A COMPARATIVE STUDY OF BENIGN EPITHELIAL LESIONS OF THE CERVIX UTERI OCCURRING IN PREGNANT AND NON-PREGNANT WOMEN

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I N D E X

INTRODUCTION

Although the study of histological changes occurring in the epithelia of the cervix uteri during pregnancy has engaged the attention of many gynaecological pathologists throughout the past four decades, information is not yet complete regarding the incidence, aetiology, nature and significance of the various lesions which have been reported.

The histological diagnosis of frank invasive carcinoma of the cervix in pregnant and non-pregnant patients has not been disputed as no significant differences in the histological criteria associated with invasive cervical carcinoma have been observed in these two groups of patients.

On the other hand, as a result of the widely held view that specific "pregnancy changes" were prone to occur in the epithelia of the cervix of the pregnant patient, histological interpretation of benign and pre-invasive lesions of the cervix, occurring during pregnancy, has been approached with considerable caution and uncertainty. The most consistently reported features of such "pregnancy changes" are characterised principally by cellular hyperplasia and, in many instances, atypical cellular morphology and increased mitotic activity. The tissues most frequently involved are the stratified squamous epithelium of the ectocervix and the immature squamous epithelium in endocervical foci of squamous

metaplasia. The majority of writers have consistently observed cellular hyperplasia of the endocervical columnar epithelium in pregnant patients, but atypical cellular changes have been less commonly found in the columnar epithelium. Consequently, the most pronounced atypical changes have been reported in the squamous components of cervical epithelia, and, in many instances, considerable difficulty has been experienced in differentiating the resulting histological features from those of carcinoma in situ. These changes are reported in a variety of forms showing varying degrees of cellular atypism and hyperplasia, and various terms have been introduced by different authors to describe varying degrees of the same basic lesion. Uncertainty was added to the histological interpretation of disturbing "pregnancy changes" by several published reports of cases showing complete histological regression in the postpartum period, indicating that the majority of such "changes" were reversible.

More recently, as a result of widespread histological investigation of cervical lesions both in pregnant and non-pregnant patients, the concept of specific pregnancy changes in cervical epithelia has been widely rejected, mainly on the basis that identical lesions may occur in the non-pregnant organ. Nevertheless, it is generally believed that the incidence of benign hyperplastic changes in the cervical epithelia is higher during pregnancy than in the non-pregnant state. While widely varying results have been

reported, the literature lends support to the above belief. However, no series has ever been published of strictly comparable pregnant and non-pregnant patients in whom comparative evaluation of benign epithelial lesions has been made.

The present thesis was undertaken to compare the histological features of benign epithelial lesions occurring in the cervix uteri of pregnant women with those of non-pregnant women. In order to obtain material that would allow the most accurate comparison it was necessary to investigate the histological features of the cervix uteri in a group of pregnant patients and a comparable group of non-pregnant patients. Information suitable for comparative study was thus obtained on the following:

1. The relative incidence of benign epithelial lesions of the cervix occurring in pregnant and non-pregnant women.

2. The effects of pregnancy on the histological characteristics of benign epithelial lesions observed in the cervix of the non-pregnant patient.

3. The occurrence of specific pregnancy changes in the epithelia of the cervix.

4. The occurrence, during pregnancy, of atypical cervical epithelial lesions, the histological characteristics of which might simulate those of carcinoma in situ.

HISTORICAL REVIEW OF RELEVANT PAST WORK

The macro- and microscopic changes in the cervix uteri during pregnancy have engaged increasing universal interest for more than 100 years. The present-day concepts regarding the histological changes occurring in the cervical epithelia of the pregnant woman have been derived from the accumulation of much published work by numerous investigators, particularly in Europe and North America.

Initially, attention was focussed largely on the anatomical changes in the uterus, such as the formation of the lower uterine segment during pregnancy, and cervical dilatation during labour; but for the past four decades, interest has been concentrated particularly in study of the cellular characteristics of the cervical epithelia during pregnancy.

Stieve (1927) was one of the first to publish a detailed and comprehensive description of the histological changes occurring in the cervix during gestation, and one of the most significant aspects which he observed and illustrated was the striking proliferative and hyperplastic change in the cells of the endocervical mucosa and glands. He reported that this proliferative epithelial change was progressive during pregnancy and resulted in a considerable increase in depth occupied by the glands of the endocervix, with the ultimate formation of a "honeycomb appearance" of the tissues surrounding the cervical canal. Evidence of increased secretory

activity was found in the proliferating endocervical mucosa and glands.

Hofbauer (1933), presenting the results of routine histological examination of 29 specimens of gravid uteri, stated that the purpose of his paper was "to direct attention to peculiar and hitherto unknown manifestations of hyperplasia of both the surface mucosal epithelium and the glandular epithelium of the cervix in pregnant women", and suggested "possibly a new avenue of approach to the problem of carcinoma of the cervix in women previously pregnant". Although squamous metaplastic lesions in the endocervical epithelium of non-pregnant women had been described by several earlier writers including Schottlaender (1912), Meyer (1923), Fluhmann (1928) and Novak (1929), and these writers had introduced different descriptive terms for the same lesion, such as "epidermization," "epidermidization" and "epidermidalization," Hofbauer (1933) described similar endocervical lesions in the uteri from his series of 29 pregnant patients but interpreted the associated epithelial characteristics as specific pregnancy changes. Furthermore, he reported that the proliferating endocervical epithelium, which he designated "epithelial hyperplasia exhibiting certain features of metaplasia," frequently appeared to have a distinct invasive character with downgrowths into connective tissue although other definite criteria of invasive cancer were absent.

Levey (1934) obtained 12 cervices from the uteri of pregnant women during the first, second, third, fourth, fifth and eighth months of pregnancy, and described serial histological features of the cervix during the different stages of pregnancy. The principal features observed consisted of proliferative activity in the columnar epithelium of the endocervical mucosa and glands, resulting in areas of stratification and of atypical multilayered epithelium, of which the majority of component cells were described as "transitional" in type. The proliferative changes in the endocervical epithelium were progressive throughout pregnancy and were most pronounced in the eighth month, when maximum secretory activity was observed in the cervical glands, but no definite histological changes were found in the stratified squamous epithelium of the portio vaginalis during pregnancy. He concluded that these changes were generally accepted as a physiological process which he, too, interpreted as specific during pregnancy.

Subsequent interpretation of histological changes in the cervical epithelia during pregnancy was considerably influenced by contemporary advances in knowledge of the histogenesis of squamous metaplasia and squamous carcinoma of the cervix in non-pregnant women.

Following the important work of Carmichael and Jeaffreson (1939; 1941), Auerbach and Pund (1945), Howard et al. (1951) and Rosenthal and Hellman (1952), the role of the basal or reserve cells, found in the epithelium of the human cervical canal, in the histo-

genesis of squamous metaplasia, became widely accepted, although the origin of the basal cells remained a subject of speculative uncertainty. Furthermore, the investigations and findings of these workers revealed that squamous metaplasia of the endocervical epithelium occurred in varying proportions in women of all ages and also, frequently, in the cervix of the foetus. The cumulative result of these detailed observations contributed to the gradual emergence of a clearer understanding of the various stages of squamous metaplasia, culminating in a comprehensive histopathological classification of the lesion by Fluhmann (1961).

According to Novak and Galvin (1951), scant clinical attention was aroused in the study of carcinoma in situ of the cervix until Schiller's (1928) work, despite the fact that the concept of intra-epithelial carcinoma was first introduced by Schottlaender and Kermauner (1912). The relationship of carcinoma in situ to the histogenesis of invasive squamous carcinoma of the cervix subsequently received general acceptance after the accumulation of a vast amount of research and serial histological studies in many international centres. The histopathological criteria necessary for a diagnosis of carcinoma in situ of the cervix, however, have never received precise definition, and the ultimate microscopical diagnosis of the lesion still lacks the complete certainty generally associated with the diagnosis of invasive squamous carcinoma.

Reviewing the literature, Peale (1959) concludes that much of the uncertainty associated with the histopathological diagnosis of carcinoma in situ is concerned with the difficulty in the interpretation of borderline lesions, and with the incomplete knowledge regarding the proportion of cases of carcinoma in situ which will progress to invasive cancer of the cervix. The reported incidence of invasive carcinoma developing from pre-invasive lesions has varied considerably in different series of published cases, and intervals of up to 10 years be fbre evidence of invasion appeared have been recorded. Apparent regression of intra-epithelial lesions has been observed in varying proportions of every series, and evaluation of this phenomenon has always proved difficult unless the whole cervix were available following the initial biopsy diagnosis. Some relevant information regarding the significance of carcinoma in situ has been provided by the work of Petersen (1955; 1956) who reported a series of 127 untreated cases of cervical "precanceroses". In approximately 50 per cent of the cases he was unable to demonstrate persistence of the lesion after the first year of follow-up. Invasive carcinoma developed in 4 per cent of the cases by the end of the first year, in 22 per cent by the end of the fifth year, and in 33 per cent by the end of the ninth year.

Initially, opinion was divided concerning the aetiological relationship between squamous metaplasia of the endocervix and malignancy. It was generally agreed that the metaplastic squamous

epithelium was, in itself, essentially a benign lesion, but, while some writers including Fluhmann (1928), Meyer (1941) and Nesbitt and Hellmann (1952) considered that malignancy was unlikely ever to develop from such lesions, others such as Carmichael and Jeaffreson (1941) expressed the belief that squamous metaplasia in the cervix could give rise to neoplastic growth. Auerbach and Pund (1945) were among the first writers to suggest that squamous metaplasia and carcinoma in situ of the cervix had a common ancestral cell, and developed in the same locus within the cervical canal. Howard et al. (1951) claimed that they could trace the histogenesis of intra-epithelial carcinoma as it appeared in seven cases of squamous metaplasia with atypical epithelial changes, and concluded that carcinoma in situ usually began in the endocervix.

Opinion regarding the site of origin of in situ cancer at this period, however, was not unanimous, and the view that neoplastic change developed initially in the stratified squamous epithelium of the ectocervix, particularly in the zone surrounding the external cervical os, was held by probably the majority of gynaecological pathologists. In a review of the anatomical distribution of intra-epithelial epidermoid carcinomas of the cervix, Foote and Stewart (1948) reported that in 24 out of their series of 27 cases, the lesions were either limited to the portio vaginalis or situated both on the portio vaginalis and within the cervical canal. They concluded that the portio vaginalis was a more frequent site of origin than the endocervical canal.

The accumulation of evidence concerning the relationship of carcinoma in situ to invasive squamous carcinoma of the cervix stimulated a large-scale investigation into atypical cellular transformations in cervical epithelia which might be identified with the earliest stages of the histogenesis of neoplastic lesions. Inevitably, following the earlier histological reports of specific proliferative changes in the cervical epithelium during pregnancy, intensified study of cervical epithelial lesions in pregnant women was conducted by numerous investigators who reported widely varying views and differing interpretations concerning atypical lesions in the epithelia of both the ectocervix and the endocervix in pregnant women.

Fluhmann (1948) reported histological evidence of basal cell hyperactivity in foci of epidermidization in six of 32 cervical erosions occurring in pregnant patients. Four of these patients showed excessive hypertrophy of normal stratified squamous epithelium of the ectocervix. He concluded that these "abnormal proliferations" were especially prone to occur during pregnancy and that basal cell hyperactivity was difficult to differentiate from early carcinoma. Investigation of the cellular characteristics of the squamous epithelium and squamo-columnar junction in 22 pregnant and 46 non-pregnant uteri was carried out by Danforth (1950) who deduced that although no specific changes were found in the pregnant patients, certain cellular deviations in the direction of hyper-

activity occurred more frequently in the pregnant group. He emphasized that during pregnancy the attitude toward equivocal or borderline cervical cancer should be particularly conservative, for the possibility of regression of such suggestive lesions would appear to be at least as good as the possibility of progression to frank malignancy.

Similar views were expressed by Epperson et al. (1951) who investigated the histological changes in both the glandular and stratified squamous epithelia of the cervix in 286 pregnant women. They described three grades of basal cell hyperactivity in the ectocervical epithelium and reported five such cases which, they maintained, would have been called in non-pregnant women, intra-epithelial carcinoma, but which showed complete regression in the postpartum period. No suspicious lesions were found in the endocervix either in hyperplastic columnar epithelium or in foci of epidermidization. In a continuation and expansion of the work of Epperson et al. (1951), Nesbitt and Hellman (1952) reported the histopathological and cytological findings in the cervices of a further 300 pregnant women using the same histopathological grading of lesions showing basal cell hyperactivity. They found basal cell hyperactivity in the stratified squamous epithelium of the ectocervix in 6.8 per cent of their patients, but in addition, described basal cell hyperactivity in foci of epidermidization in 10.7 per cent of the 300 patients. Intra-epithelial carcinoma was diagnosed

histologically in two patients but the lesions in both patients showed complete regression to normal epithelium within 6 months after parturition. The combined results of these authors prompted Nesbitt and Hellman (1952) to counsel considerable caution in the final assessment and treatment of cases during pregnancy that fulfilled the usual histological criteria for the diagnosis of intra-epithelial carcinoma of the cervix. No comparative findings in non-pregnant women were presented by either group of authors.

The prevailing attitude of doubt regarding the significance of suspicious epithelial lesions in pregnant women, generated by numerous contemporary publications, was further influenced by a report by Novak and Galvin (1951), who analysed 25 cases in whom an histological diagnosis of intra-epithelial carcinoma of the cervix had been made erroneously. The source of error in 14 cases was attributed to misinterpretation of the histological features of basal cell hyperactivity in the presence of either pregnancy or acute pelvic inflammatory disease.

Despite the accumulation of a considerable volume of evidence suggesting reversible atypical pregnancy changes in the cervical epithelia, opinions challenging the validity of these phenomena were expressed by several writers.

Murphy and Herbut (1950) found no instances of obvious or borderline malignant activity in the cervical epithelia of 50 pregnant women, and Garrow and Greene(1951), investigating 96 pregnant

and 50 non-pregnant patients, found no specific changes in the cervical epithelia during pregnancy. The latter authors diagnosed pre-invasive carcinoma of the ectocervical epithelium in nine of the pregnant patients, seven of whom showed gross macroscopic cervical lesions. They concluded that if the criteria for the diagnosis of pre-invasive carcinoma were present, the diagnosis was valid even if the patient was pregnant.

Greene et al. (1953) categorically denied that pregnancy caused specific changes in the cervical epithelia although they affirmed that "metaplasias" and "hyperplasias" of glandular elements were more common and more prominent during pregnancy than in the non-pregnant state. They reported 14 cases of carcinoma in situ of the cervix in pregnant patients, 12 of whom showed persistence of the lesion postpartum for periods varying from 6 weeks to 29 months. Similar findings were published by Marsh and Fitzgerald (1956) who diagnosed histologically 20 cases of carcinoma in situ of the cervix in an extensive investigation of 3,970 pregnant patients, and found persistence of the lesion in 18 patients for periods up to 31 months after termination of pregnancy.

During the past decade, opinion in the literature has predominantly supported the views of earlier writers who contended that firstly, no specific changes in the cervical epithelia occurred during pregnancy, and secondly, that histological assessment of cervical lesions showing the microscopic criteria necessary for a diagnosis of carcinoma in situ should be the same in pregnant as in

non-pregnant patients. Evidence corroborating these views has been adduced by numerous authors including Slate et al. (1957), Beecham and Emich (1959), Johnson et al. (1960), Fluhmann (1961), and Rutledge et al. (1962).

Previous reports of evanescent lesions in the cervical epithelia during pregnancy, histologically indistinguishable from carcinoma in situ, have not been substantiated by the majority of recent investigators. The general view is held that cases of borderline neoplasia may be encountered in the cervical epithelia of pregnant women, but identical lesions are found in the cervices of non-pregnant women. The associated abnormal proliferative reaction involves basal cells either in the stratified squamous epithelium of the ectocervix or in foci of endocervical squamous metaplasia, or frequently in both of these structures simultaneously, and results in the formation of a wide spectrum of atypical epithelial patterns. The diversity of histological appearances presented by the abnormal squamous cells is reflected in the varied terminology used by different investigators who have described such lesions in detail. Reagan and Patten (1962), reviewing this subject, referred to the variety of terms previously introduced, such as atypia; atypical, restless, unquiet or irregular epithelium; atypical hyperplasia; basal cell hyperactivity or hyperplasia; precancerous metaplasia; metaplasia with atypicality; anaplasia and dissociated intra-epithelial anaplasia; and they designated

collectively these reactions under the term dysplasia, in accordance with previous studies by Reagan et al. (1953).

While the consensus of opinion, presently, is that dysplastic lesions of the cervical epithelium present similar histological features both in pregnant and non-pregnant women, the view that these reactions are more prevalent during pregnancy continues to receive support (Reagan and Patten, 1962). Prolonged follow-up studies of dysplastic lesions detected both in pregnant and in non-pregnant women have been carried out by Walters and Reagan (1956) and Johnson et al. (1960). The results of these studies have shown that regression of dysplasia occurs similarly both in pregnant and in non-pregnant women in 50 to 66 per cent of cases, but an appreciable minority of cases show persistence or recurrence of the dysplastic reaction in every series studied. Walters and Reagan (1956) reported that three of the 63 lesions detected during pregnancy progressed to carcinoma in situ 8 to 17 months postpartum, and one pregnant patient with dysplasia developed invasive squamous carcinoma of the cervix 15 months after confinement. Johnson et al. (1960) reported that one of their series of 89 pregnant patients, in whom dysplasia of the cervical epithelium had been diagnosed, developed carcinoma in situ during the fifth year of follow-up.

In recent years, interest has been concentrated on the occurrence of dysplastic change particularly in foci of squamous

metaplasia in the cervical canal. While it has been established that dysplasia may develop in the basal cells of either the ecto-cervical stratified squamous epithelium or the cervical canal epithelium, the latter site has been the focus of increasing attention as a result of an accumulation of evidence identifying the cervical canal as the commonest site of origin of pre-invasive and early invasive cancer of the cervix. Corroborating the preliminary observations of earlier investigators, Carson and Gall (1954) reported that all of their 56 cases of carcinoma in situ originated within the cervical canal, and only two extended to the portio vaginalis. Fidler and Boyd (1960) and Fluhmann (1960) similarly concluded from their series of 20 and 50 patients respectively that the commonest site of origin of pre-invasive and early invasive carcinoma of the cervix was the cervical canal, including the squamo-columnar junction.

Belief that the histogenesis of cervical carcinoma is represented by a spectrum of changes from atypism of the cervical epithelium through anaplasia and carcinoma in situ to invasive carcinoma is expressed by Johnson et al. (1960). They consider that regression of these lesions is possible but less likely to occur as the invasive stage is approached, and they refer to further evidence that the natural course of this spectrum occurs over 15 to 20 years and is unaffected by intervening pregnancies. On the other hand, Haines and Taylor (1962) suggest that it is

possible that basal cell hyperplasia, stimulated during pregnancy, may progress occasionally to carcinoma.

The tremendous volume of research which has accumulated in the study of cervical epithelial changes has resulted also in the recognition and differentiation of benign hyperplasia of the cervical epithelia from atypical proliferative changes constituting dysplasia, although the histological borderline dividing dysplasia from carcinoma in situ of the cervix remains imprecise. Simple hyperplasia of the basal cells in the ectocervical and endocervical epithelium is now identified both in pregnant and non-pregnant women and the consensus of opinion appears to favour an increased incidence of these benign changes during pregnancy.

Opinion is unanimous regarding the increased proliferative activity of the columnar epithelium in the endocervix during pregnancy, but the significance of this change in relation to the ultimate development of adenocarcinoma of the cervix is at present unknown. Anaplastic or dysplastic changes in cervical columnar epithelium, analagous to those observed in squamous epithelium in the tissues of the cervix, have not been described. Nevertheless, evidence of considerable hyperplasia of the columnar elements in the endocervix during pregnancy has been repeatedly confirmed since Stieve's (1927) original observations. Measurement of the depth of the glandular mucosa of the endocervix was carried out by Fluhmann (1961), who recorded that the maximum depth of mucosa attained at term varied from 3 to 6 millimetres, while the depth of

the mucosa in non-pregnant women varied from 1.2 to 3.5 millimetres. The latter author introduced a new concept of the anatomical structure of the cervical glands, which he illustrated by plastic reconstruction from serial microscopic sections of thick cleared preparations of cervices, and which he considered represented an intricate system of clefts or grooves with innumerable secondary clefts or tunnels lined by columnar epithelium.

Hypertrophy of the endocervical mucosa during pregnancy frequently results in "eversion" of the mucosa at the level of the external cervical os. The increased incidence of cervical erosion during pregnancy noted by several authors including Fluhmann (1948) and McLaren (1961) has been ascribed by the latter to the physiological mechanism of mucosal eversion, involution of which in the postpartum period eventuates in apparent "healing" of large numbers of the "erosions".

In a recent comprehensive review and interpretation of cervical epithelial changes, Fluhmann (1961) states: "The epithelia of the cervix uteri during the course of gestation undergo marked proliferation, but there are no modifications peculiar to pregnancy. Changes that do exist mirror the intense hormonal stimulation which leads to growth and active secretion, but they are likewise seen in the non-pregnant. The oft-repeated statement that the hormonal stimulus of pregnancy may lead to a type of dysplasia and carcinoma in situ that is fleeting in duration, and disappears within 6 months

postpartum, seems unfortunate"....."It has been stated that it is difficult or impossible to diagnose carcinoma in situ during pregnancy with certainty. The implications of the last statement may lead to tragic results if it should receive widespread acceptance without due reservations."

MATERIALS AND METHODS

I. PREGNANCY SERIES

CLINICAL MATERIAL

Histological examination of tissue from the cervix uteri was carried out in 110 pregnant women receiving treatment in three main hospitals in Belfast between 1st October 1959 and 28th February 1962. The patients were under treatment in the gynaecological department of Musgrave Park Hospital or in the obstetrical wards of the Royal Maternity and Belfast City Hospitals. These 110 patients constitute the Pregnancy Series.

SELECTION OF CLINICAL MATERIAL

Cervical tissue from 108 pregnant patients was obtained during various operative obstetrical procedures carried out under general anaesthesia, while the remaining two patients had cervical polypi only removed during examination without anaesthesia. Thus, selection of pregnant patients for purposes of the present study was almost entirely dependent on the various obstetrical complications, developing during their pregnancy, which necessitated pelvic examination under anaesthesia and which afforded an opportunity to obtain cervical biopsy material simultaneously, without added risk to the patients themselves (Table I).

TABLE I

Pregnancy Series. Obstetrical complications in 110 pregnant patients necessitating operative treatment under general anaesthesia

Obstetrical complication	No. of patients	Primary operative procedure
Threatened abortion	8	*Pelvic examination and assessment.
Inevitable or incomplete abortion	88	Evacuation of uterus.
Antepartum haemorrhage	9	Pelvic examination to exclude placenta praevia.
Placenta praevia accreta	1	Caesarean hysterectomy.
Pre-eclamptic toxaemia	2	Surgical induction of labour.
Prolonged pregnancy	1	Pelvic assessment.
Unsuspected early pregnancy	1	Manchester operation.
Total number of patients	110	

*Includes 2 patients who had cervical polypi removed without anaesthesia.

The largest group of cases providing cervical biopsy material was derived from operations for abortion in the first or second trimesters of pregnancy. Cervical tissue was obtained inadvertently during an early unsuspected pregnancy in one patient who underwent a Manchester operation for utero-vaginal prolapse. The patient was a grand multipara who gave no history of amenorrhoea

and whose menstrual periods were profuse and frequent. Dilatation and curettage yielded a moderate amount of endometrium and subsequent histological examination revealed the presence of decidua and chorionic villi associated with a pregnancy estimated to have been approximately 6 weeks in duration.

The clinical state of the cervix was noted in each patient, but no case showing clinical features of frank malignancy of the cervix was included in the Pregnancy Series. Table II shows the recorded clinical appearance of the cervices in the 110 pregnant patients at the time of obtaining the biopsy material.

TABLE II

The macroscopic appearance of the cervix uteri in 110 pregnant patients.

Macroscopic appearance of cervix uteri	No. of cases	Percentage of total
Erosion +/- chronic infection	39	35.4
Chronic infection	19	17.3
Polypi	7	6.4
No macroscopic lesion	45	40.9
Total number of cases	110	100.

CLINICAL FEATURES

Age groups

The distribution by age groups of the 110 pregnant patients is shown in Table III. The youngest patient was 19 years of age and the oldest 46 years.

TABLE III

Age distribution in 110 pregnant patients

Age	Number of patients
Under 21	7
21 - 25	16
26 - 30	24
31 - 35	24
36 - 40	24
41 - 45	12
Over 45	3
Total	110

Parity

Table IV denotes the distribution of the 110 patients in relation to the total number of previous viable and non-viable pregnancies. Twenty-one patients were primigravidae and the remaining 89 patients had had one to 12 previous pregnancies.

TABLE IV

Distribution of 110 pregnant patients in relation to total number of previous pregnancies

Total number of previous pregnancies	Number of patients
0	21
1-3	43
4-6	23
Over 6	23
Total	110

Marital status

One hundred and eight of the pregnant patients were married and two were single at the time of the investigation. Both unmarried patients were primigravidae.

Trimester of pregnancy

Biopsy material from the cervices of the 110 patients was obtained on only one occasion during each patient's pregnancy.

TABLE V

Pregnancy Series. Distribution of cases in each trimester

	Trimester			Total
	First	Second	Third	
Number of cases	65	31	14	110

Table V shows the distribution of the 110 cases in relation to the trimester during which the histological investigation was carried out. Inevitable or incomplete abortion constituted the commonest obstetrical complication necessitating operative treatment under general anaesthesia in these patients, and resulted in the largest number of biopsy investigations occurring in the first trimester.

