estrogen oral contraceptives had the highest percentage of mild/moderate dysplasia for users both 12 months or less and more than 12 months users. The frequency of condyloma was highest for clients with more than 12 months usage of 50 mcg. estrogen oral contraceptives and lowest for clients with 12 months or less usage of 50 mcg. estrogen oral contraceptives. Frequency of condyloma was lowest for both estrogen dosages of oral contraceptives with 12 months or less of use and highest for both estrogen dosages of oral contraceptives with more than 12 months of use.

There were significant differences for the incidence of dysplasia between $\leq$ 35 mcg. estrogen and 50 mcg. estrogen oral contraceptive users and between ON 1/35 and Ovral users. Differences were also found in the incidence of condyloma between norgestrel-containing and other oral contraceptive users.

CHAPTER FIVE

Summary, Conclusions, Implications and Recommendations

This study was conducted to determine the relationship between specific oral contraceptives and cervical intraepithelial neoplasia (CIN), and to determine if the duration of use and the content of oral contraceptives were related to CIN. The investigator's motivation for this study was the potential increased CIN risk that may be associated with the use of specific oral contraceptives. The investigator was also concerned with the need for further investigation of the association between condyloma and oral contraceptive use. Differences between CIN levels associated with specific oral contraceptive use by the study population provided insight into this problem.

Epidemiological concepts for the investigation of disease, and Chrisman and Fowler's Systems-in-Change model (1980) were utilized for investigation of the relationship between oral contraceptives and CIN. Epidemiological concepts and the Systems-in-Change model provided a systematic approach to investigate the interaction of host, agent and environmental factors which apply to CIN and associated oral contraceptive use.

This study analyzed 52 clinical records of clients

who attended colposcopy clinic over a four-month period. A two-stage investigator-designed data collection form was utilized to obtain selected demographic data and information pertaining to oral contraceptive use and CIN diagnoses. Part one of the data collection form was completed by the colposcopy clinic nurse who collected information pertaining to type and duration of oral contraceptive use by clients. Part two was completed by the investigator who obtained demographic information and colposcopy diagnoses from client clinical records. Analysis of data was conducted based on the 52 client clinical records.

The mean age of the study population was 23.3 years and most of the clients included in the study were black. The most frequent contraceptive used by clients was ON 1/50 and the mean duration of use varied from six months to 96 months. The most frequent CIN diagnosis was mild dysplasia followed by condyloma. Fisher's exact one-tail test, Chi-square, ANOVA and Estimates of Relative Risk (ERR) were utilized to analyze data.

Discussion and Conclusions

Major findings in this study indicated that 50 mcg. estrogen oral contraceptive use was associated with a greater risk of severe dysplasia/CIS than risk associated with $\leq$ 35 mcg. estrogen oral contraceptive use. Norgestrel-containing oral contraceptive users had a greater risk of

severe dysplasia/CIS than users of other oral contraceptives.

The percentage of condyloma associated with norgestrel-containing oral contraceptive use was somewhat lower than for other oral contraceptive users in the study. The majority of condyloma diagnoses coexisted with dysplasia. The duration of oral contraceptive use was not associated with the level of CIN in this study.

Fisher's exact one-tail test and ANOVA showed a statistically significant difference in the incidence of dysplasia between $\leq$ 35 mcg. estrogen and 50 mcg. estrogen oral contraceptive users. Fisher's exact one-tail test also showed statistically significant differences in the incidence of dysplasia between ON 1/35 users and Ovral users. Differences in the incidence of condyloma between norgestrel-containing oral contraceptives and other oral contraceptive users was also statistically significant with Fisher's exact one-tail test.

The investigator concluded that there were differences between specific oral contraceptives and the associated incidence of CIN. The investigator also concluded that these differences were not associated with duration of use.

The clients in this study were younger than study participants in previous research. However, findings from this study regarding the age range for highest prevalence of CIN support other study findings. Age may

be a factor in the development of CIN because of the vulnerability to carcinogenic influences associated with a high degree of cellular activity in younger populations. Findings from this study also support previous research findings of a higher incidence of CIN among the black population.