Confirmation of pregnancy was obtained in every patient having incomplete or inevitable abortion during the first trimester by histological examination of material removed from the uterine cavity in each case. Verification of the presence of chorionic villi in the uterine curettings was particularly essential in patients in whom curettage yielded only a small quantity of tissue as a result of spontaneous abortion of the major portion of the ovum before admission to hospital.

Clinical identification of the foetus or placenta was achieved in each patient investigated during the second and third trimesters.

Sources of biopsy material

The various types of pathological specimens obtained from the 110 pregnant patients for histological study of cervical tissue are contained in Table VI. One hundred and three of the patients were investigated by cervical biopsy, which included small cervical polypi in two cases. From five patients, only cervical polypi,

TABLE VI

Pregnancy Series. Source of cervical tissue for histological study

Pathological specimen	Number of patients
Biopsy of cervix	101
Biopsy of cervix including cervical polyp	2
Cervical polyp	5
Amputated cervix	1
Uterus	1

without biopsy material from the cervix were obtained for histological examination. Operative treatment in the remaining two patients yielded the total cervix for study in each case, one patient having a Manchester operation during an early unsuspected pregnancy, and the other requiring Caesarean hysterectomy for placenta praevia accreta in the thirty-sixth week of pregnancy.

CLINICAL AND PATHOLOGICAL METHODS

Technique employed for cervical biopsy in pregnant patients

After consideration of the conventional techniques generally used in biopsy of the cervix it was decided that a

standard method should be developed in the present investigation and that this method should provide the maximum amount of cervical epithelium for informative histological study while inflicting the minimum risk to the patient or her pregnancy from the procedure. The principal undesirable complications to be avoided were:-

1. Excessive bleeding from the biopsy site, which would result in deterioration in the patient's peripheral circulatory state, especially in the presence of obstetrical complications already associated with haemorrhage.
2. Interference with the function of the internal cervical os following removal of tissue from this region.
3. The formation of fibrous scarring at the site of biopsy in the cervix, which, in a subsequent labour, might result in cervical laceration with possible extension to involve the lower uterine segment.
4. The development of local sepsis in the pelvic organs.

The technique ultimately accepted on the basis of these requirements entailed the removal by cold knife dissection under strict asepsis, of a rectangular superficial plaque of epithelium from a quadrant of the cervix, including the minimum amount of underlying cervical stroma, and incorporating epithelium, whenever possible, from the portio vaginalis, the squamo-columnar junction and the cervical canal. In 85 out of the 103 patients who underwent cervical biopsy, tissue was removed from one quadrant of the

cervix, either the anterior or posterior quadrants being selected. Of the remaining 18 patients, two quadrants of the cervix were biopsied in 17, and three quadrants in one. Multiple quadrant biopsy of the cervix was undertaken in the latter group of cases during the later stages of the investigation when increasing confidence and experience were gained in the use of the technique.

This cervical biopsy procedure was carried out in every patient selected for investigation, after completion of the relevant operative treatment required for the primary obstetrical complication. In each instance, the general condition of the patient was carefully assessed after the primary obstetrical operation, and biopsy of the cervix was not performed unless both the obstetrician and the anaesthetist were satisfied that the additional procedure would not constitute any significant hazard to the patient.

Technical details of biopsy procedure

Biopsy of a single quadrant of the cervix was performed in the following manner:-

The cervix was grasped by two pairs of Littlewood's tissue forceps, one pair of forceps being applied to each lateral angle of the cervix which was held steady. Sponge-holding forceps with fine blades were substituted to grasp similarly the highly vascular cervix of patients in the third trimester of pregnancy in

order to obviate the brisk bleeding associated with the smallest puncture wounds in such cervices. Using a small tenotomy scalpel blade attached to a Bard-Parker handle, the biopsy site was delineated by four superficial incisions on the cervical epithelium, forming a rectangular area extending from the normal squamous epithelium of the portio vaginalis proximally to the cervical canal. The long axis of the rectangular portion of tissue coincided with the axis of the cervical canal.

One corner of the biopsy area, over the portio vaginalis was then undercut by superficial strokes with the scalpel until a small portion of epithelium was freed. The free corner of biopsy tissue was grasped lightly by small finely-toothed dissecting forceps, after which repeated superficial undercutting strokes of the scalpel resulted in the removal of a thin plaque of the biopsy area previously delineated.

Transient, brisk capillary oozing of blood occurred from the raw biopsy site in the majority of cases, but this was controlled by local pressure using a gauze swab. Arterial bleeding was not encountered following this technique of biopsy in any patient and haemostatic control of bleeding by suture or cautery was not required. Vaginal packing was not employed, the raw cervical biopsy sites being allowed to drain freely.

In those patients submitted to multiple quadrant biopsy of the cervix, biopsy of each quadrant was carried out in an identical manner.

Complications associated with biopsy technique

Primary or secondary haemorrhage from the biopsy site did not occur in any of the 103 patients submitted to cervical biopsy by the described technique.

Biopsy of the cervix did not stimulate abortion or premature labour in any patient investigated while the pregnancy was continuing.

No case of pelvic sepsis was observed following the biopsy procedure in any trimester. Complete healing with re-epithelialization of the biopsy site and without cicatricial deformity was uniformly observed in patients who reported for pelvic examination, 6 weeks after abortion or confinement.

HISTOPATHOLOGICAL TECHNIQUE

Preparation of specimens for histological examination

Pathological specimens of cervix from all patients in the Pregnancy Series were submitted to the pathology department of either the Royal Victoria Hospital, or the City Hospital, Belfast, depending on the related obstetrical or gynaecological units into which the patients had been admitted.

Biopsy specimens of cervical tissue, including isolated cervical polypi, were fixed in Helly's solution. A paraffin block of each specimen was then prepared and one to four sections

of the block were cut and mounted on slides for staining. Sections of cervical biopsy specimens were cut in the plane of the long axis of the material corresponding to the axis of the cervical canal. This technique ensured that ascending levels of cervical epithelium were represented in the histological section.

The total cervix, obtained from two of the pregnant patients, was initially fixed in 10 per cent formalin solution. On the following day each specimen of cervix was cut in two to three blocks which were embedded in paraffin wax. One section was then prepared from each block and mounted for staining.

All sections of cervical tissue were stained with Harris's haematoxylin and eosin.

Histological examination of specimens

In the first instance, specimens of cervical tissue from each patient in the Pregnancy Series were examined by the senior pathologists in the Royal Victoria and City Hospitals, Belfast, each pathologist being responsible for specimens submitted to his department from the associated clinical department of obstetrics and gynaecology. After the pathologists' report had been recorded, all relevant histological sections were collected in a separate file.

Subsequently, the writer of the present thesis undertook a detailed histological examination of the cervical tissue obtained

from each pregnant patient, an average of 10 minutes being spent on microscopic study of the sections from each case. A detailed description of the characteristics of the ectocervical and endocervical epithelia and the squamo-columnar transitional zone was recorded in every instance where these tissues were available in the prepared sections. Associated histological changes in the cervical stroma were also noted. Individual specimens of cervical polypi were similarly studied.

Complete observations were entered in a previously prepared standard proforma containing collated clinical and histopathological findings in respect of each patient.

Histological criteria required for the diagnosis of epithelial lesions of the cervix

Conformity of opinion regarding the basic histological criteria required for the diagnosis of cervical epithelial lesions was held by both senior pathologists associated with the present investigation. In addition, the terminology used in reporting such lesions was uniform and confusion of lesions from this source was avoided.

Benign epithelial lesions

The criteria fulfilled for the histological diagnosis of the principal benign epithelial lesions observed during the present

investigation were as follows:-

1. Stratified squamous epithelium

Basal cell hyperplasia. The main histological feature in basal cell hyperplasia consisted of evidence of abnormal proliferative activity in the basal layers of the stratified squamous epithelium. While the morphology of the single layer of basal cells, columnar or cuboidal in shape, with deeply staining nuclei of uniform size, was not significantly altered, the parabasal zone contained four or more layers of highly immature non-vacuolated cells with fairly large nuclei which exhibited a slight tendency to hyperchromatism. No alteration occurred in the histological characteristics of cells in the clear or cornified zones.

The consequent increase in depth of the parabasal zone frequently resulted in a total increase in thickness of the stratified squamous epithelial layer, but this was not an invariable finding. Instances of hyperplasia of the basal cells were noted in relatively "thin" portions of stratified squamous epithelium in which the thickness of the clear and cornified zones was reduced. Not more than two-thirds of the total depth of the squamous epithelial layer was occupied by basal and parabasal cells in any section showing hyperplasia.

Polarity of the hyperplastic epithelial cells was not disturbed, although evidence of normal maturation of cells deep to the clear zone was lacking. Polarity and maturation of cells in the superficial zones were normal.

The size of the hyperplastic, immature parabasal cells varied within relatively small limits but individual cells showed no evidence of atypism or anaplasia. Evidence of increased nuclear mitotic figures was frequently noted in the basal layer of cells, but infrequently in the parabasal cells. Nuclei in prophase or telophase were the most commonly recognised mitotic figures observed.

The formation of rete pegs, and evidence of extension of the proliferating basal cells in irregular projections into the underlying cervical stroma was not a constant feature associated with basal cell hyperplasia. No interruption of the continuity of the basal cell layer or basement membrane was visible in sections showing hyperplasia.

2. Columnar epithelium

(a) Benign hyperplasia

Benign hyperplasia of the columnar elements of the cervical epithelium was identified if evidence of hyperplastic change was present in either or both of the columnar epithelial components of the cervix. Thus, hyperplasia of the columnar

epithelium lining the cervical canal, or undue proliferative activity in the cervical glandular epithelium, or hyperplastic changes occurring simultaneously in both of these structures were accepted as criteria of benign hyperplasia of the columnar epithelium of the cervix. The hyperplastic columnar cells showed concomitant evidence of increased secretory activity.

Cervical canal. Benign hyperplasia of the columnar epithelial lining of the canal was recognised by the appearance of two or more layers of columnar cells in the epithelial surface, which resulted in stratification of the cells and "festooning" of the cervical canal surface lining. Individual columnar cells showed little variation in cytoplasmic or nuclear size and no evidence of nuclear hyperchromatism or anaplasia.

Cervical glands. Excessive proliferative activity in cervical glandular epithelium was demonstrated by evidence of a considerable increase in the number of glands of varying size, many of which occurred in dense aggregations which resembled a "honeycomb" pattern. Few of these glands were passively dilated but the majority showed evidence of active secretion of mucin. In many instances, the cervical glands also showed stratification of their epithelial lining of columnar cells, with consequent infolding of epithelium resulting in the appearance of "glands within glands." Individual columnar cells were readily identified by their form and normal staining reactions, and no tendency to

anaplasia or dedifferentiation of columnar epithelium was present.

(b) Squamous metaplasia

The histological criteria accepted for the diagnosis of squamous metaplasia required the identification of foci of multi-layered squamous cells of varying size and maturity undermining or replacing the columnar epithelium of either the cervical canal or the cervical glands. The thickness of the squamous metaplastic foci varied from layers of two or more cells to fully developed mature squamous epithelium showing stratification. Squamous metaplasia occurring in the squamo-columnar transitional zone required clear histological differentiation from contiguous stratified squamous epithelium of the ectocervix and, in cases of doubt, was not accepted unless associated metaplastic changes were present at a higher level in the cervical canal epithelium or in the cervical glands.

Individual cells of squamous metaplastic foci showed no undue variations in cytoplasmic or nuclear size, stained evenly and closely resembled the cells of the parabasal zone of normal stratified squamous epithelium. Mitoses were infrequent and nuclear hyperchromatism was absent in the immature squamous cells.

In the present investigation, three principal varieties of squamous metaplasia were identified, derived from those described by Carmichael and Jeaffreson (1941) and Fluhmann (1959):-

(i) Compact squamous metaplasia. This form was characterised by solid masses of squamous cells which were either uniformly immature or showed varying degrees of maturation towards stratified squamous epithelium. No vacuolation due to mucin-secreting columnar elements was present in these solid foci of squamous cells.

(ii) Squamo-columnar metaplasia. In this variant of squamous metaplasia, foci of metaplastic squamous epithelium contained a varying number of vacuoles, which are generally interpreted as secretory globules of mucin derived from columnar elements in the metaplastic foci. In many instances the vacuoles appeared empty or contained small quantities of cellular debris associated with degenerative changes in the columnar cells. The general appearance of the atypical epithelium varied considerably from discrete foci containing a few small vacuoles, situated usually near the surface columnar epithelium of the cervical canal, to extensive areas containing the abnormal epithelial cells arranged in trabeculae enclosing gland-like lumina, the cells showing some secretory activity. These "trabeculations" frequently projected from the surface of the cervical canal and assumed a festooned appearance.

(iii) Tenuous squamous epithelium. As advocated by Fluhmann (1959), tenuous squamous epithelium was regarded as a variant of squamous metaplasia, occurring in the squamo-columnar

transitional zone. Sudden or gradual thinning of the mature stratified squamous epithelium of the ectocervix was observed as it extended from the normal area towards the columnar mucosa. From some 20 to 30 rows of squamous cells in orderly arrangement the abnormal epithelium diminished to a thickness of 8 to 10 cells until the layer was composed of two to three rows of squamous cells at which level, the columnar epithelium of the canal was frequently observed undermined by the squamous layer. From the upper limit of the attenuated squamous epithelium columnar epithelium extended normally upwards in the cervical canal.

In the majority of instances, a fairly definite line of demarcation was visible between normal ectocervical squamous epithelium and tenuous squamous epithelium, in which the parabasal type of squamous cells predominated. In cases of doubt, the association of tenuous squamous epithelium with the other varieties of squamous metaplasia previously described was regarded as evidence of the metaplastic nature of the abnormal squamous epithelium.

Atypical epithelial lesions showing features suggestive of neoplasia

Histological lesions of the cervical squamous epithelium, showing various atypical cellular transformations suggestive of malignancy but lacking adequate criteria to fulfill the requirements

for a diagnosis of carcinoma in situ, were designated collectively by the term dysplasia. It was fully appreciated that dysplasia, as an histological entity, lacked precision and frequently was impossible to differentiate from carcinoma in situ. While accepting these limitations, the writer resolved that the subject of dysplastic change in the cervical squamous epithelium merited careful consideration during the course of the present investigation as previous reports in the literature had yielded widely conflicting evidence of the incidence, nature and significance of atypical epithelial lesions in the cervix during pregnancy.

In the present study, the cellular characteristics comprising the general histological pattern of dysplasia are defined as follows:

Cellular features

Abnormal variations in cytoplasmic and nuclear size with increased mitotic activity involving the cells of both basal and parabasal zones.

The occasional presence of giant and multinucleated cells.

Lack of uniformity in staining reaction of nuclei.

Loss of polarity of cells in the basal layers.

Evidence of partial loss of normal maturation and stratification of cells in the deeper layers of the squamous epithelium.

Finally, emphasis was placed pre-eminently on the absence of involvement of the total thickness of squamous epithelium, the dysplastic characteristics being limited to the deeper layers of the epithelium, with the superficial squamous cells showing evidence of normal differentiation and maturation.

II. CONTROL SERIES

CLINICAL MATERIAL

One hundred and ten non-pregnant patients were selected to form the Control Series. These patients underwent various gynaecological operations in the gynaecological departments of the Royal Victoria Hospital, Musgrave Park Hospital, the Samaritan Hospital for Women, and the Ulster Hospital for Women and Children, Belfast, between 1st January 1959 and 30th June 1962, a period of investigation which corresponded in time as closely as possible to that of the Pregnancy Series.

PRINCIPLES GOVERNING SELECTION OF CONTROL SERIES

After prolonged consideration, it was resolved that the Control Series should constitute a strictly comparable group of non-pregnant patients who were individually matched for age, parity and marital status with each patient in the Pregnancy Series. The predominant aim of this scheme was to eliminate any possible influence of three major factors on the comparative histological findings in the two series of patients. These three factors were age, number of previous pregnancies and marital status. Consequently, it should be possible to assess the results of the investigation largely in relation to the gravid state, the remaining major feature of

difference between the two groups.

In order to eliminate any influence or effect of recent pregnancy on the cervical histology of non-pregnant multiparous patients, it was required that each multipara would qualify for inclusion in the Control Series only if the time lapse between the date of termination of her last pregnancy and the date of cervical biopsy exceeded 12 weeks.

METHODS OF SELECTION OF NON-PREGNANT PATIENTS

In the first instance a comprehensive list of the age, number of previous pregnancies and marital status of each patient in the Pregnancy Series was compiled. Reference was then made to the files of benign histopathological reports covering the years 1959 to 1962, in the pathology departments of the Royal Victoria and City Hospitals, Belfast, to which all gynaecological specimens from the various hospitals in Belfast and adjacent regions were submitted. Histological reports on cervical tissue removed from all patients whose ages lay within the age limits of the Pregnancy Series were recorded, and cross reference was made subsequently to the clinical case records of each patient thus identified.

The clinical records of some 1,200 gynaecological patients were obtained by this method, and each non-pregnant patient whose

age, parity and marital status matched one patient in the Pregnancy Series was selected for inclusion in the Control Series. In this manner, 80 non-pregnant patients were found suitable for inclusion as paired controls.

The remaining 30 patients in the Pregnancy Series for whom no matched non-pregnant patient was obtained by reference to pathological records, were paired by a prospective selection of non-pregnant patients for cervical biopsy. As a result of this programme during the last third of the period of investigation, cervical biopsy material was obtained from 30 non-pregnant patients admitted for various gynaecological operations from the waiting lists of the various hospitals previously mentioned. These 30 patients individually matched the remaining 30 pregnant patients in respect of the required three major factors.

The clinical state of the cervix was noted in every non-pregnant patient, but, as in the Pregnancy Series, cases of invasive malignant disease of the uterus were excluded from the investigation. Table VII describes and compares the incidence of the macroscopic changes seen in the cervices in the two groups.

TABLE VII

The macroscopic appearance of the cervix uteri in 110 non-pregnant patients (Control Series) and 110 pregnant patients (Pregnancy Series)

Macroscopic appearance of cervix uteri	Control Series		Pregnancy Series	
	No. of patients	Percentage of total	No. of patients	Percentage of total
Erosion +/- chronic infection	48	43.6	39	35.4
Chronic infection	34	31.0	19	17.3
Polypi	4	3.6	7	6.4
No macroscopic lesion	24	21.8	45	40.9
Total number of cases	110	100.0	110	100.0

CLINICAL FEATURES

Age groups

The distribution by age groups of the 110 non-pregnant patients was identical to that of the 110 pregnant patients (Table VIII). Each non-pregnant patient was in the same year of life as the corresponding pregnant patient.

TABLE VIII

Age distribution in 110 non-pregnant patients (Control Series) and 110 pregnant patients (Pregnancy Series)

Age	Number of patients	
	Control Series	Pregnancy Series
Under 21	7	7
21 - 25	16	16
26 - 30	24	24
31 - 35	24	24
36 - 40	24	24
41 - 45	12	12
Over 45	3	3
Total	110	110

Parity

Each pregnant patient was matched with a non-pregnant patient of identical age for the total number of previous viable and non-viable pregnancies. Thus, in the instance of a primigravida aged 20 years included in the Pregnancy Series the corresponding non-pregnant patient required to be aged 20 years and to have had no previous pregnancy in order to qualify for inclusion in the Control Series. Similarly, a patient aged 35 years investigated during her eighth pregnancy required a non-pregnant "Control" patient aged 35 years who had had seven previous

viable and non-viable pregnancies, respectively matched in number. Table IX shows the parity distribution of the 110 non-pregnant and 110 pregnant patients for comparison.

TABLE IX

Distribution of 110 non-pregnant patients (Control Series) and 110 pregnant patients (Pregnancy Series) in relation to total number of previous viable and non-viable pregnancies

Total number of previous pregnancies	Number of patients	
	Control Series	Pregnancy Series
Nil	21	21
1 - 3	43	43
4 - 6	23	23
Over 6	23	23
Total	110	110

Marital status

The two unmarried primigravidae in the Pregnancy Series were matched with two single, non-pregnant nulliparous patients of identical age. The remaining 108 non-pregnant patients were married. Consequently, the marital status of each patient in both series was identical.

Time lapse since last pregnancy

The median interval elapsing between the termination of the last pregnancy and the removal of cervical tissue for histological examination in the 89 parous patients was two years. The shortest interval recorded was 13 weeks in one patient, and the longest 15 years also in one patient.

Associated gynaecological conditions

Table X shows the various primary benign gynaecological lesions necessitating operative treatment of patients in the Control Series.

TABLE X

Control Series. Primary gynaecological condition in 110 non-pregnant patients

	No. of patients
Cervical infection +/- erosion	41
Excessive or irregular menstrual bleeding	33
Utero-vaginal prolapse	21
Primary dysmenorrhoea	5
Endometriosis	3
Chronic pelvic pain	3
Infertility	2
Uterine fibroids	1
Dermoid cyst of ovary	1
Total number of patients	110

Histological examination of endometrium from every non-pregnant patient was carried out, curettage being performed, in addition to cervical biopsy or amputation, in all cases not requiring treatment by hysterectomy. No histological evidence of early unsuspected pregnancy or recent abortion was found in any of the patients, and no case of genital cancer was included in the series.

Source of biopsy material

Table XI denotes the varieties of pathological specimens obtained from the 110 non-pregnant patients and available for histological study of the cervix. Also included in Table XI, for comparison, are the corresponding figures in respect of the Pregnancy Series.

TABLE XI

Source of cervical tissue for histological study in the Control Series and in the Pregnancy Series

Pathological specimen	Number of patients	
	Control Series	Pregnancy Series
Biopsy of cervix	69	101
Biopsy of cervix including cervical polyp	4	2
Cervical polyp	-	5
Amputated cervix	19	1
Uterus	18	1
Total number of patients	110	110

A total of 73 non-pregnant patients were submitted to biopsy of the cervix. Four of these specimens included cervical polypi. In the remaining 37 non-pregnant patients, the whole cervix was available for histology, in 19 cases following Manchester operation and in 18 following total abdominal hysterectomy or vaginal hysterectomy.

CLINICAL AND PATHOLOGICAL METHODS

Operative techniques employed

The majority of patients investigated by cervical biopsy were dealt with by different operators. In these cases a conventional wedge biopsy of the cervix centred on the squamo-columnar junction was excised. The superficial cervical biopsy technique, adopted in the investigation of the Pregnancy Series, was employed in the remaining non-pregnant patients on whom the author personally operated, tissue being excised routinely from the anterior and posterior quadrants of the cervix.

Conventional operative gynaecological techniques for abdominal and vaginal hysterectomy and Manchester operation were employed by various operators in the four gynaecological departments in which the patients included in the investigation were treated.

HISTOPATHOLOGICAL TECHNIQUE

Preparation of specimens for histological examination

Specimens of cervical tissue from all patients in the Control Series were submitted to the departments of pathology of either the Royal Victoria Hospital or the City Hospital, Belfast, according to the particular gynaecological units which they served. Consequently, the techniques employed in preparation of cervical tissue for histological examination in all cases included in the Control Series were identical to those described for cervical specimens in the Pregnancy Series.

Histological examination of specimens

Histological sections of cervical tissue from 110 patients included in the Control Series were obtained from the laboratory files of the pathology departments in the Royal Victoria and City Hospitals, Belfast. Each microscopic slide was entered subsequently in a separate file for further detailed scrutiny. The histological reports, previously issued by the senior pathologists concerned, were available in respect of each specimen of cervical tissue.

A systematic histological study of cervical tissue obtained from each non-pregnant patient in the Control Series was then undertaken by the present author. The detailed examination

of histological sections was conducted according to the routine method adopted in the Pregnancy Series, an average of 10 minutes similarly being spent on the study of cervical tissue from each non-pregnant patient.

Histological findings were recorded in each case, on a previously prepared comprehensive proforma containing collated clinical and pathological features.

Histological criteria required for the diagnosis of epithelial lesions of the cervix

The criteria for diagnosis of epithelial lesions of the cervix adopted in the investigation of non-pregnant patients were identical to those obtaining in the study of the Pregnancy Series. An uniform classification, therefore, of benign and suspicious epithelial lesions was maintained in the investigation of both pregnant and non-pregnant patients.

RESULTS OF

PERSONAL INVESTIGATIONS

MODE OF PRESENTATION OF RESULTS

The results of the present histological investigation are presented on a comparative basis between the Pregnancy and Control Series of patients in the case of every epithelial lesion relevant to both groups. Evaluation of results in any selected sub-group of patients in the Pregnancy Series is compared with that in the corresponding sub-group of the Control Series.

The histological characteristics and incidence of benign lesions of the cervical epithelium are described in the two major anatomical fields of the cervical surface - the stratified squamous epithelium of the ectocervix and the columnar epithelium of the endocervix, the histological boundary between these two compartments being the squamo-columnar junction. When considered relevant to the investigation, associated histological findings in the underlying cervical stroma are recorded.

Microphotographs of histological sections are presented to illustrate microscopic features observed in the cervical tissue of both pregnant and non-pregnant women. Microphotographs of several comparable lesions in both series of patients have been taken in order to illustrate comparative features.

Statistical analysis of results is presented in each section where this is applicable. The conventional definition of

results held to be statistically significant is employed in the present investigation. Thus, results unlikely to arise by chance more than once in 20 trials ($P < 0.05$) are accepted as statistically significant. Most of the tests of significance used in the present thesis are based on the χ^2 test to which Yates' correction has been applied (Hill, 1955).

BENIGN EPITHELIAL LESIONS OF THE CERVIX

ECTOCERVIX

Stratified squamous epithelium of the ectocervix was included in cervical material obtained from 79 pregnant and 78 non-pregnant patients respectively in each series (Table XII).

TABLE XII

The number of patients in the Pregnancy and Control Series in whom stratified squamous epithelium of the ectocervix was available for histological study

	Pregnancy Series		Control Series	
	No. of cases	Percentage of total	No. of cases	Percentage of total
Ectocervix included in pathological specimen	79	71.8	78	70.9
Ectocervix not included in pathological specimen	31	28.2	32	29.1
Total	110	100.0	110	100.0

The absence of ectocervical epithelium in approximately 30 per cent of patients in both Pregnancy and Control Series was attributed to inadequacy of the biopsy material which failed to include a portion

of the portio vaginalis. In many of these patients, however, extensive erosions were present over the portio vaginalis, which resulted in contraction of the area of squamous surface available for biopsy.

Fortuitously, the 31 pregnant and 32 non-pregnant women whose cervical biopsy did not include ectocervical stratified squamous epithelium were distributed fairly evenly in relation to age and parity groups in each series (Figs. 1, 2, 3 and 4). The resulting sample of patients in whom ectocervical epithelium was available for study in the Pregnancy Series was comparable in terms of age and parity with that in the Control Series.

Basal Cell Hyperplasia

Comparative incidence

Histological characteristics of basal cell hyperplasia of the stratified squamous epithelium of the ectocervix were found in 14 (17.7 per cent) of the 79 pregnant patients, compared with 10 (12.8 per cent) of the 78 non-pregnant women (Table XIII). The difference in incidence of this lesion between the pregnant and the non-pregnant women is not statistically significant.

The remaining 65 pregnant and 68 non-pregnant patients showed no abnormal histological features in the basal layers of the stratified squamous epithelium.

TABLE XIII

The histological findings in the basal layers of the stratified squamous epithelium of the ectocervix, in 79 pregnant and 78 non-pregnant patients

	Pregnancy Series		Control Series	
	No. of cases	Percentage of total	No. of cases	Percentage of total
Normal basal layer	65	82.3	68	87.2
Basal cell hyperplasia	14	17.7	10	12.8
Total No. of cases	79	100.0	78	100.0

$\chi^2 = 0.838$
D.F. = 1
$0.50 > P > 0.30$

Influence of age

Table XIV and Fig. 1 illustrate the distribution of basal cell hyperplasia in 14 pregnant patients in relation to the age groups of the patients and also in relation to the age groups of all patients in the Pregnancy Series. The corresponding results for the 10 non-pregnant patients in the Control Series are shown in Table XV and Fig. 2. The figures available from analysis of cases of basal cell hyperplasia in both series are too small for statistical comparison in relation to age distribution of the lesion. However, the general trend of age distribution of basal cell hyperplasia is

similar in both series, the lesion occurring in pregnant and non-pregnant patients aged 21 to 41 years.

TABLE XIV

Distribution of basal cell hyperplasia in 14 pregnant patients in relation to age groups of all patients in the Pregnancy Series

Histological features of stratified squamous epithelium of ectocervix	Age groups							Total No. cases
	Under 21	21-25	26-30	31-35	36-40	41-45	Over 45	
Stratified squamous epithelium absent	4	3	10	5	7	2	-	31
Normal basal layer	3	11	11	14	13	10	3	65
Basal cell hyperplasia	-	2	3	5	4	-	-	14
Total No. of cases	7	16	24	24	24	12	3	110

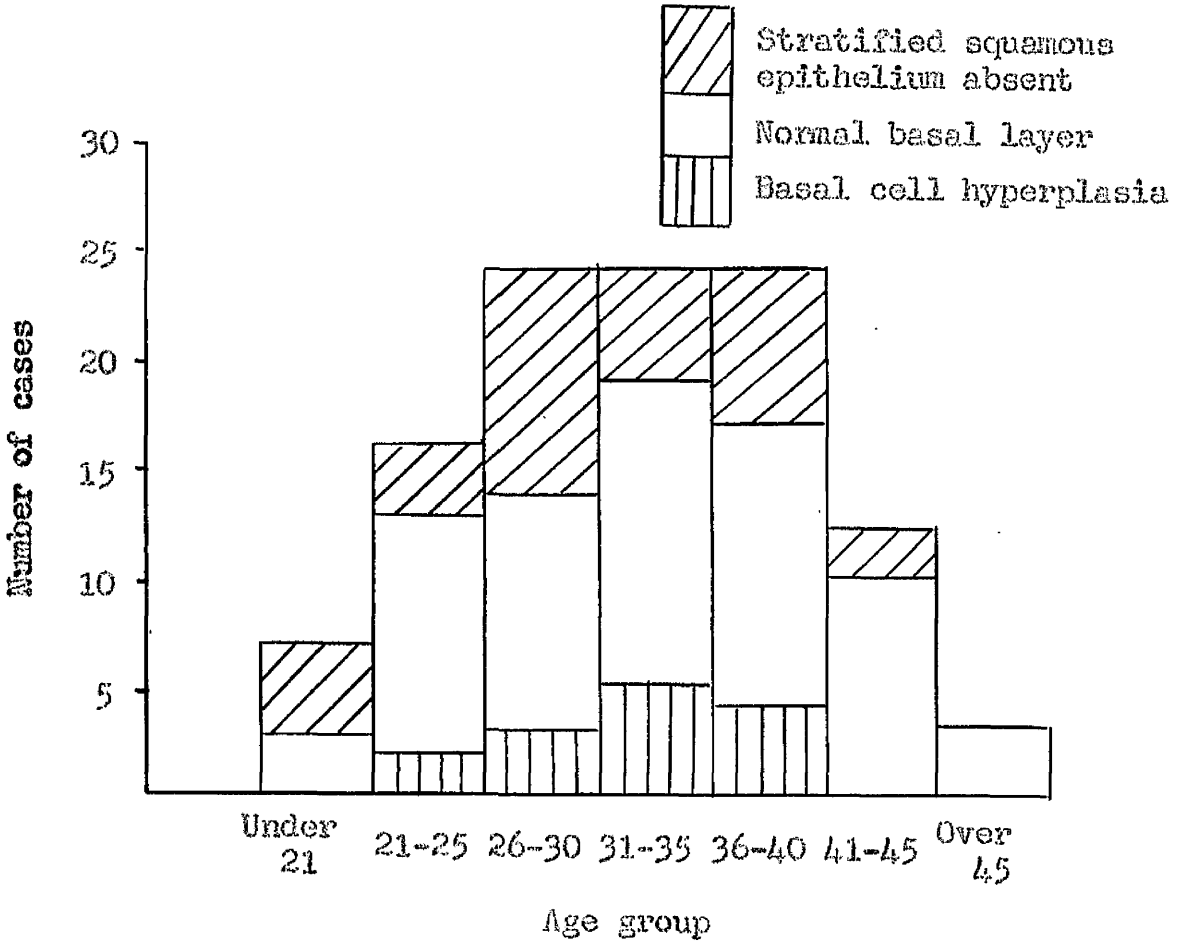

Figure 1. Pregnancy Series. Distribution of 14 cases of basal cell hyperplasia in relation to age groups of total series.

TABLE XV

Distribution of basal cell hyperplasia in 10 non-pregnant patients in relation to age groups in all patients in the Control Series

Histological features of stratified squamous epithelium of ectocervix	Age groups							Total No. of cases
	Under 21	21-25	26-30	31-35	36-40	41-45	Over 45	
Stratified squamous epithelium absent	5	8	6	8	3	2	-	32
Normal basal layer	2	7	15	15	17	9	3	68
Basal cell hyperplasia	-	1	3	1	4	1*	-	10
Total No. of cases	7	16	24	24	24	12	3	110

*1 patient aged 41 years

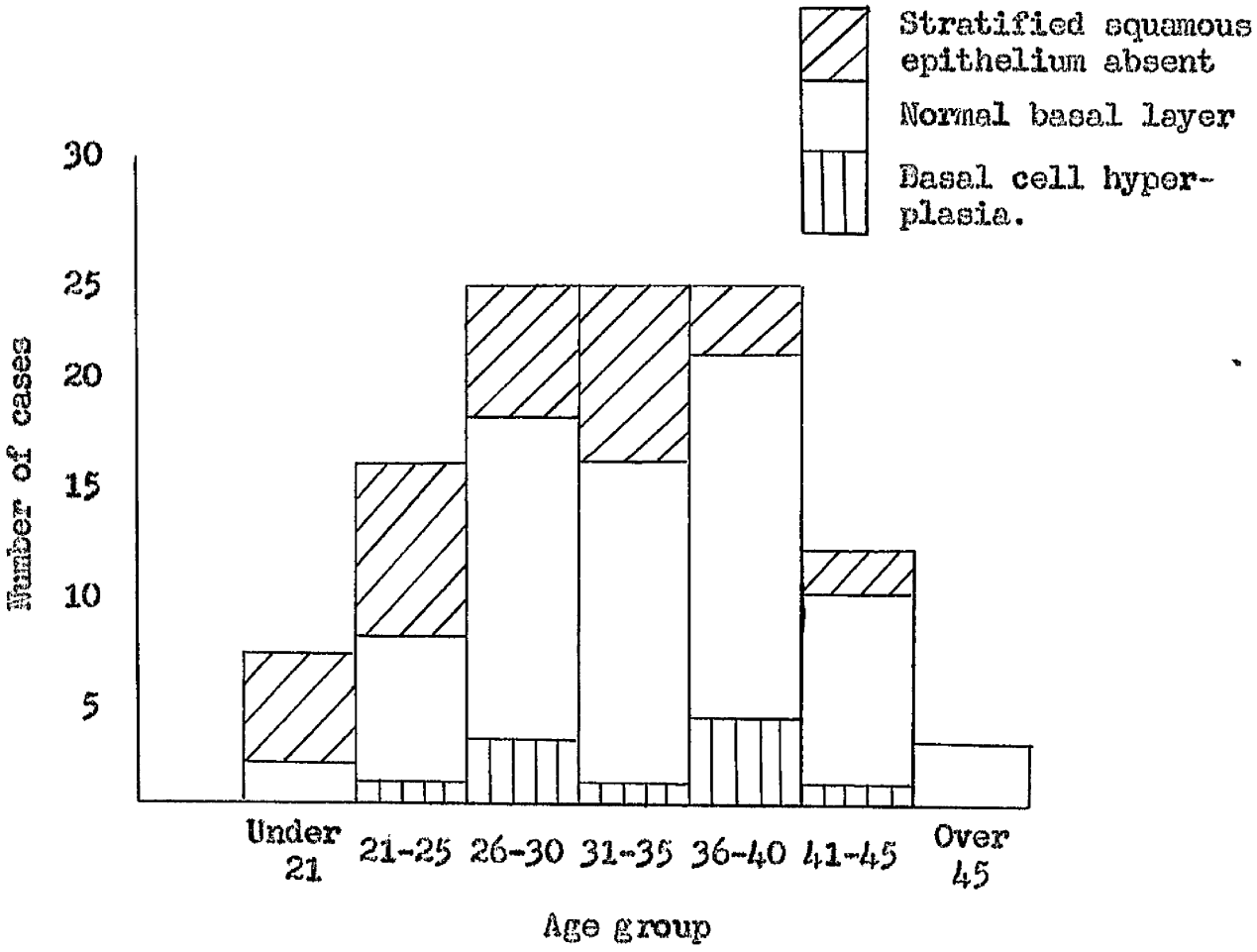

Figure 2. Control Series. Distribution of 10 cases of basal cell hyperplasia in relation to age groups of total series.

Influence of parity

The relationship of basal cell hyperplasia to parity in pregnant and non-pregnant patients was investigated (Tables XVI and XVII; Figures 3 and 4). As in the study of age distribution of the lesions, the individual figures in relation to parity groups in both series were not sufficiently large to permit statistical evaluation and comparison. Despite the paucity of material, the results available indicate that basal cell hyperplasia occurs in pregnant and non-pregnant women of all parities studied and also in those who have had no previous pregnancy.

TABLE XVI

Distribution of basal cell hyperplasia in 14 pregnant patients in relation to parity* groups of all patients in the Pregnancy Series

Histological features of stratified squamous epithelium of ectocervix	Total number of previous viable and non-viable pregnancies				Total No.of cases
	Nil	1-3	4-6	Over 6	
Stratified squamous epithelium absent	9	14	4	4	31
Normal basal layer	9	23	15	18	65
Basal cell hyperplasia	3	6	4	1	14
Total No. of cases	21	43	23	23	110

*Parity includes the total number of previous viable and non-viable pregnancies.

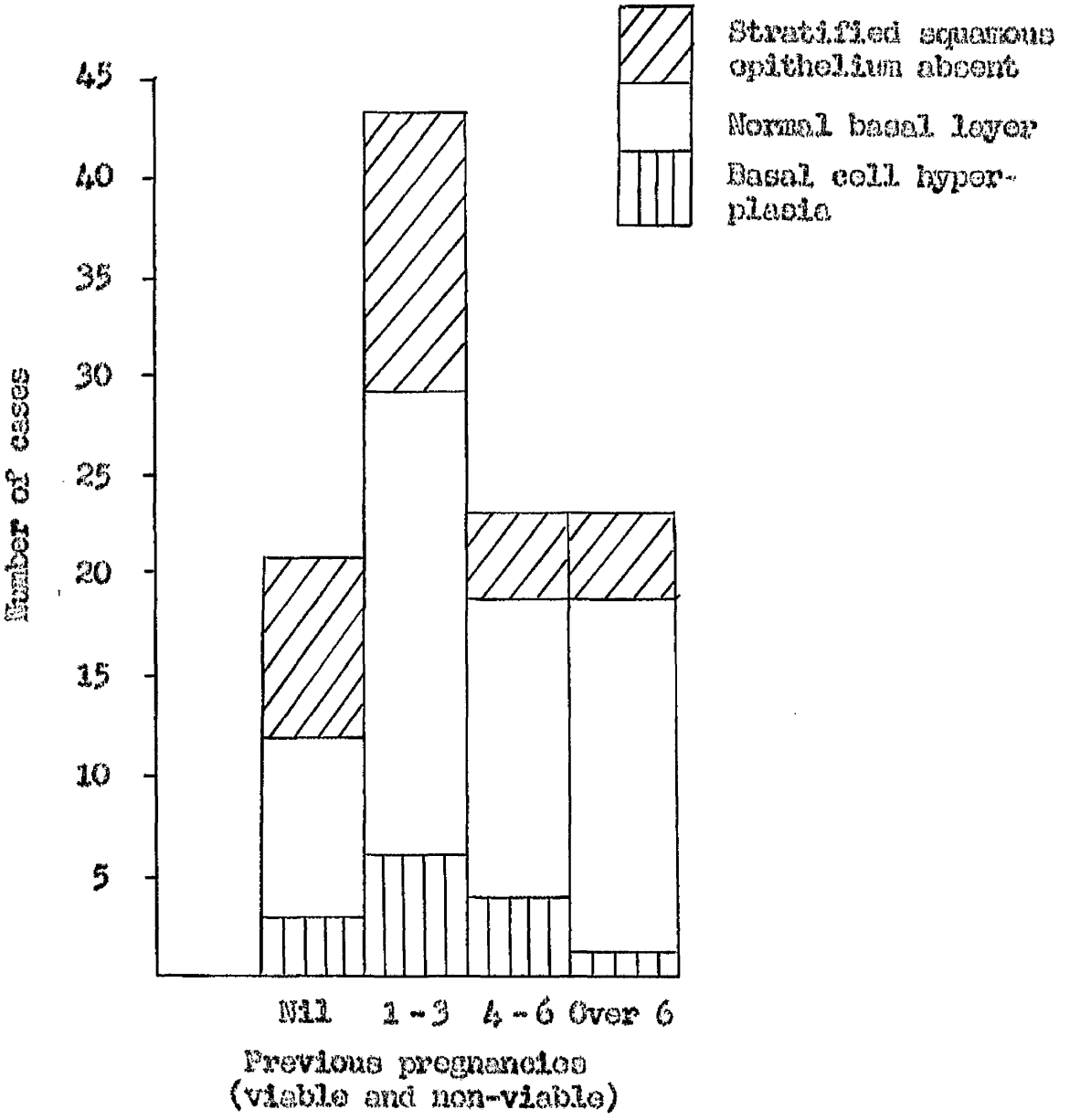

Figure 3. Pregnancy Series. Distribution of 14 cases of basal cell hyperplasia in relation to parity groups of total series.

TABLE XVII

Distribution of basal cell hyperplasia in 10 non-pregnant patients in relation to parity* groups of all patients in the Control Series

Histological features of stratified squamous epithelium of ectocervix	Total number of previous viable and non-viable pregnancies				Total No.of cases
	Nil	1-3	4-6	Over 6	
Stratified squamous epithelium absent	7	15	5	5	32
Normal basal layer	12	26	15	15	68
Basal cell hyperplasia	2	2	3	3	10
Total No. of cases	21	43	23	23	110

*Parity includes the total number of previous viable and non-viable pregnancies.

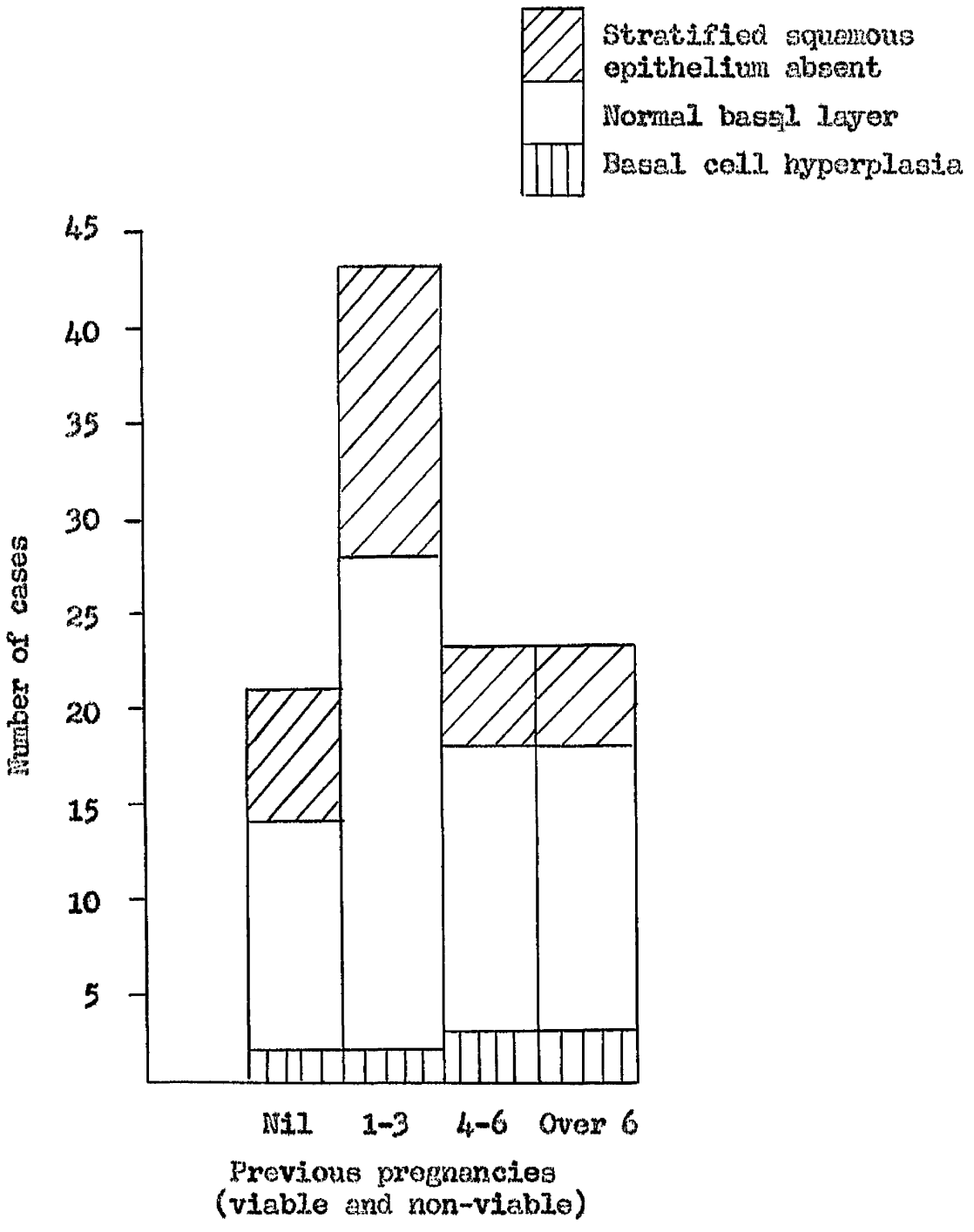

Figure 4. Control Series. Distribution of 10 cases of basal cell hyperplasia in relation to parity groups of total series.

Trimester distribution

Distribution of the 14 cases of basal cell hyperplasia in the Pregnancy Series was studied in relation to the trimester of pregnancy during which specimens of cervical tissue were obtained from the patients (Figure 5). The lesion was observed in a small proportion of patients in each trimester of pregnancy, the largest number and proportion of cases occurring in the second trimester.

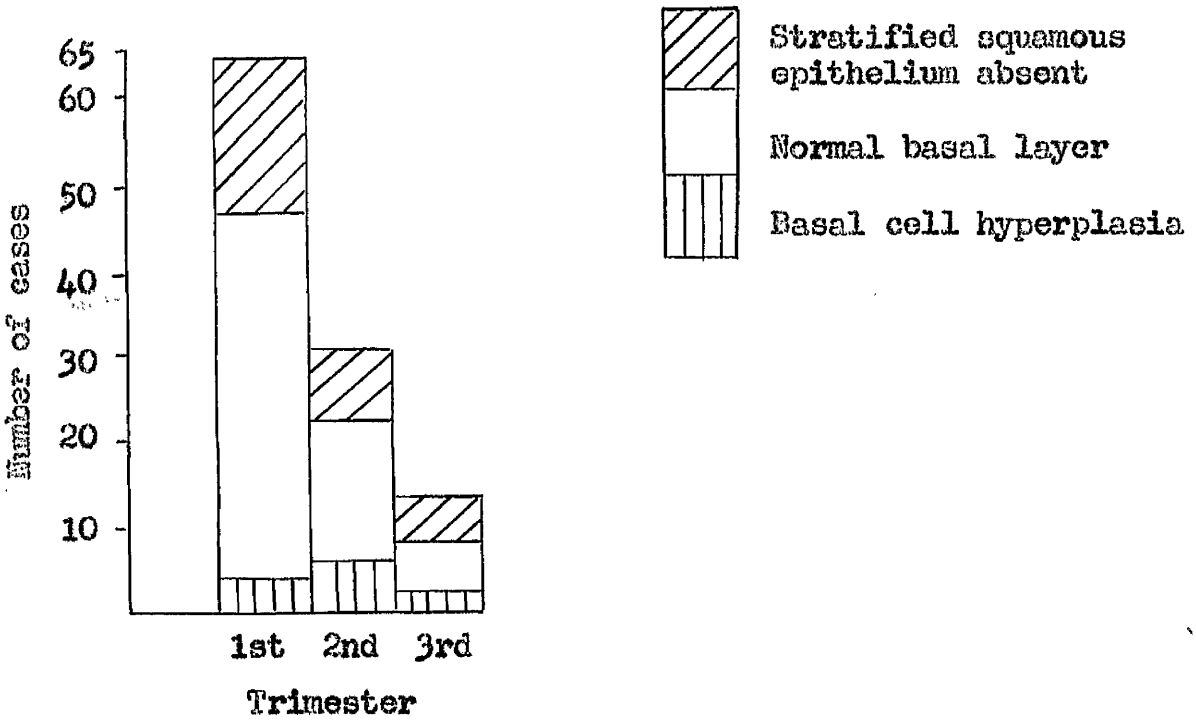

Figure 5. Pregnancy Series. Distribution of 14 cases of basal cell hyperplasia in relation to trimester of pregnancy.

Keratinization of the ectocervical epithelium

Comparative incidence

Excessive formation of keratin in the cornified zone of the stratified squamous epithelium was noted histologically in three of 79 pregnant and 21 of 78 non-pregnant women (Table XVIII). The difference in incidence of keratinization between the two groups is statistically highly significant.

TABLE XVIII

The incidence of keratinization of the ectocervical stratified squamous epithelium in 79 pregnant and 78 non-pregnant patients

Histological findings ectocervical epithelium	Pregnancy Series	Control Series
	No. of cases	No. of cases
Keratinization	3 (3.8)	21 (26.9)
Normal cornification	76 (96.2)	57 (73.1)
Total number studied	79	78

Figures in parentheses denote percentage incidence of keratinization and cornification in each group.

$$\chi^2 = 14.45$$
$$D.F. = 1$$
$$P < 0.001$$

Influence of utero-vaginal prolapse

Comparative statistical evaluation of the influence of utero-vaginal prolapse on the incidence of keratinization in the pregnant and non-pregnant series of women is not possible, as individual patients in each series were not matched for the factor of prolapse. In any event, such an effort to match pregnant and non-pregnant patients for degrees of prolapse would have been extremely difficult, in view of the rarity of major degrees of utero-vaginal prolapse complicating pregnancy.

Of the 21 non-pregnant patients who had keratinized ectocervical epithelium, 13 were suffering from major degrees of utero-vaginal prolapse. None of the three pregnant patients showing keratinization of the ectocervical epithelium had any significant degree of prolapse, but on the other hand, a major degree of utero-vaginal prolapse was not observed in any patient in the Pregnancy Series.

Age and parity

The age and parity distribution of three pregnant and 21 non-pregnant patients showing keratinization of the ectocervical stratified squamous epithelium are contained in Tables XIX and XX. In the non-pregnant group of patients, the majority of women were more than 35 years of age and had had one or more previous pregnancies. All three pregnant patients were multiparous and two patients were more than 35 years of age.