The incidence of condyloma was somewhat higher in this study than noted in previous research. This could be due to an increase in detection of condyloma in the general population. The increased finding of condyloma among oral contraceptive users could be due to the increased viability of condyloma on vulnerable cervical epithelium.

The association of 50 mcg. estrogen oral contraceptive use with a greater risk of severe dysplasia/CIS was also supported by previous research. This finding may be due to an estrogenic stimulation of cellular maturation which may increase the vulnerability of the oral contraceptive user to carcinogenic influences.

The present study finding of a low incidence of condyloma associated with norgestrel-containing oral contraceptive use was not noted in previous research. The reason for the low incidence is unclear. It is possible that this oral contraceptive has a protective effect, or it could be associated with other confounding factors, such as number of sexual partners.

Although the incidence of condyloma was slightly higher among longer duration oral contraceptive users, this

study did not support previous research which indicated that duration of oral contraceptive use was associated with CIN.

The final results of data analysis in this study supported the hypothesis that use of norgestrel-containing oral contraceptives was associated with a greater frequency of severe CIN changes than use of other oral contraceptive products.

The study results did not support the hypothesis that longer duration of oral contraceptive use was associated with a greater frequency of severe CIN changes.

Implications

There were several important findings in this study. One important finding was the association between 50 mcg. estrogen oral contraceptive use and the increased risk of severe dysplasia/CIS. Another important study finding was the increased severe dysplasia/CIS risk and the decreased condyloma risk associated with norgestrel-containing oral contraceptive use. Lack of association between duration of oral contraceptive use and CIN was also an important study finding.

This study emphasized the importance and recognition of epidemiological concepts in the development of disease. In utilizing epidemiological concepts it is important to recognize that patterns of disease depend upon the inter-

action of agent, host and environment which may be affected by time. Based on the findings of this study, specific oral contraceptive use by clients may affect the internal physiological and immunological environment of the client. Duration (time) of oral contraceptive use did not have a significant effect on disease outcome in this study. Based on present study findings, the clinical stage of CIN and potential risk that the client may progress to actual cervical cancer may be most affected by the estrogen dosage of the oral contraceptive.

CIN changes may be a function of multiple client systems. Disequilibrium may occur as the client moves from one developmental stage to another, such as from adolescence to young adulthood. The disequilibrium associated with the effects of the oral contraceptive agent may promote vulnerability for stress on the client system. The inability of the client to compensate for this stress may lead to the development of disease.

The Systems-in-Change model (1980) is an important and necessary approach to assessment of the multiple client systems associated with the development of disease. Utilizing the systems approach in assessing the client, the nurse practitioner can intervene in the progression of CIN by evaluating biological, social and personal systems of the client. The nurse practitioner needs to assess for signs of dysfunction including environmental

variables which may influence the functioning of these systems. Client assessment is based on the actual or potential dysfunction of one or more of the client systems and the development of CIN.

Based on assessment of the client who is using oral contraceptives, the nurse practitioner can intervene to reduce client risk of CIN. The practitioner's plan of care should include provision of appropriate client teaching and counseling regarding the development of CIN, and prescribing the lowest possible estrogen dosage oral contraceptive that will be effective for the client.

Utilizing the Systems-in-Change model (1980) and epidemiological concepts for assessment and intervention in the development of disease, the nurse practitioner can promote the optimal well-being of clients who are using oral contraceptives.

Recommendations for Further Research

Several recommendations for further research are suggested:

1. Replication of this study with a larger and more diverse population to determine if differences in CIN diagnoses and associated oral contraceptive use are the same as those found in this study.

2. Further investigation of demographic variables associated with CIN such as, number of sexual partners and

age of first sexual intercourse.

3. Further research that utilizes a demographically matched control group in order to clarify the possible association between CIN and oral contraceptive use.

4. Further investigation of the association between CIN and the estrogen and progestogen components of oral contraceptives.