TABLE XIX

Keratinization of ectocervical stratified squamous epithelium in relation to age groupings of three pregnant and 21 non-pregnant patients

Age group	Pregnancy Series	Control Series
	No. of cases	No. of cases
35 years and under	1	8
Over 35 years	2	13
Total	3	21

TABLE XX

Keratinization of ectocervical stratified squamous epithelium in relation to parity of three pregnant and 21 non-pregnant patients

Parity	Pregnancy Series	Control Series
	No. of cases	No. of cases
Nulliparous	0	2
Multiparous	3	19
Total	3	21

ENDOCERVIX

Columnar epithelium of the endocervix was included in cervical tissue obtained from 105 pregnant and 109 non-pregnant women respectively in each series (Table XXI). The remaining five pregnant patients in whom endocervical epithelium was not available for study had been treated by removal of cervical polypi without simultaneous biopsy of the cervix. The individual non-pregnant patient excluded from investigation of the endocervical epithelium had had cervical biopsy which included only ectocervical stratified squamous epithelium.

TABLE XXI

The number of patients in the Pregnancy and Control Series in whom columnar epithelium of the endocervix was available for histological study

Pathological specimens of cervix	Pregnancy Series		Control Series	
	No. of cases	Percentage of total	No. of cases	Percentage of total
Endocervix included in pathological specimen	105	95.5	109	99.1
Endocervix not included in pathological specimen	5	4.5	1	0.9
Total	110	100.0	110	100.0

The squamo-columnar transitional zone was identified histologically in 79 pregnant and 77 non-pregnant patients. As previously described (Table XII), stratified squamous epithelium of the ectocervix was obtained only from 79 pregnant and 78 non-pregnant patients, and continuity of the epithelia of ectocervix and endocervix was vizualised in all 79 specimens from the pregnant group and all but one of the 78 specimens of the non-pregnant group.

Benign hyperplasia of columnar epithelium

Comparative incidence

Histological features of benign hyperplasia of the columnar epithelium of the endocervix were observed in 34 (32.4 per cent) of the 105 specimens from pregnant patients and 20 (18.3 per cent) of the 109 specimens from non-pregnant women (Table XXII). This difference in incidence between the pregnant group and non-pregnant group of patients is statistically significant.

The endocervical columnar epithelium studied included the surface epithelium of the cervical canal and the epithelium lining the cervical glands. The distribution of hyperplastic changes in these sites is illustrated in Table XXIII.

TABLE XXII

Comparative incidence of benign hyperplasia of columnar epithelium in the endocervix in 105 pregnant and 109 non-pregnant patients

Endocervical columnar epithelium	Pregnancy Series		Control Series	
	No. of cases	Percentage of total	No. of cases	Percentage of total
Benign hyperplasia	34	32.4	20	18.3
No hyperplasia	71	67.6	89	81.7
Total	105	100.0	109	100.0

$\chi^2 = 4.863$
D.F. = 1
$0.05 > P > 0.02$

TABLE XXIII

Distribution of benign hyperplasia of columnar epithelium in the endocervix of 34 pregnant and 20 non-pregnant patients

Columnar cell hyperplasia Site	Pregnancy Series	Control Series
	Number of cases	Number of cases
Surface epithelium only	1	1
Surface + gland epithelium	11	3
Gland epithelium only	22	16
Total	34	20

Hyperplastic features occurred more frequently in the cervical gland epithelium in both series of patients. However, the surface epithelium of the cervical canal was involved in a larger proportion of pregnant than of non-pregnant patients.

In order to make comparison of the incidence of benign hyperplasia in the pregnant and the non-pregnant patients more accurate, each patient in the Pregnancy Series was matched with a patient in the Control Series, who was of identical age, parity and marital status. From the two series, it was possible to match 104 patients, from whom endocervical epithelium was available for comparative study. Thirty-four (32.7 per cent) of the 104 pregnant and 20 (19.2 per cent) of the non-pregnant women showed histological features of benign hyperplasia of the endocervical columnar epithelium (Table XXIV). The difference in incidence of the lesion between the two matched groups is statistically significant.

TABLE XXIV

Comparative incidence of benign hyperplasia of columnar epithelium in the endocervix in 104 pregnant and 104 non-pregnant patients (Each pregnant patient matched for age, parity and marital status with a non-pregnant patient)

Endocervical columnar epithelium	Pregnancy Series		Control Series	
	No. of cases	Percentage of total	No. of cases	Percentage of total
Benign hyperplasia	34	32.7	20	19.2
No hyperplasia	70	67.3	84	80.8
Total	104	100.0	104	100.0

$\chi^2 = 4.227$
D.F. = 1
$0.05 > P > 0.02$

Trimester distribution of benign hyperplasia

The occurrence of benign hyperplasia of the endocervical columnar epithelium in relation to the trimesters of pregnancy was investigated in 105 pregnant patients and the results are shown in Table XXV. Although the incidence of benign hyperplasia varied appreciably in each trimester, and the highest incidence occurred during the third trimester, these variations are not statistically significant.

TABLE XXV

Incidence of benign hyperplasia of the endocervical columnar epithelium in 105 pregnant patients in relation to the trimesters of pregnancy

Trimester	Hyperplasia	No hyperplasia	Total No. pregnant patients
	No. of patients	No. of patients	
First	21 (33.3)	42	63
Second	8 (26.7)	22	30
Third	5 (41.7)	7	12
All trimesters	34 (32.4)	71	105

Figures in parentheses denote percentage incidence of hyperplasia in each trimester.

$$\chi^2 = 0.925$$
$$D.F. = 2$$
$$0.70 > P > 0.50$$

Influence of age

The actual effect that age might have on the incidence of benign hyperplasia was investigated in the pregnant and non-pregnant women. The results in both series of patients were analysed according to age groups (Tables XXVI and XXVII). These results are illustrated graphically in Figure 6, examination of which suggests considerable variation in incidence of the lesion between pregnant and non-pregnant patients in at least one age group, namely those patients aged 31 to 35 years. The small numbers of cases occurring in most age groups, particularly those in Control Series patients, were judged to be insufficient to justify valid statistical comparison.

TABLE XXVI

Incidence of benign hyperplasia of the endocervical columnar epithelium in 105 pregnant patients in relation to age groups

Histological findings in Pregnancy Series	Number of patients					Total No.of patients
	Age groups					
	19-25	26-30	31-35	36-40	41-46	
Hyperplasia	8 (34.8)	5 (22.7)	13 (56.5)	5 (22.7)	3 (20)	34 (32.4)
No hyperplasia	15	17	10	17	12	71
Total	23	22	23	22	15	105

Figures in parentheses denote percentage incidence of hyperplasia in each group.

TABLE XXVII

Incidence of benign hyperplasia of the endocervical columnar epithelium in 109 non-pregnant patients in relation to age groups

Histological findings in Control Series	Number of patients					Total No. of patients
	Age groups					
	19-25	26-30	31-35	36-40	41-46	
Hyperplasia	5 (21.7)	3 (12.5)	4 (17.4)	6 (25)	2 (13.3)	20 (18.3
No hyperplasia	18	21	19	18	13	89
Total	23	24	23	24	15	109

Figures in parentheses denote percentage incidence of hyperplasia in each group.

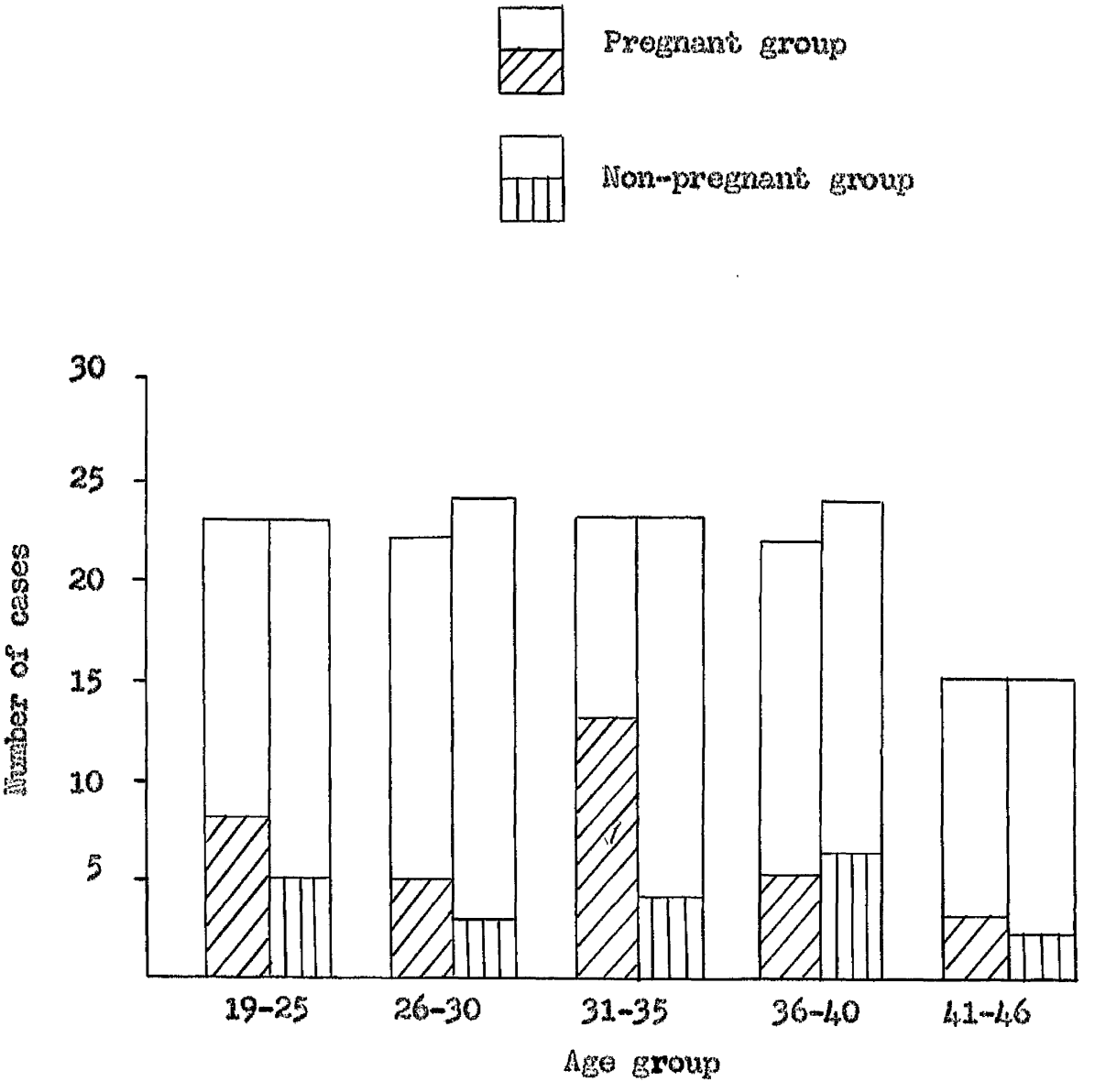

Figure 6. Comparative incidence of benign hyperplasia of the endocervical columnar epithelium in 105 pregnant and 109 non-pregnant patients in relation to age group. (Shaded areas denote benign hyperplasia).

It was considered that the most relevant statistical information obtainable in the present series of cases would result from evaluation of the incidence of benign hyperplasia in relation to wider age groups, involving larger samples. Accordingly, the results were analysed in both series in relation to two larger age groups consisting of patients aged 30 years and under, and patients over 30 years of age.

Preliminary investigation of the Pregnancy Series patients revealed no significant variation in the incidence of hyperplasia in patients under or over the age of 30 years (Table XXVIII).

TABLE XXVIII

Incidence of benign hyperplasia of the endocervical columnar epithelium in 105 pregnant patients in relation to the higher and lower age groups

Histological findings in Pregnancy Series	Number of patients		Total No. of patients
	Age groups		
	30 years and under	Over 30 yrs.	
Hyperplasia	13 (29)	21 (35)	34(32.4)
No hyperplasia	32	39	71
Total	45	60	105

Figures in parentheses denote percentage incidence of hyperplasia in each group.

$$\chi^2 = 0.204$$
$$D.F. = 1$$
$$0.70 > P > 0.50$$

Similarly, there was no significant difference in the distribution of hyperplasia among patients in the Control Series in relation to age (Table XXIX).

TABLE XXIX

Incidence of benign hyperplasia of the endocervical columnar epithelium in 109 non-pregnant patients in relation to the higher and lower age groups

Histological findings in Control Series	Number of patients		Total No. of patients
	Age groups		
	30 years and under	Over 30 years	
Hyperplasia	8 (17)	12 (19.4)	20(18.3)
No hyperplasia	39	50	89
Total	47	62	109

Figures in parentheses denote percentage incidence of hyperplasia in each group.

$\chi^2 = 0.0038$
D.F. = 1
$0.98 > P > 0.95$

The results in Tables XXVIII and XXIX are incorporated graphically in Figure 7 for comparative evaluation. Despite the appreciable differences in incidence of hyperplasia between pregnant and non-pregnant women in the same age groups, these variations are not statistically significant (Tables XXX and XXXI).

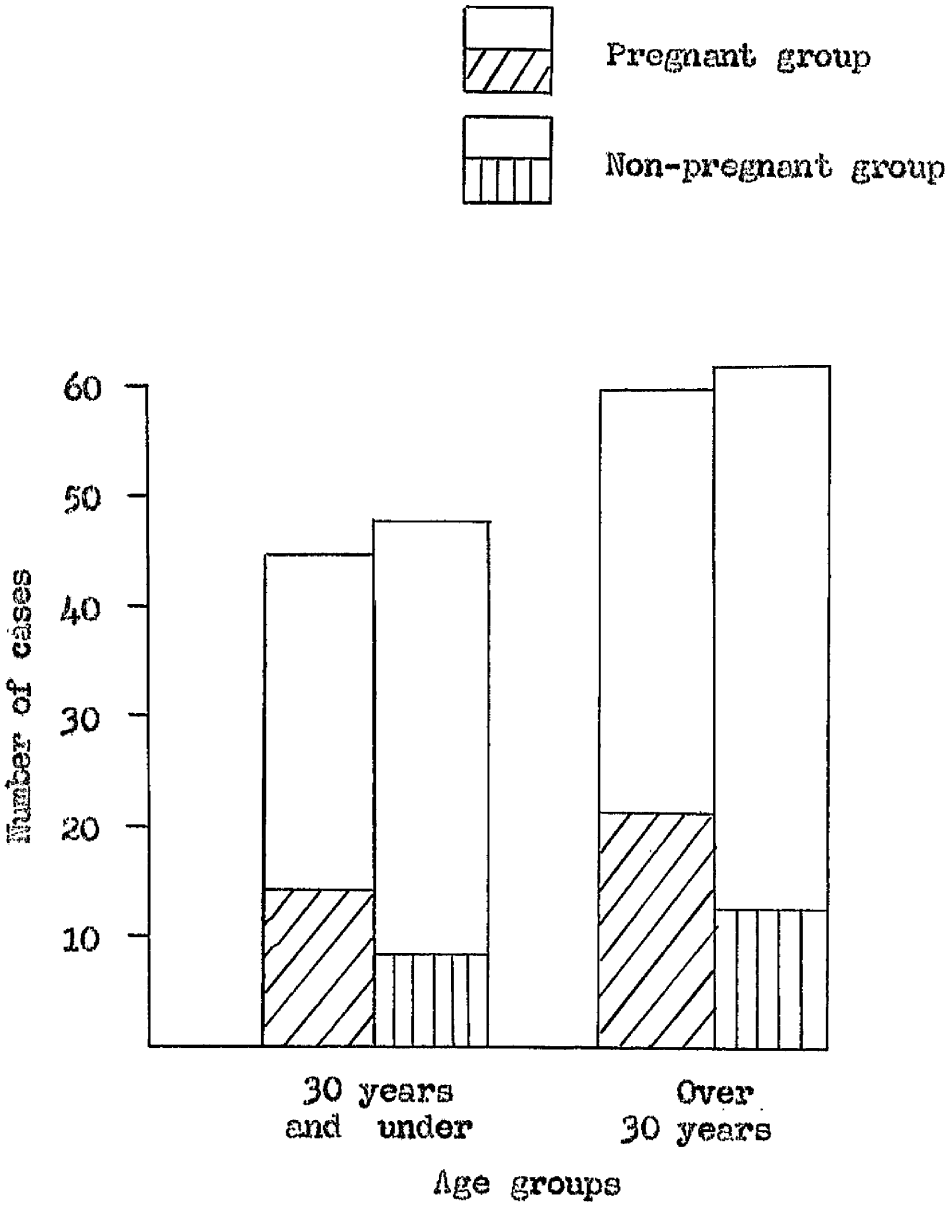

Figure 7. Comparative incidence of benign hyperplasia of the endocervical columnar epithelium in 105 pregnant and 109 non-pregnant patients in relation to the higher and lower age groups. (Shaded areas denote benign hyperplasia).

TABLE XXX

Comparative incidence of benign hyperplasia of the endocervical columnar epithelium in 45 pregnant and 47 non-pregnant patients aged 30 years and under

Histological findings	Group aged 30 years and under	
	Pregnancy Series	Control Series
	Number of patients	Number of patients
Hyperplasia	13 (29)	8 (17)
No hyperplasia	32	39
Total	45	47

Figures in parentheses denote percentage incidence of hyperplasia in each group.

$\chi^2 = 1.227$
D.F. = 1
$0.30 > P > 0.20$

TABLE XXXI

Comparative incidence of benign hyperplasia of the endocervical columnar epithelium in 60 pregnant and 62 non-pregnant patients over 30 years of age

Histological findings	Group aged over 30 years	
	Pregnancy Series	Control Series
	Number of patients	Number of patients
Hyperplasia	21 (35)	12 (19.4)
No hyperplasia	39	50
Total	60	62

Figures in parentheses denote percentage incidence of hyperplasia in each group.

$\chi^2 = 3.031$
D.F. = 1
$0.10 > P > 0.05$

Influence of parity

The relationship of parity to the incidence of benign hyperplasia was investigated by analysing the results in both series in groups of patients who had had varying numbers of previous viable and non-viable pregnancies, and in women who had had no previous pregnancy. In the Pregnancy Series benign hyperplasia occurred in patients in all parity groups and also in primigravidae, the highest incidence being found in women who had had one to six previous pregnancies (Table XXXII).

TABLE XXXII

Incidence of benign hyperplasia of the endocervical columnar epithelium in 105 pregnant patients in relation to the total number of previous viable and non-viable pregnancies

Histological findings in Pregnancy Series	Number of patients				Total No. of patients
	Previous pregnancies*				
	0	1-3	4-6	>6	
Hyperplasia	6(30)	16(40)	9(40.9)	3(13)	34(32.4)
No hyperplasia	14	24	13	20	71
Total	20	40	22	23	105

*Includes viable and non-viable pregnancies.

Figures in parentheses denote percentage incidence of hyperplasia in each group.

In the Control Series, benign hyperplasia was not found in the group of 20 patients who had had no previous pregnancy, while the distribution of hyperplasia in the remaining patients was fairly

uniform in relation to different parity groups (Table XXXIII).

TABLE XXXIII

Incidence of benign hyperplasia of the endocervical columnar epithelium in 109 non-pregnant patients in relation to the total number of previous viable and non-viable pregnancies

Histological findings in Control Series	Number of patients				Total No. of patients
	Previous pregnancies*				
	0	1-3	4-6	>6	
Hyperplasia	-	9(20.9)	5(21.7	6(26.1)	20(18.3)
No hyperplasia	20	34	18	17	89
Total	20	43	23	23	109

*Includes viable and non-viable pregnancies.

Figures in parentheses denote percentage incidence of hyperplasia in each group.

The results in Tables XXXII and XXXIII are represented graphically in Figure 8 for comparative study. Comparison of the results in identical groups of each series of patients suggests that the greatest difference in incidence of hyperplasia occurs in women who have had no previous pregnancy. Subsequent pregnancies up to the sixth, appear to be associated with a consistently higher incidence of the lesion in gravid patients than in non-pregnant women of identical parity groups. However, the figures in individual parity groups are too small for statistical comparison.

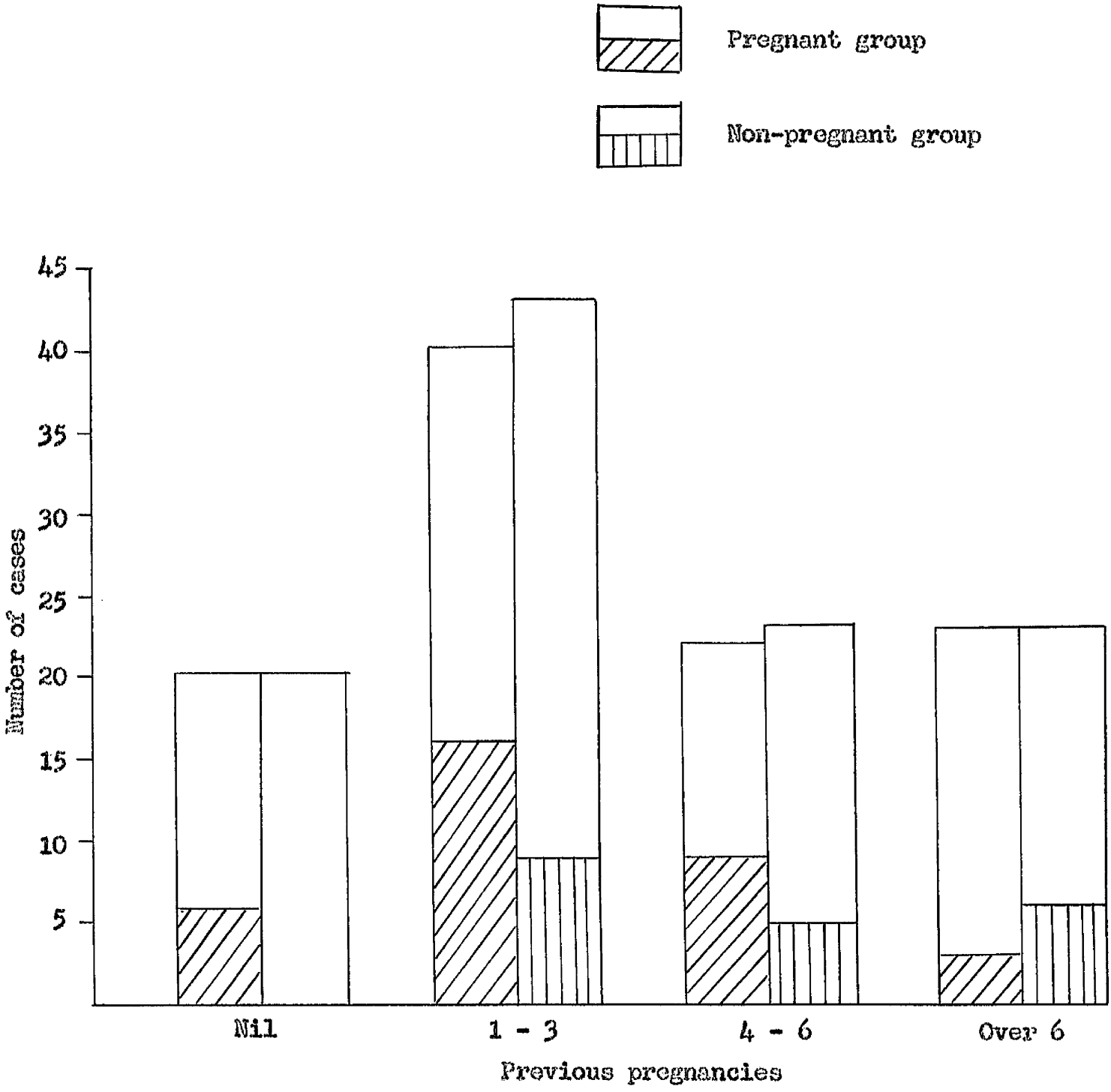

Figure 8. Comparative incidence of benign hyperplasia of the endocervical columnar epithelium in 105 pregnant and 109 non-pregnant patients in relation to the total number of previous viable and non-viable pregnancies. (Shaded areas denote benign hyperplasia).

Accordingly, in order to achieve statistical interpretation of the results available, the Pregnancy and Control Series of patients were each divided into two groups, consisting of women who had had three or less previous pregnancies and women who had had more than three previous pregnancies. Table XXXIV shows a greater incidence of hyperplasia in the lower parity group than in the higher parity group among the 105 pregnant patients, but this difference in incidence between the two groups is not statistically significant.

TABLE XXXIV

Distribution of benign hyperplasia of the endocervical columnar epithelium in 105 pregnant patients in relation to higher and lower parity groups

Histological findings in Pregnancy Series	Number of patients: Previous pregnancies* 0-3	Number of patients: Previous pregnancies* More than 3	Total No. of patients
Hyperplasia	22(36.7)	12(26.7)	34(32.4)
No hyperplasia	38	33	71
Total	60	45	105

*Includes viable and non-viable pregnancies.

Figures in parenthesis denote percentage incidence in each group.

$$\chi^2 = 0.762$$
$$D.F. = 1$$
$$0.50 > P > 0.30$$

The corresponding results in the study of 109 non-pregnant patients also show no significant variation in incidence of hyperplasia in the two parity groups (Table XXXV).

TABLE XXXV

Distribution of benign hyperplasia of the endocervical columnar epithelium in 109 non-pregnant patients in relation to higher and lower parity groups

Histological findings in Control Series	Number of patients		Total No. of patients
	Previous pregnancies*		
	0-3	More than 3	
Hyperplasia	9(14.3)	11(23.9)	20(18.3)
No hyperplasia	54	35	89
Total	63	46	109

*Includes viable and non-viable pregnancies.

Figures in parentheses denote percentage incidence in each group.

$$\chi^2 = 1.065$$
$$D.F. = 1$$
$$0.50 > P > 0.30$$

Figure 9 affords a graphic representation of the results contained in Tables XXXIV and XXXV and illustrates the preponderant incidence of benign hyperplasia in pregnant compared with non-pregnant women in relation to both the lower and higher parity groups.

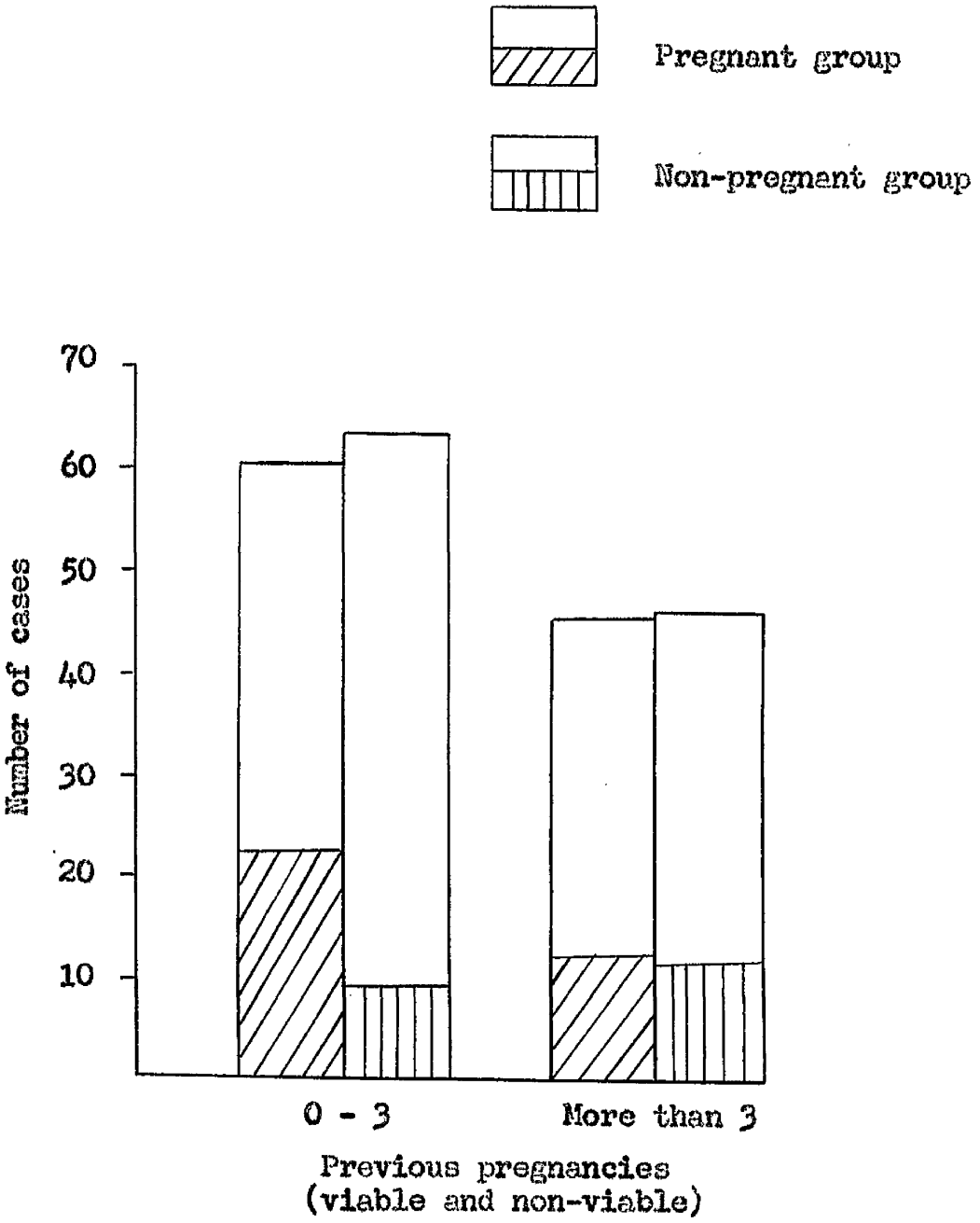

Figure 9. Comparative incidence of benign hyperplasia of the endocervical columnar epithelium in 105 pregnant and 109 non-pregnant patients in relation to the higher and lower parity groups. (Shaded areas denote hyperplasia).

There is a significantly higher incidence of hyperplasia in the 60 pregnant patients who have three or fewer previous pregnancies than in the 63 non-pregnant patients of identical parities (Table XXXVI).

TABLE XXXVI

Comparative incidence of benign hyperplasia of the endocervical columnar epithelium in 60 pregnant and 63 non-pregnant patients who had had three or less previous pregnancies

Histological findings	Group having 0-3 previous pregnancies	
	Pregnancy Series	Control Series
	Number of patients	Number of patients
Hyperplasia	22 (36.7)	9 (14.3)
No hyperplasia	38	54
Total	60	63

Figures in parentheses denote percentage incidence of hyperplasia in each group.

$$\chi^2 = 7.023$$
$$D.F. = 1$$
$$0.01 > P > 0.001$$

The incidence of hyperplasia in the remaining 45 pregnant patients who have more than three previous pregnancies does not differ significantly from that in the 46 non-pregnant patients in the same parity group (Table XXXVII).

TABLE XXXVII

Comparative incidence of benign hyperplasia of the endocervical columnar epithelium in 45 pregnant and 46 non-pregnant patients who had had more than three previous pregnancies

Histological findings	Group having ≥ 3 previous pregnancies	
	Pregnancy Series	Control Series
	Number of patients	Number of patients
Hyperplasia	12 (26.7)	11 (23.9)
No hyperplasia	33	35
Total	45	46

Figures in parentheses denote percentage incidence of hyperplasia in each group.

$\chi^2 = 0.00372$
D.F. = 1
$0.98 > P > 0.95$

Associated chronic inflammatory reaction

The possible effect of chronic inflammatory changes in the subjacent cervical stroma in relation to the occurrence of benign hyperplasia of the endocervical columnar epithelium was investigated. The relevant histological findings in the cervical stroma were noted in the 34 pregnant and 20 non-pregnant patients in whom benign hyperplasia was found (Table XXXVIII). The incidence of associated chronic inflammatory changes in the pregnant patients does not differ significantly from that in the non-pregnant patients.

TABLE XXXVIII

The incidence of associated chronic inflammatory changes in the cervical stroma of 34 pregnant and 20 non-pregnant patients showing benign hyperplasia of the endocervical columnar epithelium

Histological findings in cervical stroma	Benign hyperplasia	
	Pregnant Group	Non-pregnant group
	Number of patients	Number of patients
Chronic inflammation	27 (79.4)	20 (100)
No inflammatory change	7	-
Total	34	20

Figures in parentheses denote percentage incidence of chronic inflammatory changes in each group.

$$\chi^2 = 3.082$$
$$D.F. = 1$$
$$0.10 > P > 0.05$$

Squamous metaplasia

Comparative incidence

Squamous metaplasia was noted in the cervical canal of 36 (34.3 per cent) of 105 pregnant patients and in 37 (33.9 per cent) of 109 non-pregnant patients (Table XXXIX). The incidence of squamous metaplasia in the pregnant group does not differ significantly from the incidence of squamous metaplasia in the non-pregnant group.

TABLE XXXIX

Comparative overall incidence of squamous metaplasia in the cervical canal of 105 pregnant and 109 non-pregnant patients

Endocervical epithelium histological findings	Pregnancy Series		Control Series	
	No. of cases	Percentage of total	No. of cases	Percentage of total
Squamous metaplasia	36	34.3	37	33.9
No squamous metaplasia	69	65.7	72	66.1
Total	105	100.0	109	100.0

$\chi^2 = 0.00839$
D.F. = 1
$0.95 > P > 0.90$

Further evidence to support these results was obtained by comparing patients in the Pregnancy Series with those in the Control Series who were of identical age, parity and marital status. Table XL shows the incidence of squamous

metaplasia in 104 pregnant and 104 non-pregnant patients matched for age, parity and marital status. The incidence of squamous metaplasia is identical in both groups of patients.

TABLE XL

Comparative incidence of squamous metaplasia in 104 pregnant and 104 non-pregnant patients. (Each pregnant patient matched for age, parity and marital status with a non-pregnant patient)

Endocervical epithelium Histological findings	Pregnancy Series		Control Series	
	No. of cases	Percentage of total	No. of cases	Percentage of total
Squamous metaplasia	36	34.6	36	34.6
No squamous metaplasia	68	65.4	68	65.4
Total	104	100.0	104	100.0

$\chi^2 = 0$
D.F. = 1
P = 1

Trimester distribution of squamous metaplasia

Table XLI shows the distribution of squamous metaplasia among the 105 pregnant patients in relation to each trimester of pregnancy. The highest incidence of the lesion is found in the

second trimester, but the variation in incidence of squamous metaplasia among patients in each trimester is not statistically significant.

TABLE XLI

Incidence of squamous metaplasia in 105 pregnant women in relation to the trimesters of pregnancy

Trimester	Squamous metaplasia	No squamous metaplasia	Total No. of pregnant patients
	No. of patients	No. of patients	
First	21 (33.3)	42	63
Second	12 (40)	18	30
Third	3 (25)	9	12
Total	36 (34.3)	69	105

Figures in parentheses denote percentage incidence of squamous metaplasia in each trimester.

$\chi^2 = 0.902$
D.F. = 2
$0.70 > P > 0.50$

Influence of age

Although initial assessment of the results showed that the overall incidence of squamous metaplasia in the Pregnancy Series did not differ significantly from the overall incidence in the Control Series, it was considered desirable to submit the

results to further analysis in order to evaluate the actual influence of age on the incidence of squamous metaplasia in each group of pregnant and non-pregnant women.

Tables XLII and XLIII show the incidence of squamous metaplasia of the endocervix related to age groups of patients in the Pregnancy and Control Series respectively.

TABLE XLII

The incidence of squamous metaplasia in 105 pregnant patients in relation to age groups

Histological findings in Pregnancy Series	Number of patients					Total No. of patients
	Age groups					
	19-25	26-30	31-35	36-40	41-46	
Squamous metaplasia	6 (26)	10 (45.6)	11 (47.8)	4 (18.2)	5 (33.3)	36 (34.3)
No squamous metaplasia	17	12	12	18	10	69
Total	23	22	23	22	15	105

Figures in parentheses denote percentage incidence of squamous metaplasia in each group.

TABLE XLIII

The incidence of squamous metaplasia in 109 non-pregnant patients in relation to age groups

Histological findings in Control Series	Number of patients					Total No. of patients
	Age groups					
	19-25	26-30	31-35	36-40	41-46	
Squamous metaplasia	5 (21.7)	6 (25.)	7 (30.4)	12 (50.)	7 (46.7)	37 (33.9)
No squamous metaplasia	18	18	16	12	8	72
Total	23	24	23	24	15	109

Figures in parentheses denote percentage incidence of squamous metaplasia in each group.

The combined results in Tables XLII and XLIII are presented graphically in Figure 10 for comparison. The incidence of squamous metaplasia in the pregnant group of women is highest in patients in the age groups 26-30 and 31-35 years. A different pattern of age incidence of squamous metaplasia is seen in the non-pregnant patients, in whom the incidence of the lesion shows a progressive rise with increasing age, the maximum incidence occurring in women aged 36-40 and 41-46 years. The figures in individual age groups in both series are too small to justify statistical comparison.

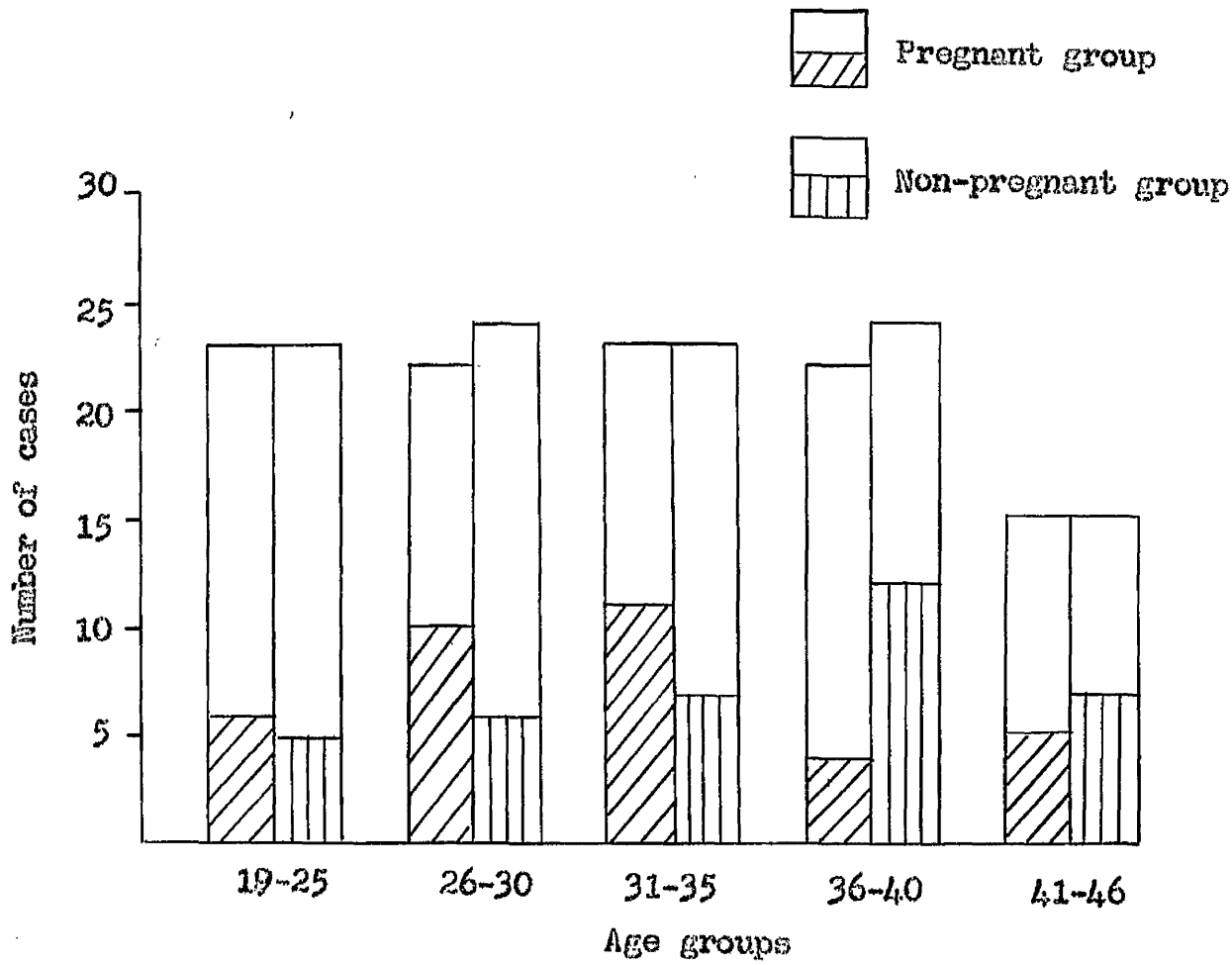

Figure 10. Comparative incidence of squamous metaplasia in 105 pregnant and 109 non-pregnant patients in relation to age groups. (Shaded areas denote squamous metaplasia).

Accordingly, the results in each series were analysed in relation to the larger age groups consisting of patients aged 30 years and under, and patients over 30 years of age, in order to obtain statistical comparison.

In the pregnant group of patients the incidence of squamous metaplasia in women aged 30 years or less does not differ significantly from the incidence of the lesion in women over 30 years of age (Table XLIV). Similarly, in the non-pregnant group, the difference in incidence of squamous metaplasia between the higher and lower age groups is not statistically significant, although the probability value in this instance is only slightly greater than 0.05 (Table XLV).

TABLE XLIV

Incidence of squamous metaplasia in 105 pregnant women in relation to higher and lower age groups

Histological findings in Pregnancy Series	Number of patients		Total No. of patients
	Age groups		
	30 yrs. and under	Over 30 yrs.	
Squamous metaplasia	16 (35.6)	20 (33.3)	36(34.3)
No squamous metaplasia	29	40	69
Total	45	60	105

Figures in parentheses denote percentage incidence of squamous metaplasia in each group.

$\chi^2 = 0.000804$
D.F. = 1
$0.98 > P > 0.95$

TABLE XLV

Incidence of squamous metaplasia in 109 non-pregnant women in relation to higher and lower age groups

Histological findings in Control Series	Number of patients		Total No. of patients
	Age groups		
	30 years and under	Over 30 years	
Squamous metaplasia	11 (23.4)	26 (41.9)	37(33.9)
No squamous metaplasia	36	36	72
Total	47	62	109

Figures in parentheses denote percentage incidence of squamous metaplasia in each group.

$$\chi^2 = 3.309$$
$$D.F. = 1$$
$$0.10 > P > 0.05$$

Comparison of the combined results in Tables XLIV and XLV, presented graphically in Figure 11, shows that the incidence of squamous metaplasia is higher in pregnant women 30 years of age and under, than in non-pregnant women in the same age group. On the other hand, the incidence of squamous metaplasia in patients over 30 years of age is lower in pregnant women than in the non-pregnant. Statistical evaluation of these results reveals that the differences in incidence between pregnant and non-pregnant women in the same age groups is not significant (Tables XLVI and XLVII).

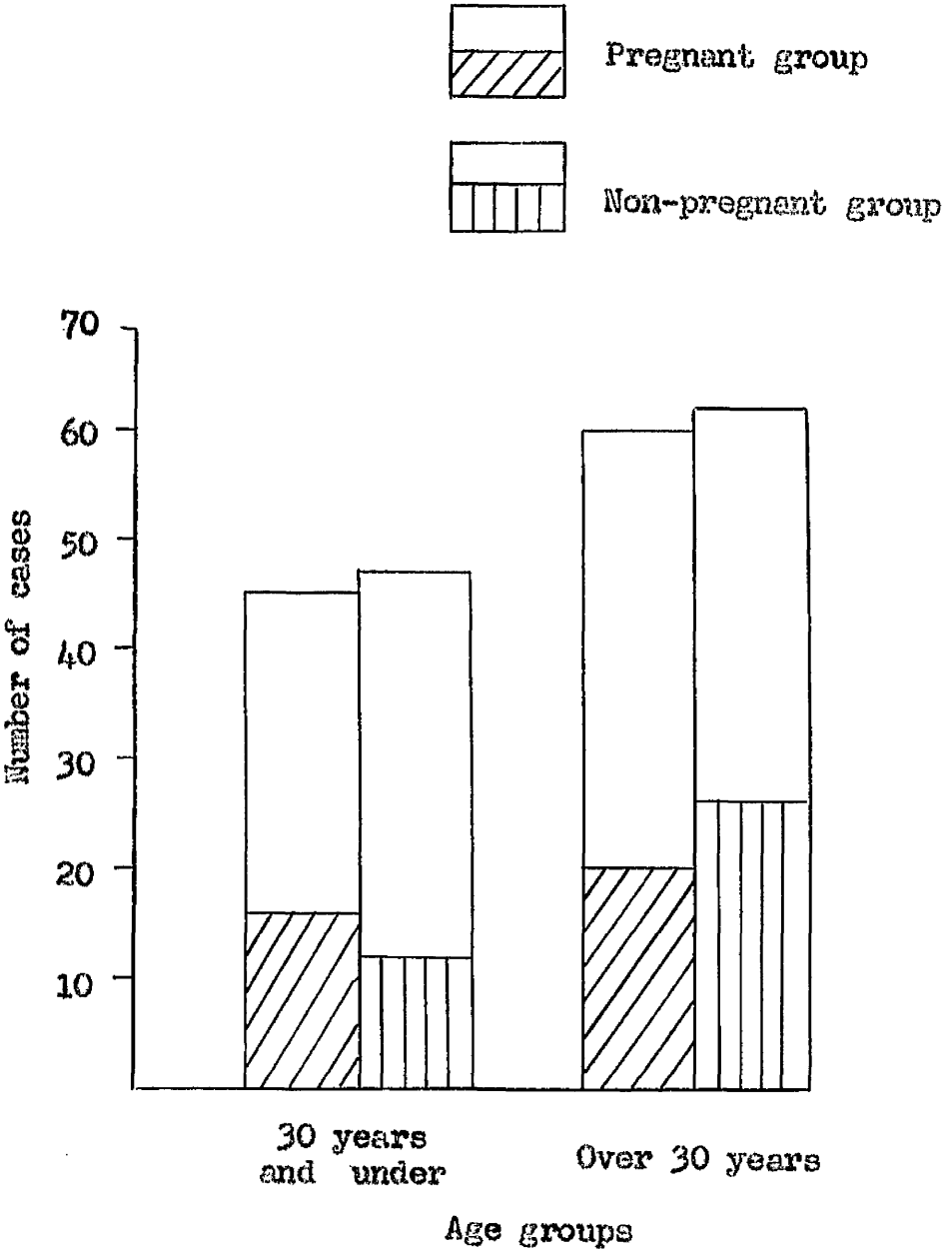

Figure 11. Comparative incidence of squamous metaplasia in 105 pregnant and 109 non-pregnant patients in relation to the higher and lower age groups. (Shaded areas denote squamous metaplasia).

TABLE XLVI

Comparative incidence of squamous metaplasia in 45 pregnant and 47 non-pregnant patients aged 30 years and under

Histological findings	Group aged 30 years and under	
	Pregnancy Series	Control Series
	No. of patients	No. of patients
Squamous metaplasia	16 (35.6)	11 (23.4)
No squamous metaplasia	29	36
Total	45	47

Figures in parentheses denote percentage incidence of squamous metaplasia in each group.

$\chi^2 = 1.104$
D.F. = 1
$0.30 > P > 0.20$

TABLE XLVII

Comparative incidence of squamous metaplasia in 60 pregnant and 62 non-pregnant patients over 30 years of age

Histological findings	Group aged over 30 years	
	Pregnancy Series	Control Series
	No. of patients	No. of patients
Squamous metaplasia	20 (33.3)	26 (41.9)
No squamous metaplasia	40	36
Total	60	62

Figures in parentheses denote percentage incidence of squamous metaplasia in each group.

$\chi^2 = 0.6294$
D.F. = 1
$0.50 > P > 0.30$

Influence of parity

The relationship of parity to the incidence of squamous metaplasia in pregnant and non-pregnant women was investigated. Table XLVIII shows the distribution of squamous metaplasia in 105 pregnant patients in relation to the numbers of previous viable and non-viable pregnancies. The lesion is found in pregnant

TABLE XLVIII

The incidence of squamous metaplasia in 105 pregnant patients in relation to the numbers of previous viable and non-viable pregnancies

Histological findings in Pregnancy Series	Number of patients				Total No. of patients
	Previous pregnancies*				
	0	1-3	4-6	>6	
Squamous metaplasia	6(30)	16(40)	8(36.4)	6(26)	36(34.3)
No squamous metaplasia	14	24	14	17	69
Total	20	40	22	23	105

*Includes viable and non-viable pregnancies.

Figures in parentheses denote percentage incidence of squamous metaplasia in each group.

patients in all parity groups including primigravidae and the highest incidence of squamous metaplasia occurs in those who have had 1-3 previous pregnancies. The corresponding results in 109 non-pregnant patients show a different pattern of incidence in

relation to parity, a progressive rise in incidence of squamous metaplasia occurring as parity increases (Table XLIX). Thus, the highest incidence of squamous metaplasia in relation to parity in non-pregnant patients is found in women who have had more than six previous pregnancies. The combined results in Tables XLVIII and XLIX are presented graphically in Figure 12.

TABLE XLIX

The incidence of squamous metaplasia in 109 non-pregnant patients in relation to the numbers of previous viable and non-viable pregnancies

Histological findings in Control Series	Number of patients				Total No.of patients
	Previous pregnancies*				
	0	1-3	4-6	>6	
Squamous metaplasia	4(20)	11(25.6)	9(39.1)	13 (56.6)	37(33.9)
No squamous metaplasia	16	32	14	10	72
Total	20	43	23	23	109

*Includes viable and non-viable pregnancies.

Figures in parentheses denote percentage incidence of squamous metaplasia in each group.