5. Further investigation of the relationship between oral contraceptive use and the development of condyloma.

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APPENDIX A

SPECIFIC ORAL CONTRACEPTIVES

Five Oral Contraceptives by Brand Name and Progestogen and Estrogen Composition (Dong and Eoff, 1978)

Brand Name	Progestogen	Estrogen
Ortho Novum 1/50	1.0 mg. norethindrone	50 mcg. mestranol
Ovral	0.5 mg. norgestrel	50 mcg. ethinyl estradiol
Ortho Novum 1/35	1.0 mg. norethindrone	35 mcg. ethinyl estradiol
LoOvral	0.3 mg. norgestrel	30 mcg. ethinyl estradiol
Loestrin 1.5	1.5 mg. norethindrone acetate	20 mcg. ethinyl estradiol

APPENDIX B

FACTORS RELEVANT TO CERVICAL CANCER

Factors Studied for Their Relevance to Cervical Cancer (Rotkin, 1981)

Sociocultural:

- race (increased risk, nonwhite)
- religion (decreased risk among Jewish, Amish, Mormons and Nuns)
- economic status (increased risk: poverty and deprivation)
- education (increased risk with less education)

Marital:

- marriage (increased risk)
- early marriage, multiple marriage and separation (increase risk)

Sexual:

- age at onset of coitus (increased risk with early onset)
- number of sexual partners (increased risk)
- frequency of coitus (not related)
- promiscuity (extreme risk)

Reproductive:

- nongravidity/nonparity (not related; no risk with celibacy)
- gravidity/parity (no risk demonstrated)
- menses (not related)
- contraception (not resolved for oral contraceptive)
- sterility (doubtful risk)

Traumatic:

- abortion (not related)
- injury - postpartum or from glans (not related)

Exogenous:

- noncircumcision in coital partners (not related by itself)
- transmissible agents - sperm, HSV2, monilia, trichomonas, venereal disease, chemical carcinogens, etc. (not resolved, possibly all)

Hormones and medications: (little information)

Endogenous:

- genetic (not resolved, but conventional studies not related)
- personality/psychosocial (not resolved)
- adolescence (direct risk variable)
- blood group (not related)

Pathologic:

- cellular morphology (progression of stages)
- squamous metaplasia (related to adolescence)

New Hypotheses:

- specific proteins (theoretical, proposed form lab)
- smoking (some evidence, not resolved)

APPENDIX C

DATA COLLECTION FORM

Data Collection Form

Part One:

Client Name _____
Oral Contraceptive _____
Duration of Use _____

Part Two:

Age _____
Race _____
Diagnosis _____

Part One:

Client Name _____
Oral Contraceptive _____
Duration of Use _____

Part Two:

Age _____
Race _____
Diagnosis _____

Part One:

Client Name _____
Oral Contraceptive _____
Duration of Use _____

Part Two:

Age _____
Race _____
Diagnosis _____

Part One:

Client Name _____
Oral Contraceptive _____
Duration of Use _____

Part Two:

Age _____
Race _____
Diagnosis _____

APPENDIX D

CONSENT FORM TO REVIEW CLIENT MEDICAL RECORDS

Consent Form for Utilization of Client Medical Records

I am a graduate student in the Community Health Nursing and Family Nurse Practitioner Program in the Medical College of Virginia School of Nursing. For my thesis, I am planning a retrospective study concerning the relationship between specific oral contraceptives, duration of use and precursor uterine cervical tissue changes. In order to obtain this information, I would like to review the medical records of clients seen in the Colposcopy Clinic. No identifying data will be obtained from the record, and all information will remain confidential. Clinical records meeting study criteria will be reported to me by the colposcopy nurses and the following information will be obtained from the record.

1) Specific oral contraceptive used by the client

2) Duration of oral contraceptive use

3) Colposcopy diagnosis

4) Client age

This study has been approved by the research committee in the M.C.V. School of Nursing. Enclosed you will find a two page outline of the planned research. This study is to be conducted under the direction of E. Christa Stern, Dr.P.H., School of Nursing, with Voelker Schneider, M.D., M.C.V. Department of Surgical Pathology, and Betsy Bampton, R.N., COGNP, M.C.V. School of Nursing. Permission is requested for review of client records at the Colposcopy Clinic. Thank you.

Sincerely,

Barbara J. Fox, R.N., B.S.N.
Graduate Student
M.C.V. School of Nursing

E. Christa Stern, R.N., Dr.P.H.
Assistant Professor
Community Health Nursing

Consent for utilization of Colposcopy Clinic client medical records:

Position

Date

VITA