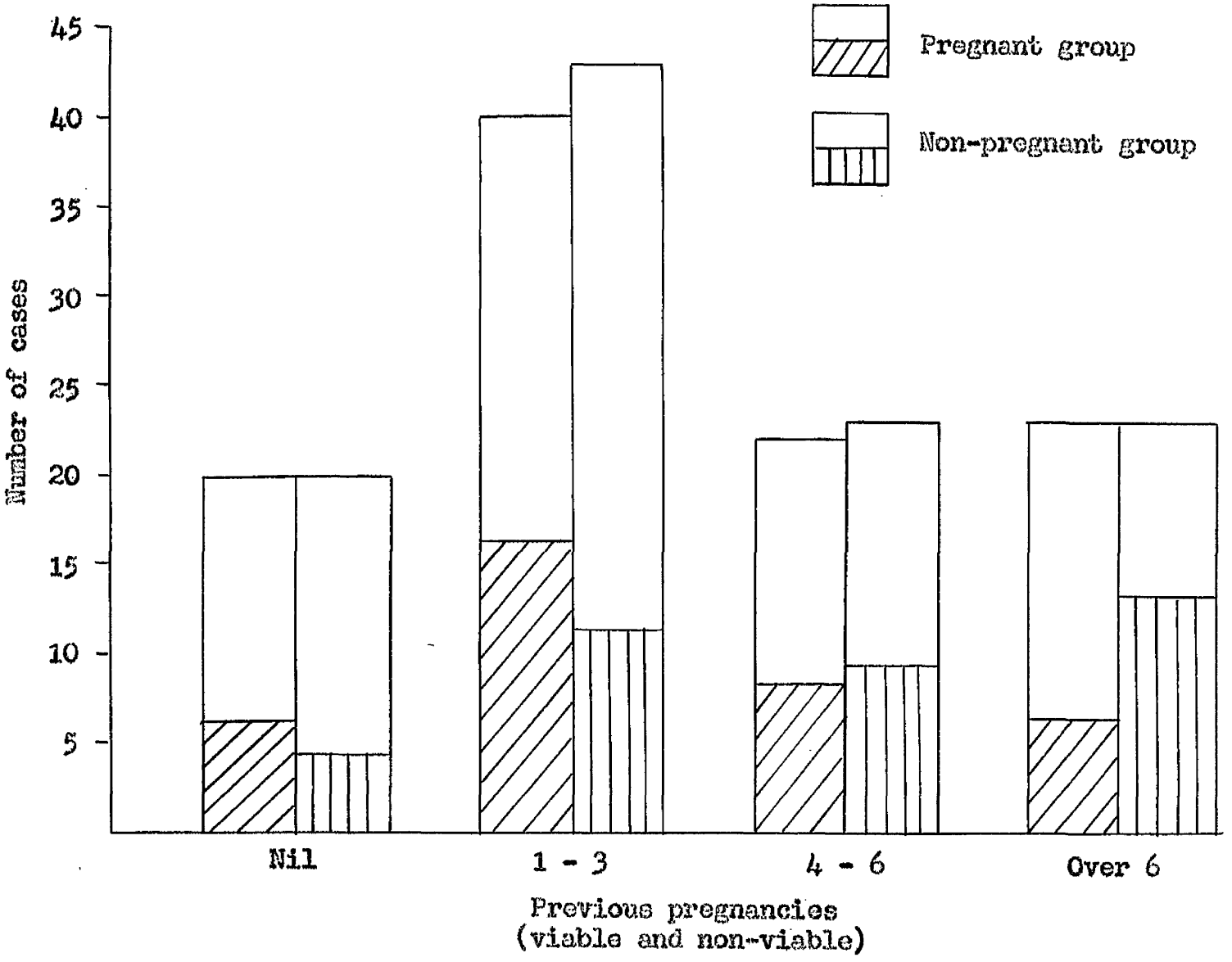

Figure 12. Comparative incidence of squamous metaplasia in the endocervix of 105 pregnant and 109 non-pregnant patients in relation to the total number of previous viable and non-viable pregnancies. (Shaded areas denote squamous metaplasia).

As the figures in individual parity groups were too small for valid statistical comparison, the patients in each series were divided into two large parity groups consisting of women who had had three or less previous pregnancies and women who had had more than three previous pregnancies. Analysis of the Pregnancy Series by this method reveals a slightly greater incidence of squamous metaplasia in the lower parity group than in the higher parity class of patients, but the difference in incidence between the two groups is not statistically significant (Table L).

TABLE L

Distribution of squamous metaplasia in 105 pregnant patients in relation to the higher and lower parity groups

Histological findings in Pregnancy Series	Number of patients		Total No.of patients
	Previous pregnancies*		
	0-3	>3	
Squamous metaplasia	22 (36.7)	14 (31.1)	36(34.3)
No squamous metaplasia	38	31	69
Total	60	45	105

*Including viable and non-viable pregnancies.

Figures in parentheses denote percentage incidence of squamous metaplasia in each group.

$$\chi^2 = 0.1488$$
$$D.F. = 1$$
$$0.70 > P > 0.50$$

Statistical evaluation of the corresponding results in the Control Series, however, reveals that the incidence of squamous metaplasia in non-pregnant women who have had more than three previous pregnancies is significantly higher than in non-pregnant women of lower parity (Table LI).

TABLE LI

Distribution of squamous metaplasia in 109 non-pregnant patients in relation to the higher and lower parity groups

Histological findings in Control Series	Number of patients		Total No. of patients
	Previous pregnancies*		
	0-3	>3	
Squamous metaplasia	15 (23.8)	22 (47.8)	37(33.9)
No squamous metaplasia	48	24	72
Total	63	46	109

*Including viable and non-viable pregnancies.

Figures in parentheses denote percentage incidence of squamous metaplasia in each group.

$$\chi^2 = 5.809$$
$$D.F. = 1$$
$$0.02 > P > 0.01$$

Comparison of the broad parity distribution of squamous metaplasia in the Pregnancy and Control Series of patients is illustrated in Figure 13, which constitutes a graphic presentation of the results in Tables L and LI. Statistically the incidence

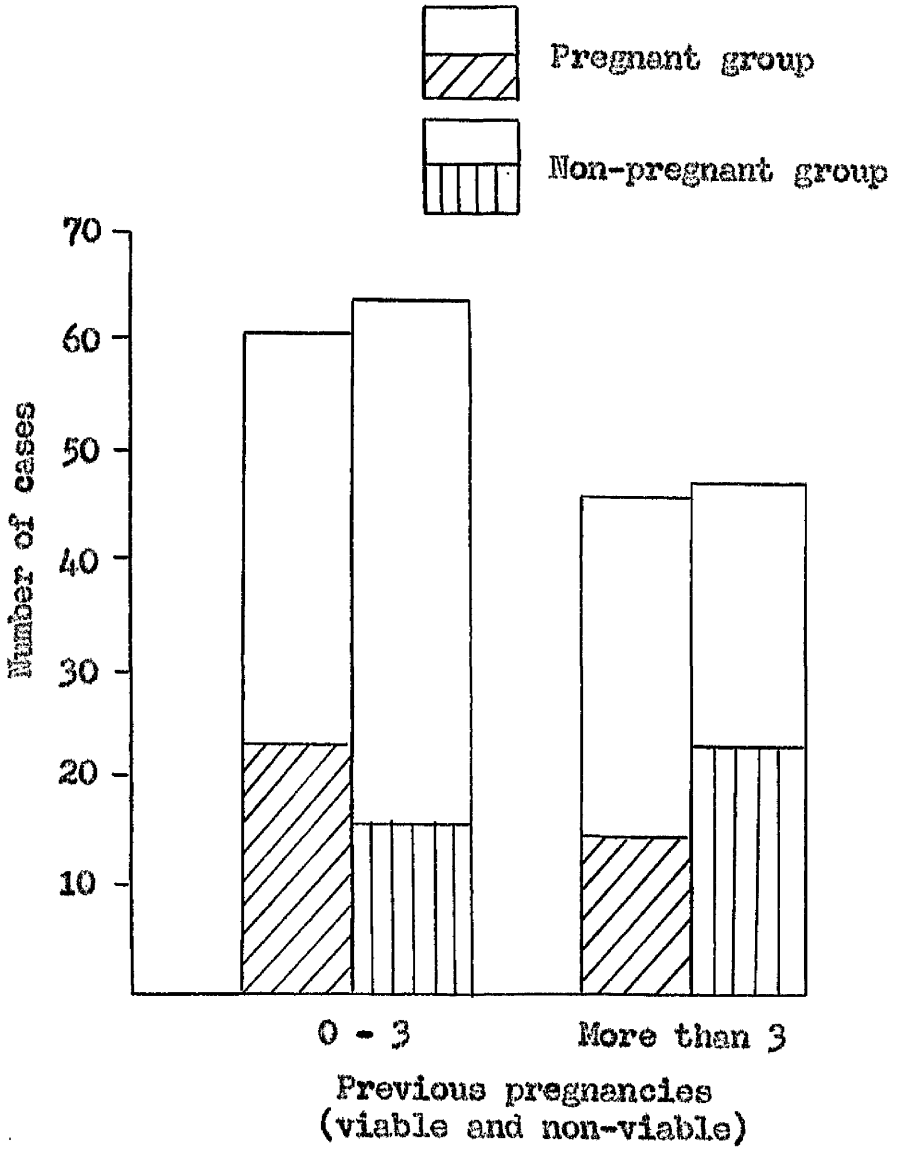

Figure 13. Comparative incidence of squamous metaplasia in 105 pregnant and 109 non-pregnant women in relation to the higher and lower parity groups. (Shaded areas denote squamous metaplasia).

of squamous metaplasia in pregnant patients who have had three or less previous pregnancies does not differ significantly from that in non-pregnant patients of identical parities (Table LII).

TABLE LII

Comparative incidence of squamous metaplasia in 60 pregnant and 63 non-pregnant patients who had had 3 or less previous pregnancies

Histological findings	Group having 0-3 previous pregnancies	
	Pregnancy Series	Control Series
	No. of patients	No. of patients
Squamous metaplasia	22 (36.7)	15 (23.8)
No squamous metaplasia	38	48
Total	60	63

Figures in parentheses denote percentage incidence of squamous metaplasia in each group.

$$\chi^2 = 1.843$$
$$D.F. = 1$$
$$0.20 > P > 0.10$$

Similarly, no significant difference in incidence of squamous metaplasia is found between pregnant and non-pregnant patients in the higher parity group (Table LIII).

TABLE LIII

Comparative incidence of squamous metaplasia in 45 pregnant and 46 non-pregnant patients who had had more than 3 previous pregnancies

Histological findings	Group having >3 previous pregnancies	
	Pregnancy Series	Control Series
	No. of patients	No. of patients
Squamous metaplasia	14 (31.1)	22 (47.8)
No squamous metaplasia	31	24
Total	45	46

Figures in parentheses denote percentage incidence of squamous metaplasia in each group.

$\chi^2 = 2.004$
D.F. = 1
$0.20 > P > 0.10$

Anatomical sites of squamous metaplasia

Study of the anatomical sites of the cervical canal involved by squamous metaplasia in 36 pregnant and 37 non-pregnant patients was carried out, and the results are shown in Table LIV, and graphically presented in Figure 14. The histological observations are divided into three groups relating to the particular sites of involvement by squamous metaplasia:-

(i) Limited to the squamo-columnar transitional zone.

(ii) Limited to the endocervix.

(iii) Involving both transitional zone and endocervix simultaneously.

The anatomical distribution of the lesion in the cervices of the pregnant patients shows an almost identical pattern to that in the non-pregnant patient.

TABLE LIV

The comparative distribution of the anatomical sites in the cervical canal involved by squamous metaplasia in 36 pregnant and 37 non-pregnant women

Sites involved by squamous metaplasia	Pregnant		Non-pregnant	
	No. of patients	Percentage of total	No. of patients	Percentage of total
Transitional zone only	10	27.8	12	32.4
Transitional zone and endocervix	12	33.3	12	32.4
Endocervix only	14	38.9	13	35.2
Total	36	100.0	37	100.0

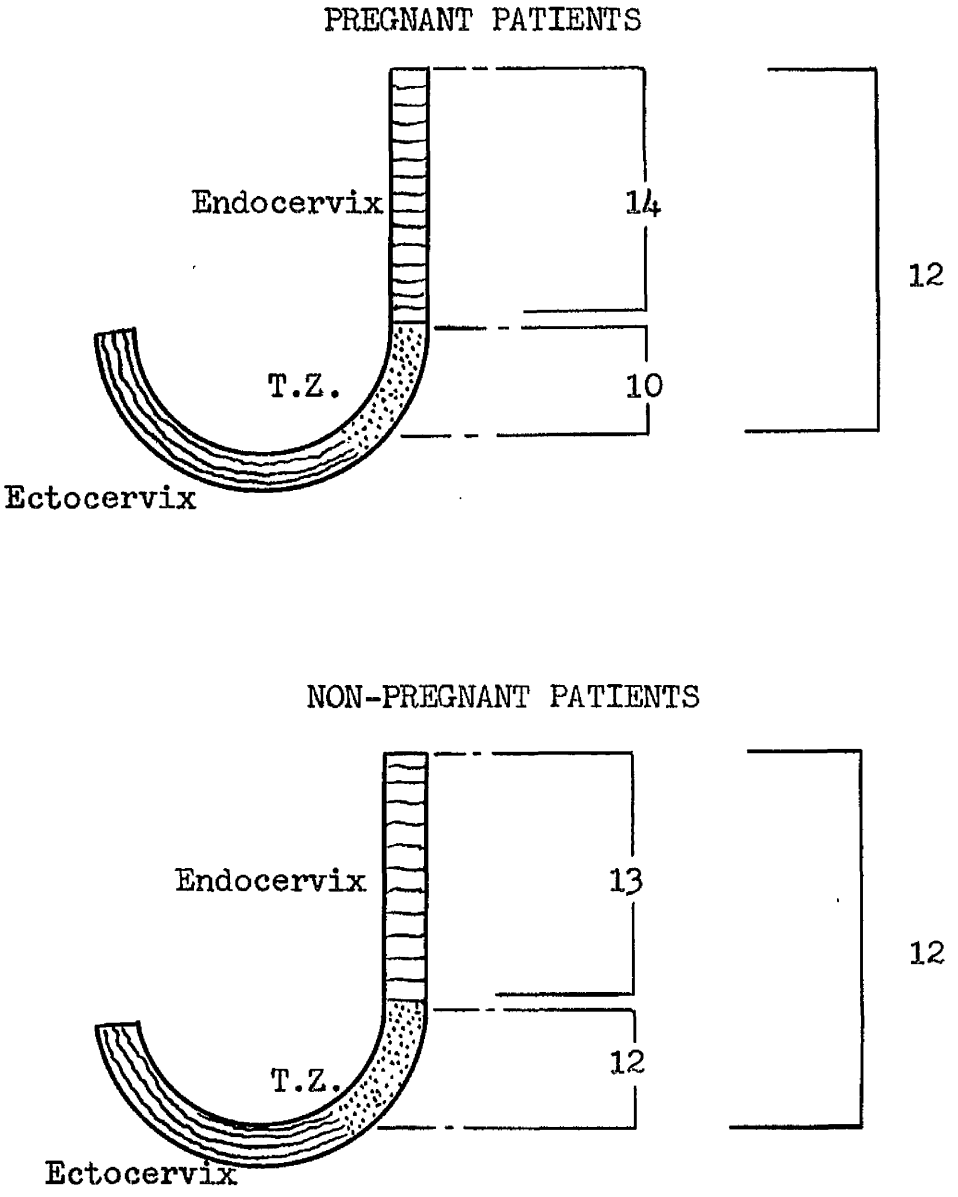

Figure 14. Site distribution of squamous metaplasia in the cervical canal of 36 pregnant and 37 non-pregnant patients.

Depth of epithelium involved in the cervical canal

In order to compare the depths of tissue involved by squamous metaplasia in the cervical canal of pregnant and non-pregnant women, particulars were recorded in every case whether the lesion was limited to the columnar epithelium of the surface of the cervical canal or to the subjacent glandular epithelium, or whether simultaneous involvement of both surface and gland epithelia was present. Table IV shows the results of study in the 36 pregnant and 37 non-pregnant women. Although the figures in each compartment are rather small for statistical comparison the results suggest that the distribution of squamous metaplasia in relation to endocervical surface and glandular epithelium is similar both in pregnant and in non-pregnant women.

TABLE IV

Comparison of depths of epithelium involved by squamous metaplasia in the cervical canal of 36 pregnant and 37 non-pregnant patients

Depth of epithelium involved by squamous metaplasia	Pregnant		Non-pregnant	
	No. of cases	Percentage of total	No. of cases	Percentage of total
Surface epithelium only	17	47.2	14	37.8
Surface and gland epithelium	18	50.	21	56.8
Gland epithelium only	1	2.8	2	5.4
Total	36	100.0	37	100.0

In all instances in which the glandular epithelium was the seat of metaplastic changes in both series of patients, only superficial cervical glands immediately subjacent to the surface columnar epithelium were involved by squamous metaplasia. Glands at a deeper level in the cervical stroma showed no evidence of squamous metaplastic change. These findings suggest that the cellular changes resulting in squamous metaplasia occur predominantly in the columnar epithelium lining the cervical canal, and that involvement of the subjacent superficial gland epithelium occurs in just over 50 per cent of cases.

Associated chronic inflammatory reaction

The relationship of chronic inflammatory changes in the cervical stroma to squamous metaplasia was investigated in the 36 pregnant and 37 non-pregnant patients (Table LVI). Histological features of chronic inflammatory infiltration were observed in 32 of the 36 cervices from pregnant women and in all 37 cervices of the non-pregnant group. The difference in incidence of chronic inflammatory changes between the pregnant and non-pregnant patients showing squamous metaplasia is not statistically significant.

TABLE LVI

The incidence of chronic inflammatory reaction in the cervical stroma of 36 pregnant and 37 non-pregnant patients in whom squamous metaplasia was found

Histological findings	Pregnant		Non-pregnant	
	No. of patients	Percentage of total	No. of patients	Percentage of total
Squamous metaplasia with chronic inflammatory reaction	32	88.9	37	100.
Squamous metaplasia without chronic inflammatory reaction	4	11.1	-	-
Total	36	100.0	37	100.0

$\chi^2 = 2.501$
D.F. = 1
$0.20 > P > 0.10$

Histological types of squamous metaplasia

Histological types of squamous metaplasia

(1) Compact squamous metaplasia.

Histological features of compact squamous metaplasia were seen in 30 of the 36 pregnant patients and 31 of the 37 non-pregnant patients. This, undoubtedly, was the commonest variety of squamous metaplasia identified, and its occurrence was relatively similar in each series of patients.

(2) Squamo-columnar metaplasia

Foci of squamo-columnar metaplasia were found in cervical specimens from six pregnant patients, while specimens from 16 non-pregnant patients showed histological features of this variant of squamous metaplasia. Co-existing foci of compact squamous metaplasia were identified histologically in all six pregnant and 16 non-pregnant patients.

(3) Tenuous squamous epithelium.

This variant of squamous metaplasia was observed in 12 pregnant and 14 non-pregnant patients. In six of the pregnant group, tenuous squamous epithelium was the sole manifestation of squamous metaplasia, the remaining six pregnant patients showing histological features of compact squamous metaplasia in addition to tenuous squamous epithelium. Similarly, of the 14 non-pregnant patients, six showed evidence of tenuous squamous epithelium only, while the remaining eight had co-existent compact squamous metaplasia in the cervical canal.

Adenomatous cervical polypi

Cervical polypi were found in seven (6.4 per cent) of the 110 pregnant patients and in four (3.6 per cent) of the 110 non-pregnant patients (Table LVII). Although almost twice the number of pregnant patients had cervical polypi, compared with the non-pregnant series, the difference in incidence between the two series is not statistically significant.

TABLE LVII

The comparative incidence of adenomatous cervical polypi in 110 pregnant and 110 non-pregnant patients

	Pregnancy Series		Control Series	
	No. of patients	Percentage incidence	No. of patients	Percentage incidence
Cervical polypi	7	6.4	4	3.6
No cervical polypi	103	93.6	106	96.4
Total	110	100.0	110	100.0

$\chi^2 = 0.3828$
D.F. = 1
$0.70 > P > 0.50$

Table LVIII shows the principal clinical features of the patients with cervical polypi in both the Pregnancy and the Control Series, as well as the main histological characteristics of the polypi. The age and parity distribution of patients in each series is similar. In the pregnant group of patients, the largest number of polypi was removed during the third trimester of pregnancy but no significant conclusions may be drawn from this fact as the majority of patients in the third trimester had not been examined vaginally during the first or second trimesters.

TABLE LVIII

The associated clinical features and histological characteristics of cervical polypi in 7 pregnant and 4 non-pregnant patients

Case No. in series	Clinical features			Histological features			
	Age	Parity*	Trimester	Type **	Chronic inflam.	Squamous metaplasia	Decidual change
PREGNANCY SERIES							
23	37	3	First	Aden	+	-	-
65	40	2	Third	"	+	+	-
71	24	0	Third	"	+	-	-
73	34	0	Third	"	-	-	-
80	29	1	Third	"	+	-	+
81	34	4	Second	"	+	-	-
3B	30	0	First	"	-	+	-
CONTROL SERIES							
C21	33	0	-	Aden	-	-	
C52	28	4	-	"	+	-	
C65	40	2	-	"	+	-	
C73	34	0	-	"	+	-	

*Parity denotes total number of previous viable and non-viable pregnancies.

**Aden = adenomatous.

All polypi were classified histologically as benign adenomatous in type. Squamous metaplastic changes were identified in two of the polypi from pregnant patients, compact and squamo-columnar forms of metaplasia being recognised in each case, but both of these patients were not submitted to cervical biopsy in addition to removal of the polypi. Consequently, the presence or absence of squamous metaplasia in the endocervical epithelium proper was not ascertained and the above results are not included in the previous section on squamous metaplasia of the endocervix. None of the polypi from the non-pregnant patients showed squamous metaplasia, but the comparative figures in both series of patients are too small to permit statistical deduction. Chronic inflammatory features were observed histologically in the majority of polypi from both pregnant and non-pregnant women. Only one of the polypi associated with pregnancy showed decidual change in the stroma.

Inflammatory changes in the cervix

Despite the fact that inflammatory disease does not constitute a primary lesion of the cervical epithelium, and consequently is strictly outwith the scope of the present investigation, the widespread occurrence, particularly of chronic cervicitis, necessitates consideration of inflammatory infiltra-

tion of cervical tissue in relation to the secondary effects on cervical epithelium, and also the possible relationship to other benign epithelial lesions. Appropriate observations of this latter aspect have already been recorded in previous sections dealing with the study of benign epithelial lesions. The present section, therefore, is included primarily in order to assess the overall incidence of histological characteristics of inflammatory disease in the cervix in both series of patients.

The histological criteria for the diagnosis of acute inflammatory changes involving the cervical stroma and epithelium were clearcut, in conformity with accepted pathological standards. The microscopical diagnosis of chronic cervicitis, on the other hand, presented difficulty in some instances when only minimal infiltration of the stroma with small round cells was observed, without appreciable associated changes in the cervical epithelium and glands. The significance of minimal round cell infiltration in the cervical stroma remains generally obscure and does not concern the present study. Accordingly, as advocated by Haines and Taylor (1962), an histological diagnosis of chronic cervicitis was made when cellular infiltration of the stroma was extensive and was associated with other evidence of inflammation such as epithelial damage and granulation tissue.

Overall incidence

Table LIX shows the incidence of all cellular inflammatory changes in the cervices of 105 pregnant and 109 non-pregnant patients from whom endocervical tissue was available for histological study.

TABLE LIX

The comparative incidence of all cellular inflammatory changes in the endocervical epithelium and stroma of 105 pregnant and 109 non-pregnant patients

Histological findings in endocervix	Pregnancy Series	Control Series
	Number of cases	Number of cases
Inflammatory reaction	78 (Acute 2 (Chronic 76	93 (Acute 1 (Chronic 92
No inflammatory reaction	27	16
Total	105	109

Only two of the pregnant patients and one non-pregnant patient showed histological features of acute cervicitis although none of these patients showed clinical signs of acute pelvic sepsis. The pregnant cases were both associated with incomplete abortion and the non-pregnant patient presented clinical features of chronic infection and erosion of the cervix with no macroscopic evidence of acute cervicitis.

After exclusion of the three patients showing histological evidence of acute cervicitis, statistical analysis of the remaining patients in the Pregnancy and Control Series revealed that the incidence of cellular chronic inflammatory changes in the cervices of 103 pregnant patients did not differ significantly from that in 108 non-pregnant patients (Table LX), although the lesion was found more frequently in non-pregnant women.

TABLE LX

The comparative incidence of cellular chronic inflammatory changes in the endocervical epithelium and stroma of 103 pregnant and 108 non-pregnant patients

Histological findings in endocervix	Pregnancy Series	Control Series
	Number of cases	Number of cases
Chronic inflammatory reaction	76 (73.8)	92 (85.2)
No inflammatory reaction	27	16
Total	103	108

Figures in parentheses denote percentage incidence of chronic inflammatory reaction in each group.

$$\chi^2 = 3.549$$
$$D.F. = 1$$
$$0.10 > P > 0.05$$

To test the validity of the foregoing statistical assessment of results from analysis of the gross number of patients in each series, evaluation of the results in the pregnant and non-pregnant groups was carried out following exclusion of unmatched patients in each group. Table LXI shows the respective incidences of cellular chronic inflammatory changes in the cervices of 101 pregnant patients and 101 non-pregnant patients, matched for age, parity and marital status; 75.2 per cent of the pregnant group and 86.1 per cent of the non-pregnant group showed chronic inflammatory cervical lesions, the difference in incidence between the groups not being statistically significant.

TABLE LXI

Comparative incidence of cellular chronic inflammatory changes in the endocervical epithelium and stroma of 101 pregnant patients and 101 non-pregnant patients. (Each pregnant patient matched for age, parity and marital status with a non-pregnant patient)

Histological findings in endocervix	Pregnancy Series	Control Series
	Number of cases	Number of cases
Chronic inflammatory reaction	76 (75.2)	87 (86.1)
No inflammatory reaction	25	14
Total	101	101

Figures in parentheses denote percentage incidence of chronic inflammatory reaction in each series.

$$\chi^2 = 3.178$$
$$D.F. = 1$$
$$0.10 > P > 0.05$$

COMPARISON OF THE HISTOLOGICAL CHARACTERISTICS OF BENIGN CERVICAL EPITHELIAL LESIONS IN PREGNANT AND NON-PREGNANT PATIENTS

Detailed study of cervical epithelial changes was carried out in all specimens of cervical tissue from pregnant and non-pregnant women with the object of observing variations in histological characteristics of epithelial lesions which might be attributable to the influence of pregnancy. This investigation necessarily involved comparison of the histological features of normal ectocervical and endocervical epithelium in addition to the study of benign epithelial lesions in the two groups of patients. Particular attention was directed to a search of cervical tissue from pregnant patients for histological evidence of abnormal proliferative activity in epithelial cells, which might not be observed in the non-pregnant patients.

ECTOCERVIX

Normal stratified squamous epithelium

The histological features of normal stratified squamous epithelium of the ectocervix were similar in both pregnant and non-pregnant patients, although increase in the total thickness of the epithelial layer was more frequently observed in specimens obtained during the third trimester of pregnancy. Parallel

increase in the thickness or proliferative activity of the basal cell strata was found only in the minority of these cases; in most instances, prominent vacuolated cells of the clear zone occupied the largest portion of the total epithelial thickness (Figure 15).

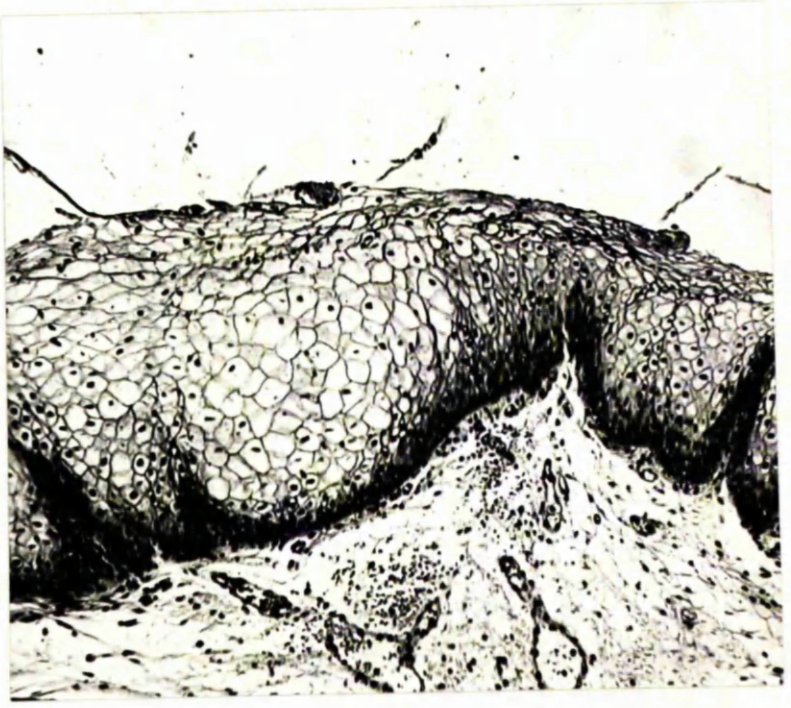

Figure 15. Normal stratified squamous epithelium of the ectocervix in a pregnant patient during the third trimester.
(Haematoxylin and eosin x 100).

Cells of the cornified zone in pregnant women showed similar characteristics to those in non-pregnant women. In the three instances of keratinization found in cervices from pregnant women,

the layer of keratin was invariably thin in comparison to the majority of cases observed in non-pregnant patients.

Basal cell hyperplasia

The histological appearances of hyperplastic basal cells in the stratified squamous epithelium of the ectocervix were similar in pregnant and in non-pregnant patients. Nuclear mitotic figures were seen with equal frequency in specimens from pregnant and non-pregnant women, and bizarre cell forms were rarely seen in either group. Figures 16 and 17 show the microscopic features of basal cell hyperplasia occurring in a pregnant and in a non-pregnant patient respectively. Normal maturation of squamous cells in the superficial zones of the stratified epithelium is present in each section.

ENDOCERVIX

Squamo-columnar transitional zone

As previously described, the squamo-columnar transitional zone was identified histologically only in 79 pregnant and 77 non-pregnant patients, in whom cervical sections showed contiguous ectocervical stratified squamous and endocervical columnar epithelium. Table LXII shows the various histological characteristics of the epithelial surface covering the transitional zone in both series of patients.

TABLE LXII

The comparative histological features of the squamo columnar transitional zone epithelium in the cervices of 79 pregnant and 77 non-pregnant patients

Histological findings in transitional zone	Pregnant group Number of patients	Control group Number of patients
Abrupt normal squamo-columnar junction	17 (21.5)	3 (4)
Squamous metaplasia	22* (27.9)	24@(31)
Epithelium partially deficient at squamo-columnar junction	40 (50.6)	50 (65)
Total	79 (100.)	77 (100.)

Figures in parentheses denote percentage incidence of epithelial characteristics in each group.

*Includes 12 specimens showing tenuous squamous epithelium.

@ " 14 " " " " "

Figure 16. Basal cell hyperplasia of the ectocervical stratified squamous epithelium in a pregnant patient during the third trimester.

(Haematoxylin and eosin x 400).

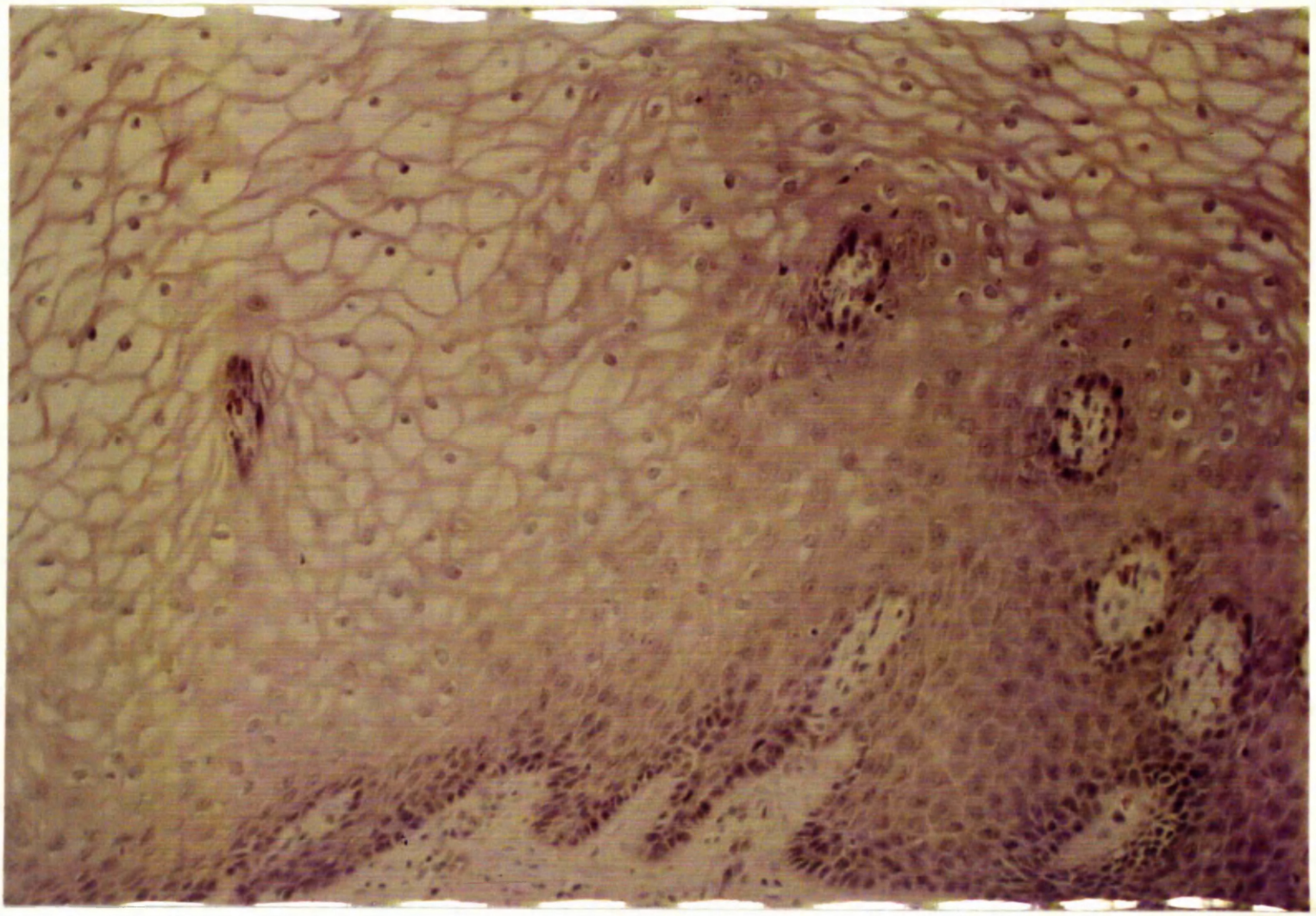

Figure 17. Basal cell hyperplasia of the ectocervical stratified squamous epithelium in a non-pregnant woman six years following her last pregnancy. Only the basal, parabasal and clear zones are included in the microphotograph owing to marked increase in the total thickness of the epithelial layer in this case.

(Haematoxylin and eosin x 400).

Abrupt normal squamo-columnar junction

No appreciable variations in the microscopical features of the epithelia were observed in cases showing an abrupt normal squamo-columnar junction, either during pregnancy or in the non-pregnant state. Figure 18 illustrates the histological appearance of an abrupt squamo-columnar junction in a pregnant patient during the first trimester.

Figure 18. Abrupt squamo-columnar junction in the cervix of a pregnant patient. Moderately heavy infiltration with chronic inflammatory cells is present in the underlying cervical stroma both in the transitional zone and in the cervical canal.

(Haematoxylin and eosin x 100).

Although a larger number of pregnant patients showed abrupt epithelial union at the cervical squamo-columnar junction, it is considered that no significance may be attached to this finding in view of numerous uncontrollable factors, such as physical and operative trauma as well as technical artefact incurred during preparation of histological sections, which must influence the results.

Squamous metaplasia

Figures 19 and 20 are photomicrographs taken at different levels of the same histological section from the cervix of a non-pregnant patient, showing features of tenuous squamous epithelium covering the transitional zone. The distal limit of the attenuated squamous epithelium adjoining normal stratified squamous epithelium is included in Figure 19 and similarly, the proximal limit merging into normal endocervical columnar epithelium is visible in Figure 20. Examples of tenuous squamous epithelium observed in the Pregnancy Series of patients showed no alteration in histological characteristics from those in the non-pregnant group.

The compact and squamo-columnar forms of squamous metaplasia seen in the cervical transitional zones were histologically identical with similar lesions occurring at a higher level in

Figure 19. Distal portion of tenuous squamous epithelium covering the cervical transitional zone in a non-pregnant patient. A small portion of stratified squamous epithelium of the ectocervix is included. The subjacent cervical stroma shows a moderately heavy chronic inflammatory reaction.
(Haematoxylih and eosin x 100).

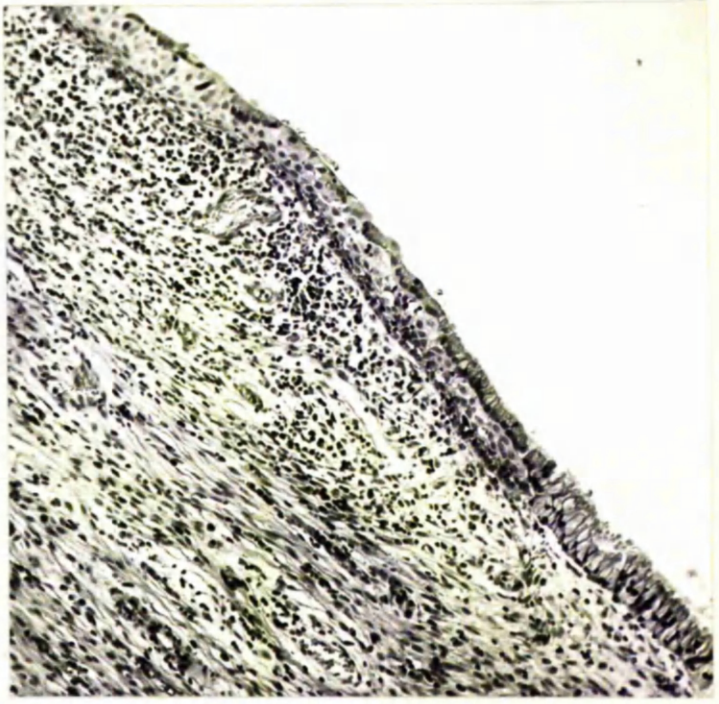

Figure 20. Proximal portion of tenuous squamous epithelium from the cervical transitional zone in the histological section illustrated in Fig. 19. Normal endocervical columnar epithelium is undermined for some distance by immature squamous cells at the upper limit of the abnormal zone.
(Haematoxylin and eosin x 100).

the cervical canal both in pregnant and non-pregnant women. Further description of compact and squamo-columnar lesions is included in the following section dealing with lesions of the endocervical columnar epithelium.

Partially deficient transitional zone epithelium

Of the 79 specimens including the transitional zone of the cervix from pregnant patients, 40 showed histological evidence of partial deficiency of the epithelial surface. Fifty of the 77 non-pregnant women showed similarly deficient transitional zone epithelium. Many of these sections from both series of patients showed associated chronic inflammatory features resulting in partial loss of the epithelial surface at the squamo-columnar junction, but the remainder presented features of traumatic disruption of epithelial continuity, either as a result of operation or technical artefact. The resulting histological patterns were, without exception, common to both pregnant and non-pregnant patients.

Endocervical epithelium

Normal endocervical columnar epithelium

Normal columnar epithelium lining the cervical canal and cervical glands in pregnant women presented no major difference in epithelial morphology from that in non-pregnant women. Minor

deviations from the microscopical appearances of normal columnar epithelium in the non-pregnant state were observed in several specimens from pregnant patients, particularly during the third trimester, and these included increase in length of the individual tall columnar cells and evidence of increased cellular secretory function. Figure 21 shows normal columnar epithelium lining the cervical canal and glands in a pregnant patient during the second trimester.

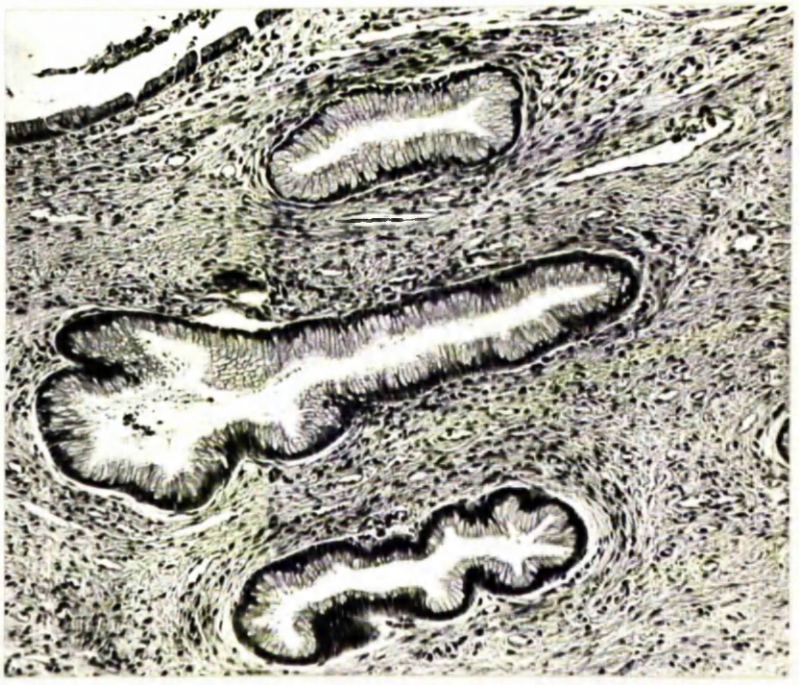

Figure 21. Normal endocervical columnar epithelium lining the canal and subjacent glands in a pregnant patient during the second trimester.

(Haematoxylin and eosin x 100).

Benign hyperplasia of columnar epithelium

This lesion was identified both in pregnant and non-pregnant patients and the histological appearances of the hyperplastic epithelium in both groups were similar in the majority of specimens examined. The most pronounced degrees of benign hyperplasia, however, were observed in specimens from pregnant patients, particularly during the third trimester, and similar histological changes were not identified in any of the non-pregnant patients. Figures 22 and 23 present the microscopical features of benign hyperplasia of the endocervical columnar epithelium in sections of the cervix from a non-pregnant and a pregnant patient respectively.

Figure 22. Benign hyperplasia of the endocervical columnar epithelium in a non-pregnant patient, 11 years following her last pregnancy. Simple proliferation of cervical glands is the predominant feature, but occasional foci of hyperplastic columnar cells, with stratification, are present. (Haematoxylin and eosin x 100).

Figure 23. Benign hyperplasia of the endocervical columnar epithelium in a pregnant patient during the third trimester. Stratification of columnar cells is prominent with "festooning" of the epithelium of the canal. Individual columnar cells are greatly hypertrophied and elongated in comparison with those in Figure 22.

(Haematoxylin and eosin x 100).

Pronounced hyperplasia of the columnar epithelium in pregnant patients was characterised by considerable stratification and "crowding" of columnar cells which resulted in a marked increase in the number of folds and projections of the epithelium lining the cervical canal and glands. Hypertrophy and elongation

of individual columnar cells with evidence of increased secretory activity in cells were constant associated features. No abnormal mitotic activity and no anaplastic features were observed in the hyperplastic epithelium. Proliferation of the cervical glands giving rise to a "honeycomb" pattern, and extension of the glands deeply into the cervical stroma, while frequently associated with pronounced epithelial hyperplasia in pregnant patients, were not peculiar to this group, as similar glandular changes were observed in non-pregnant patients.

Squamous metaplasia

(1) Compact squamous metaplasia

The cellular characteristics of foci of compact squamous metaplasia in pregnant patients were identical with those observed in non-pregnant patients. Compact masses of immature squamous cells were found in the endocervix of both pregnant and non-pregnant patients, forming foci varying widely in size and distribution in each group. Both the columnar epithelium of the cervical canal and generally the epithelial lining of the subjacent superficial cervical glands were involved in degrees varying from isolated discrete metaplastic lesions at either site, to extensive areas of metaplasia often replacing both of these structures, and completely filling gland acini. The cytoplasmic and nuclear staining characteristics of the metaplastic epithelium were uniformly similar both in pregnant and non-pregnant cases.

Occasionally, areas of mature stratified squamous epithelium were noted, in patients from both Series, replacing the columnar lining of the cervical canal at some distance from the squamo-columnar junction. Figure 24 illustrates a section from the upper portion of the cervical canal of a patient in the second trimester of pregnancy, showing moderately extensive foci of compact squamous metaplasia involving the epithelia of both the cervical canal and subjacent glands.

Figure 24. Foci of compact squamous metaplasia involving the columnar epithelium of the endocervix in a pregnant patient during the second trimester. Different stages of squamous metaplasia from proliferation of sub-cylindrical "basal" or "reserve" cells to complete replacement of cervical glands are seen in the section.

(Haematoxylin and eosin x 100).

(2) Squamo-columnar metaplasia

The cellular characteristics of endocervical foci of squamo-columnar metaplasia were similar both in pregnant and in non-pregnant patients. No difference was observed in the staining characteristics or proliferative activity of the immature squamous cells in either series. However, a greater number of sections showing exuberant "trabeculations", containing numerous vacuoles of varying sizes, was noted in a few of the pregnant patients in whom squamo-columnar metaplasia was observed, which suggested increased secretory activity of the mucin secreting columnar cells incorporated in the metaplastic foci. The histological features of one such lesion observed in a pregnant patient during the second trimester are illustrated in Figure 25, and, for comparison, a photomicrograph of squamo-columnar metaplasia occurring in the cervical canal of a non-pregnant patient is shown in Figure 26. Both sections show extensive squamo-columnar metaplasia involving the surfade of the cervical canal and the subjacent cervical glands.

Adenomatous cervical polypi

The microscopical characteristics of the epithelium in cervical polypi from pregnant patients showed no significantly different features from those in cervical polypi from non-pregnant women. In both series of patients the majority of polypi were covered by columnar epithelium consisting of a single layer of cells

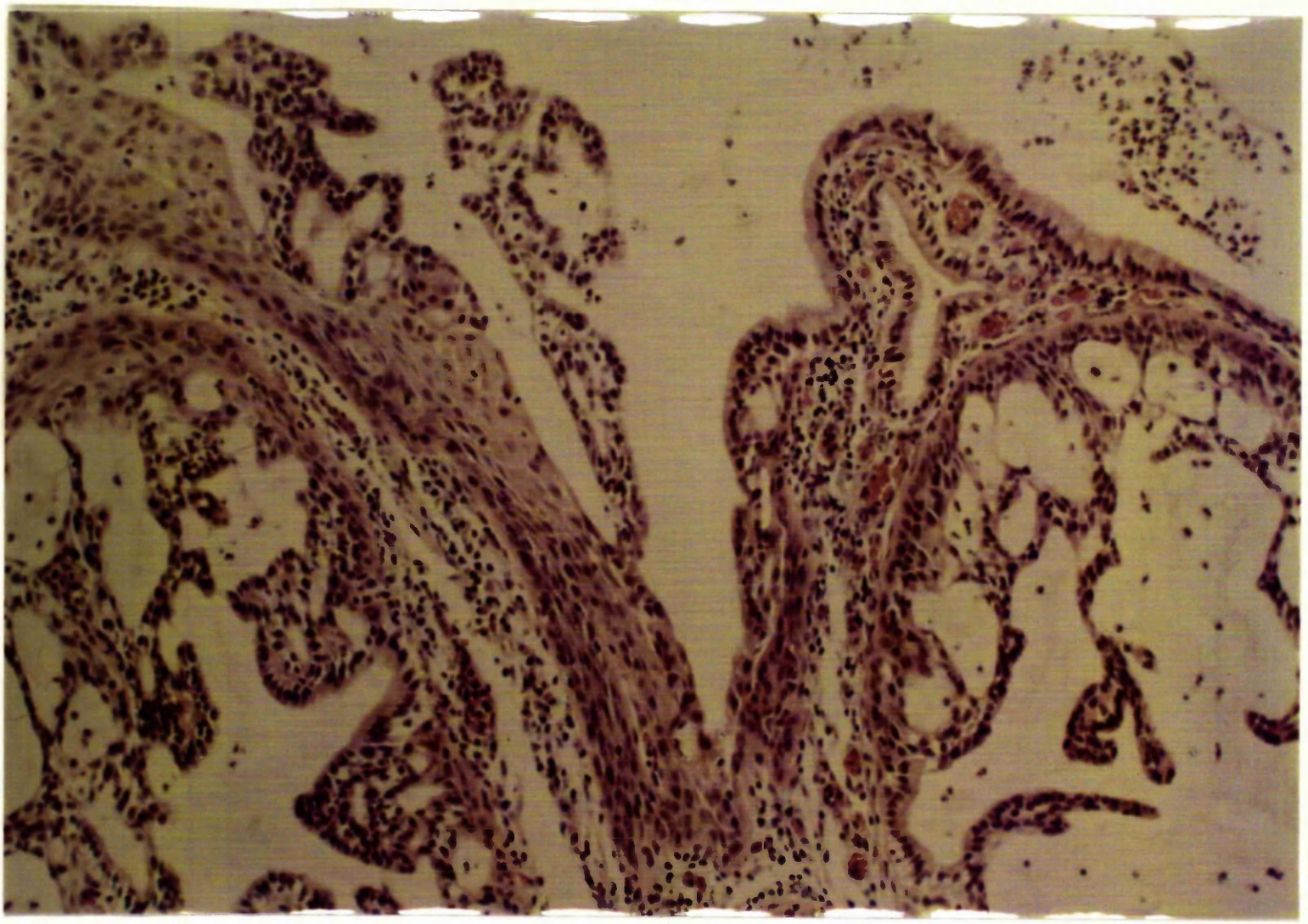

Figure 25. Squamous metaplasia of the cervical canal and glands in a pregnant patient during the second trimester. The squamo-columnar type of lesion predominates and vacuolation and "trabeculation" of the metaplastic epithelium are prominent. (Haematoxylin and eosin x 400).

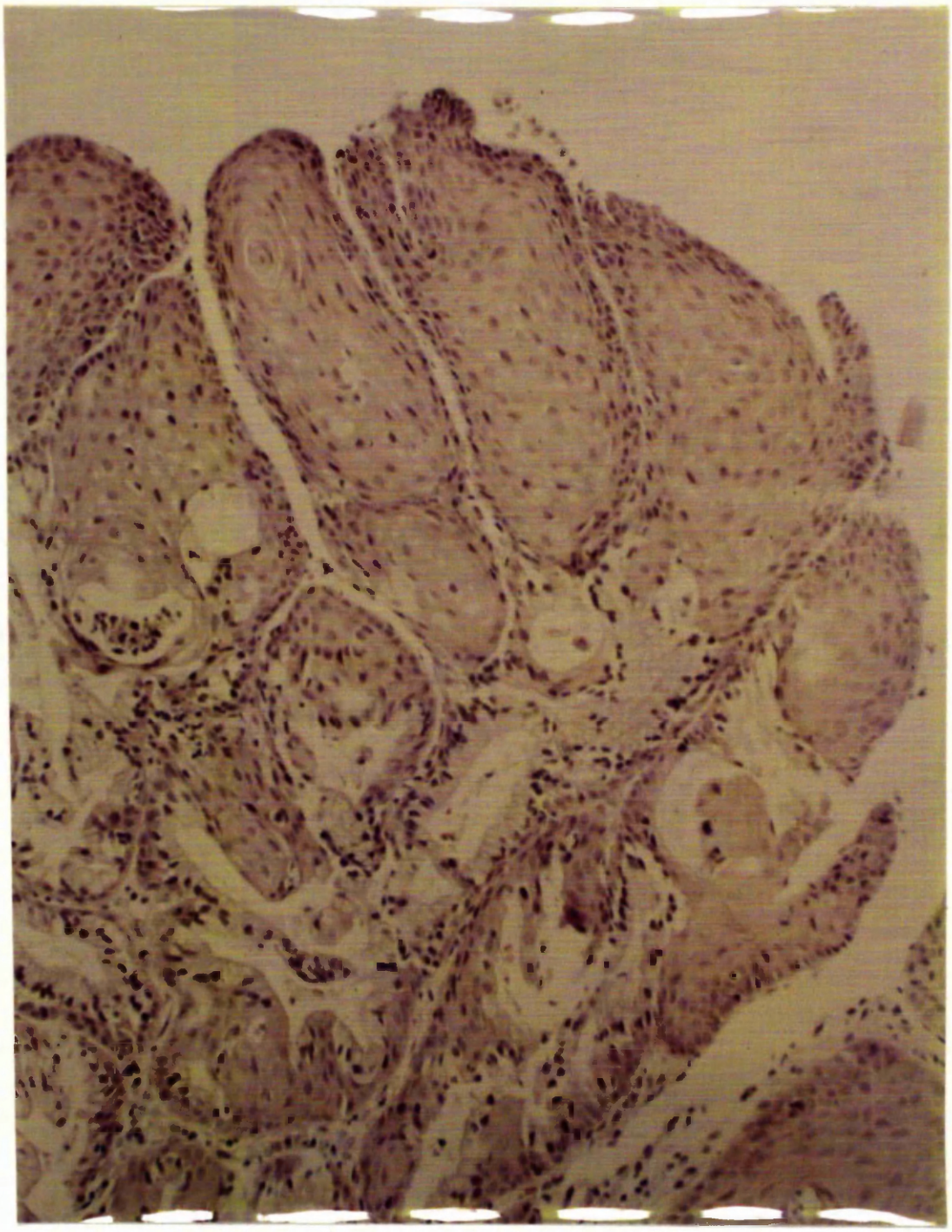

Figure 26. Extensive squamous metaplasia involving the cervical canal and glands in a non-pregnant patient 7 years following her last pregnancy. Squamo-columnar foci show less extensive vacuolation than those in Figure 25. Most of the columnar epithelium of the cervical canal and many of the cervical glands have been replaced by immature squamous epithelium.

(Haematoxylin and eosin x 400).

and contained numerous glands, many of which were widely dilated, lined by columnar cells. Squamous metaplastic changes observed in polypi from two of the pregnant patients were identical, histologically, with similar lesions found elsewhere in the cervical canal and glands of both series of patients.

Decidual cells were noted in the stroma of the cervical polyp from one pregnant patient, and these cells constituted the sole differentiating histological feature in polypi, specifically associated with pregnancy.

Extensive infiltration with chronic inflammatory cells and marked vascularisation of the stroma were features equally common in polypi from both series of patients.

Chronic inflammatory reaction

Chronic inflammatory changes involving the endocervical epithelium, glands, and cervical stroma presented the same histological appearances in pregnant and non-pregnant patients. Similar granulations and effects on cervical gland morphology were observed in both series, and no significant variation in the relative concentrations of small lymphocytes and plasma cells was detected in sections showing comparable degrees of chronic infection. Figure 27 shows the typical histological features of chronic inflammatory reaction of moderate degree in the endocervix of a non-pregnant patient.

Figure 27. Section of endocervix from a non-pregnant patient, 11 years following her last pregnancy. Moderate chronic inflammatory changes are present in the cervical stroma and glands subjacent to the cervical canal.

(Haematoxylin and eosin x 100).

SPECIFIC PREGNANCY CHANGES

Cervical epithelial changes

During the present investigation, no cellular lesion of the epithelia of the ectocervix or endocervix specific only to the state of pregnancy was found. All benign epithelial transformations noted in pregnant patients were associated with corresponding epithelial lesions in non-pregnant women. Nevertheless, two particular epithelial lesions, common to both groups of patients, showed more pronounced variations in the histological features in the pregnant women.

(1) More extreme degrees of benign hyperplasia of the columnar epithelium were seen among sections of the endocervix from pregnant women than among those from non-pregnant women. These pronounced proliferative changes occurred most frequently during the third trimester of pregnancy, but the histological characteristics of the hyperplastic epithelium in every case were essentially benign, and retained the basic features of simple epithelial hyperplasia.

(2) Similarly, more pronounced variations in histological features were observed in a limited number of squamous metaplastic lesions occurring during pregnancy. Only the squamo-columnar type of lesion in pregnant patients presented histological characteristics differing slightly from those in non-pregnant patients. Evidence of increased vacuolation in squamo-columnar foci was found in a

few endocervices from pregnant patients, with resulting formation of highly "trabeculated" epithelial patterns. It was considered that these changes indicated increased proliferative and secretory responsiveness during pregnancy of the mucin-producing cells in the squamous metaplastic foci. On the other hand, the microscopical characteristics of the immature squamous cells in foci of squamo-columnar metaplasia showed no appreciable variation during pregnancy from those observed in the non-pregnant state.

Decidual reaction

Although not concerned with the study of epithelial changes, reference to decidual reaction in the cervical stroma is purposely included in the present section for the following reasons:

The presence of decidual cells in the cervical stroma constitutes a known specific response to pregnancy in a variable proportion of cases: furthermore, difficulty has arisen in several reported instances in differentiating decidual reaction in the cervix from carcinoma, and attention has been drawn to this problem by several authors including Klein and Domeier (1946) and Lapan (1949).

Of the 105 specimens of cervical tissue from pregnant women in whom endocervical columnar epithelium and cervical stroma were available for histological study, nine (8.6 per cent) showed microscopical features of decidual reaction in the stroma (Table LXIV).

TABLE LXIV

Incidence of decidual reaction in the cervical stroma of 105 pregnant patients, in relation to trimester of pregnancy

Histological findings in cervical stroma	Number of cases			Total All trimesters
	First trimester	Second trimester	Third trimester	
Decidual reaction	1 (1.6)	3 (10)	5 (41.7)	9 (8.6)
No decidual reaction	62	27	7	96
Total	63	30	12	105

Figures in parentheses denote percentage incidence of decidual reaction in each group.

Although the numbers of cases in relation to each trimester are too small for statistical comparison, the figures suggest that the incidence of decidual reaction in the cervical stroma increases progressively during pregnancy to a maximum in the third trimester.

The microscopical features in all sections showing decidual reaction were characterised by the occurrence of scattered foci of decidual cells at varying depths in the cervical stroma. In some sections, decidual cells formed small aggregations and in others the cells were dispersed in localised areas in the stroma. In each instance, decidual cells were clearly differentiated from adjadent stromal and cervical epithelial cells. None of the

patients showed clinical or histological evidence of frank deciduosis involving the cervix.

The nine patients showing decidual reaction in the cervical stroma included primigravidae and multigravidae varying in age from 23 to 39 years. The commonest associated histological lesion in the cervical stroma was chronic inflammatory cell infiltration which was noted in seven of the nine patients.

The seven specimens of cervical polypi removed from pregnant patients were separately reviewed for histological evidence of decidual reaction. Only one polyp showed decidual change which involved a small localised area in the stroma of the polyp containing a sparse number of characteristic decidual cells.

SUSPICIOUS EPITHELIAL LESIONS

(1) Squamous epithelium

Pregnancy Series. In the pregnant group of patients, no dysplastic changes were observed in any of the sections examined containing stratified squamous epithelium of the ectocervix or foci of squamous metaplasia in the endocervix.

Control Series. In contrast, squamous epithelial changes in the cervix of one non-pregnant patient were sufficiently suspicious to warrant a diagnosis of dysplasia. This patient, who was 29 years of age, had had one non-viable and three viable pregnancies, the last pregnancy having terminated 4 years previously. The patient's cervix was amputated at Manchester operation for utero-vaginal prolapse, the cervix being described at operation as "Lacerated, infected and eroded". Histological sections from three blocks of the cervix were available for examination. Dysplastic changes were seen in extensive foci of compact squamous metaplasia partially replacing the columnar epithelium of the cervical canal and subjacent glands (Figure 28).

Although disturbing features of cellular unrest were noted in the basal layers of the squamous metaplastic epithelium, it was considered that the cellular changes in this case lacked

Figure 28. Section of the upper cervical canal from a non-pregnant patient. Dysplastic changes are present in extensive foci of squamous metaplasia at some distance from the squamo-columnar junction. A portion of one subjacent cervical gland replaced by dysplastic squamous epithelium is visible. Moderately intense chronic inflammatory change is present in the cervical stroma.

(Haematoxylin and eosin x 100).

adequate criteria to fulfil the requirements for a diagnosis of carcinoma in situ. Coincident basal cell hyperplasia was found in the stratified squamous epithelium of the ectocervix in this patient, but no tendency to dysplastic change was noted in the basal layers of the ectocervical epithelium. It is proposed indefinitely to observe the future progress of this patient by means of periodic cytological examination of cervical smears.

(2) Columnar epithelium

No suspicious epithelial changes suggestive of neoplastic transformation were observed in any section of endocervical columnar epithelium from pregnant or non-pregnant patients. Extreme instances of benign hyperplasia of the columnar epithelium or marked degrees of squamo-columnar metaplasia encountered in pregnant patients did not result in histological appearances which might have suggested malignant adenomatous change.

(3) Epithelium of cervical polypi

No suspicious cellular changes were found in the epithelia of polypi from pregnant or non-pregnant patients in the present series.

D I S C U S S I O N

INTRODUCTION

In order to avoid any possible confusion it is proposed to discuss the results of the various investigations carried out under the following main headings:

(1) The incidence of the various types of benign epithelial lesions of the cervix in pregnant and non-pregnant patients.

(2) Comparison of the histological characteristics of benign cervical epithelial lesions in pregnant and non-pregnant patients.

(3) Specific pregnancy changes.

(4) Atypical epithelial lesions.

INCIDENCE OF BENIGN EPITHELIAL LESIONS OF THE CERVIX

ECTOCERVIX

Basal cell hyperplasia

It is difficult to assess or compare the results reported in the literature regarding the incidence of basal cell hyperplasia of the ectocervical stratified squamous epithelium as many previous reports are based on differing histological criteria and lack uniform terminology. Furthermore, comparative study of the incidence of basal cell hyperplasia in comparable series of pregnant and non-pregnant women has not been made by any of the previous authors. The majority of investigators have published their findings only in series of pregnant patients, and no detailed report of the incidence of basal cell hyperplasia in non-pregnant women has appeared in the literature.

Initially, Murphy and Herbut (1950), studying the histology of the cervical epithelia in their series of 50 pregnant women, reported basal cell hyperactivity of the ectocervical epithelium in 6 per cent of their cases. The histological criteria which they described in relation to basal cell hyperactivity consisted of simple hyperplasia of the basal cell layers with no microscopical features of anaplasia. Subsequently, basal cell hyperactivity during pregnancy was reported in 24.8 per cent of 71

patients by Epperson et al. (1951), who classified the lesion in three grades depending on the relative thickness of the total epithelial layer involved by the hyperactive basal cells, the third grade being defined as total involvement of the surface epithelium of the ectocervix. The histological criteria adopted by these authors in the diagnosis of basal cell hyperactivity included anaplastic changes, without loss of polarity, in the hyperactive basal cells. Using the histological criteria defined by Epperson et al. (1951), Nesbitt and Hellman (1952) found basal cell hyperactivity in 6.8 per cent of 300 pregnant women, and in a subsequent series of 1,387 pregnant patients, Nesbitt (1955) reported an 18.3 per cent incidence of the lesion.

From a detailed study of the literature it is apparent that the histological features of basal cell hyperplasia or hyperactivity, reported by different authors, include degrees of cellular proliferation varying from simple hyperplasia of cells confined to the basal zone to anaplastic changes in hyperplastic basal cells occupying the total thickness of the stratified squamous layer. Such extreme degrees of basal cell hyperplasia as described by Epperson et al. (1951) and subsequent workers, correspond more closely, according to their histological criteria, to dysplastic lesions of the cervical epithelium.

In the present series of pregnant and non-pregnant patients, basal cell hyperplasia represents a simple proliferative change involving the basal layers of the ectocervical stratified squamous epithelium, without microscopical features of cell anaplasia. The overall incidence of basal cell hyperplasia in 79 pregnant women is 17.7 per cent. This incidence does not differ significantly from that of 12.8 per cent in a comparable group of 78 non-pregnant women. These results suggest that pregnancy is not associated with any significant increase in the proliferative activity of the basal cells of the ectocervical stratified squamous epithelium.

In a study of the possible effects of age and parity on the incidence of basal cell hyperplasia in the pregnant and non-pregnant patients, satisfactory statistical evaluation was not possible owing to the small numbers of cases with basal cell hyperplasia in each age or parity group. The results, however, suggest that the age and parity distribution of patients with basal cell hyperplasia is similar in the pregnant and non-pregnant groups.

Keratinization

Keratinization of the ectocervical stratified squamous epithelium was found in a significantly greater number of non-pregnant than in pregnant women in the present series. Papanicolaou et al. (1948) maintained that keratinization was found almost exclusively in the prolapsed cervix and that it was difficult to

escape the conclusion that it was largely the result of external irritation. Prolapse is a predominant associated factor in the present group of non-pregnant patients showing this lesion, but, as comparable major degrees of utero-vaginal prolapse were not observed in patients of the Pregnancy Series, it is not possible to determine, from the present results, whether prolapse or pregnancy, or the combined effects of both factors are associated with the significant difference in incidence of keratinization between pregnant and non-pregnant women.

ENDOCERVIX.

The results of the present study suggest that the endocervix, as distinct from the ectocervix, is the seat of more pronounced epithelial change during the course of gestation. Histological interpretation of the variety of benign epithelial transformations which occur in the endocervix is presently based on the recognition of microscopical changes involving, on the one hand, the columnar cells lining the cervical canal and glands, and, on the other hand, the subcolumnar, basal, or reserve cells which are generally regarded as the source of squamous metaplastic epithelium in the cervical canal.

Benign hyperplasia of the columnar epithelium

While it has been generally accepted since Stieve's (1927) original work that benign hyperplastic change in the endocervical

columnar epithelium during pregnancy involves simultaneously the surface epithelium of the cervical canal and the epithelium lining the cervical glands, several previous reports have been based on study of such changes predominantly in one or other of these structures. For this reason, as well as the fact that detailed reference to the age and parity distribution of benign hyperplasia in pregnant women has not been made in previous studies, accurate comparison of the results in different series is not possible.

Hyperplasia of the endocervical columnar epithelium was found in 88 per cent of nulliparae and 92 per cent of multiparae by Murphy and Herbut (1950), investigating a series of 50 pregnant women. Epperson et al. (1951) reported hyperplastic changes in cervical glands in 17.1 per cent of prenatal women and 9.1 per cent of postnatal women of varying ages and parity, among their series of 286 patients. They concluded that hyperplastic changes in the cervical glands indicated a definite reaction to the pregnancy state. Nesbitt and Hellman (1952) described three types of benign hyperplastic change in cervical glands and reported, from a study of 300 pregnant women, corresponding incidences of 28.6, 44 and 47.3 per cent.

Assessment of the incidence of benign hyperplasia of the endocervical epithelium in non-pregnant women was made by Carrow and Greene (1951), who reported their findings in a simultaneous investigation of 96 pregnant and 50 non-pregnant patients, without

reference to the age or parity of their patients. They noted hyperplastic histological changes involving either the surface columnar epithelium of the cervical canal, or the gland epithelium or both of these structures, in 44.4 per cent of the pregnant and 22 per cent of the non-pregnant patients. The highest incidence of these changes during pregnancy was observed in the third trimester. The authors concluded that, despite the increased incidence of these hyperplastic changes in the pregnant cervix, such changes were seen sufficiently often in the non-pregnant that they could no longer be considered either specifically due to pregnancy or specifically limited to the pregnant cervix. Although numerous authors have referred to the existence of hyperplastic change in the endocervical columnar epithelium of non-pregnant women, reports of the incidence of the lesion in non-pregnant patients, other than Carrow and Greene's (1951), have not been found in the literature.

During the present investigation, benign hyperplasia was observed in 32.4 per cent of patients in the Pregnancy Series and in 18.3 per cent of non-pregnant patients in the Control Series. This difference in the incidence of benign hyperplasia for pregnant and non-pregnant patients is statistically significant. As the pregnant and non-pregnant patients investigated were of identical age, parity and marital status, the findings suggest that the higher incidence of benign hyperplasia in the Pregnancy Series is due to the effect of pregnancy; but, from the investigation carried out

into the actual effect of age and parity, it would appear that this conclusion does not apply to all pregnant patients but only to pregnant patients who have had three or less previous pregnancies. Pregnant women having more than three previous pregnancies show only a slightly higher incidence of benign hyperplasia than non-pregnant women of the same parity, and the difference in incidence between the two groups is not statistically significant.

No significant relationship is found between the age of the patients and the occurrence of benign hyperplasia either in pregnant or in non-pregnant women under or over the age of 30 years. These results suggest, therefore, that in any series of pregnant and non-pregnant women, matched for age but consisting solely of patients who have had more than three previous pregnancies, the incidence of benign hyperplasia should not differ significantly between the pregnant and non-pregnant groups.

Among pregnant and non-pregnant women who have three or less previous pregnancies, the greatest difference in the incidence of benign hyperplasia occurs in patients who have had no previous pregnancy. Thus, in 20 non-pregnant nulliparae, benign hyperplasia of the endocervical columnar epithelium was not observed, while six of the 20 patients in their first pregnancy showed benign hyperplasia. Although investigation of a much larger series of patients is desirable before final conclusions may be drawn, the present results suggest that benign hyperplasia of the endocervical columnar

epithelium may, in fact, develop initially during the first pregnancy, and may persist throughout reproductive life in approximately 20 per cent of women, undergoing periodic upward fluctuations in incidence up to the sixth pregnancy. Whether the decreased incidence of the lesion in pregnant women of parity six and over, compared with that in non-pregnant women of the same parity group, reflects decreased responsiveness of the columnar cells to pregnancy hormonal stimulation ultimately as parity increases will require elucidation by further research.

The present findings suggest that, during the course of pregnancy, benign hyperplasia of the endocervical columnar epithelium occurs most frequently in the third trimester, which accords in general with the majority of published reports. However, the variations in incidence in relation to each trimester in the present series are not statistically significant, but the total number of patients in the third trimester is small.

Squamous metaplasia

The occurrence of squamous metaplasia in the cervical canal has been studied extensively by previous authors. Table LXV contains the results of several investigators who have reported the incidence of this lesion both in pregnant and in non-pregnant women. These reports indicate a wide variation in the incidence of squamous metaplasia. The results of the present

investigation suggest that this variation may be expected according to the particular age and parity distributions of patients in any series studied. Detailed analysis of the results in relation to the age and parity groups of patients was not described in any of the series of pregnant or non-pregnant women listed in Table LXV, although gross data in respect of age and parity limits were defined in the majority of instances. Consequently, comparison of the observed incidence of squamous metaplasia in one series with the incidence in any other series is subject to misinterpretation in the absence of strict correlation of age and parity factors. The reported incidence in each series may be accepted only as a relative finding, and cannot be regarded as an absolute index of the frequency of the lesion in the general population of either pregnant or non-pregnant women.

Only two reports were found in the literature describing the simultaneous investigation of parallel series of pregnant and non-pregnant patients to assess the comparative incidence of squamous metaplasia (Danforth, 1950; Carrow and Greene, 1951). No details regarding the age and parity of his pregnant or non-pregnant patients were recorded in Danforth's (1950) series, but he concluded from his findings that squamous metaplasia at the squamo-columnar junction of the cervix was more than twice as frequent in the pregnant group as in the non-pregnant group of women. In the light of the results in the present investigation, this deduction

TABLE LXV

Previously reported incidence of squamous metaplasia of the endocervix

Authors	Pregnant women		Non-pregnant women	
	Number of patients	Incidence	Number of patients	Incidence
Carmichael and Jeaffreson(1941)	-	-	334	41%
Auerbach and Pund (1945)	-	-	100	72%
Fluhmann (1948)	32	19%	-	-
Danforth (1950)	22	86%	46	43%
Murphy and Herbut (1950)	50	18%	-	-
Carrow and Greene (1951)	88	52.3%	50	No data
Epperson et al.(1951) Series 1	87	29%	-	-
Series 2	286	14.3%	-	-
Howard et al. (1951)	-	-	400	83%
Nesbitt and Hellman (1952)	300	32.7%	-	-
De Alvarez et al. (1957)	-	-	954	25%

is open to doubt, particularly in view of the absence of information regarding the age and parity distribution of his patients. Carrow and Greene (1951) observed endocervical squamous metaplasia in 52.3 per cent of their series of 88 pregnant patients of unspecified age and parity, but did not report the incidence of the lesion in

their series of 50 non-pregnant "control" patients simultaneously investigated by cervical biopsy.

The present investigation shows that the overall incidence of squamous metaplasia in the Pregnancy Series of patients is 34.3 per cent compared with an overall incidence of 33.9 per cent in the Control Series. This difference in incidence between the pregnant and non-pregnant women is not statistically significant. Confirmation of this finding was obtained by a study of 104 pregnant and 104 non-pregnant patients individually matched for age, parity and marital status, the incidence of squamous metaplasia in each group of patients being 34.6 per cent. As the pregnant and non-pregnant patients investigated were of identical age, parity and marital status, these results suggest that the state of pregnancy is not associated with any variation in the incidence of squamous metaplasia in the endocervix.

In order to ascertain whether the overall incidence of squamous metaplasia in the Pregnancy Series was biased by preponderance of the lesion in any trimester of pregnancy, statistical comparison of the incidence of squamous metaplasia in each trimester was carried out. This revealed no significant variation in the incidence of the lesion in relation to any of the three trimesters studied, and the findings suggest that the overall incidence of squamous metaplasia in the Pregnancy Series does not

reflect preponderance of the lesion in any particular trimester of pregnancy.

A significant rise in the incidence of endocervical squamous metaplasia coincident with increasing age in non-pregnant women was reported by Carmichael and Jeaffreson (1941), Auerbach and Pund (1945) and Howard et al. (1951), but no correlation between the occurrence of the lesion and parity was found by these authors. The relationship of squamous metaplasia to age and parity in pregnant patients was not defined in any of the series previously reported in the literature.

Investigation was carried out into the actual effect of age on the incidence of squamous metaplasia in the present series of pregnant and non-pregnant patients. A higher incidence of the lesion is observed in non-pregnant patients over 30 years of age than in non-pregnant patients under the age of 30, although, while highly suggestive the difference in incidence between the two age groups is not statistically significant. In contrast, study of the pregnant patients reveals a higher incidence of squamous metaplasia in women under 30 years of age than in women over the age of 30, but the difference observed is not statistically significant. Comparison of pregnant patients under 30 years of age with non-pregnant patients under 30 years shows no significant variation in the incidence of squamous metaplasia, and similarly, there is no

significant difference in the incidence of the lesion in pregnant women over 30 years when compared with non-pregnant women of the same age group.

The actual effect of parity on the incidence of squamous metaplasia in the pregnant and non-pregnant patients was similarly investigated. The results show that parity exerts a significant influence on the incidence of squamous metaplasia in non-pregnant patients, among whom a significantly higher incidence of the lesion is found in women who have had more than three previous pregnancies than in those who have had three or less previous pregnancies. Conversely, the incidence of squamous metaplasia in pregnant patients in relation to parity is reversed, the lesion appearing more frequently in the lower parity group than in the higher parity group of pregnant women, although the difference in incidence of the lesion between these two groups of pregnant patients is not statistically significant. When the results for non-pregnant patients having three or less previous pregnancies are compared with those for pregnant patients of the same parity, no statistically significant difference is observed. Similarly, no significant difference is found between the incidences of the lesion in non-pregnant and pregnant women in the higher parity groups.

The interpretation of these findings would be facilitated by study of the actual combined effect of age and parity on the incidence of squamous metaplasia in the Pregnancy and Control Series.

However, the total number of patients in each series is too small to permit statistical analysis of combined age and parity groupings.

The available results suggest that, in non-pregnant women, a significant rise in the incidence of squamous metaplasia of the cervical canal occurs in relation to increasing parity in contrast with increasing age. These observations imply that the influence of parity is more important than the influence of age in relation to the occurrence of squamous metaplasia in non-pregnant women. That age may also have an effect on the incidence of squamous metaplasia in non-pregnant women is suggested by the results of the present investigations although statistical proof of this was not obtained. This view conflicts with opinions previously expressed in the literature. Study of the combined influence of age and parity on the incidence of squamous metaplasia, however, will be required in a larger series of non-pregnant women before final conclusions regarding the relationship of age and parity may be reached.

Interpretation of the results obtained in the study of squamous metaplasia in the pregnant patients in relation to age and parity is difficult. While neither age nor parity exert any significant influence on the distribution of squamous metaplasia, the lesion occurs more frequently in pregnant women in the lower age and parity groups than in the higher age and parity groups. This age and parity distribution in pregnant patients is a reversal of

that observed in the non-pregnant patients. As the age and parity of the pregnant patients are identical with those of the non-pregnant patients, the findings suggest that a shift in the distribution of squamous metaplasia towards lower age and parity groups of women occurs under the influence of pregnancy, but, from the relatively small numbers involved in both of the present series, the variations observed lie within the limits of chance.

Comparative investigation of larger groups of pregnant and non-pregnant women of identical age and parity would appear to be the only means of throwing further light on these preliminary findings. The alternative method of studying the cellular behaviour of squamous metaplastic lesions in the same patient during and between successive pregnancies cannot be justified in view of the necessity for multiple and repeated cervical biopsies.

Cellular chronic inflammatory changes

In common with the findings of previous authors including Carmichael and Jeaffreson (1941) and Haines and Taylor (1962) histological evidence of chronic inflammatory infiltration of the cervical stroma was found in the majority of women both in the Pregnancy and in the Control Series. The overall incidence of chronic inflammatory reaction in 103 pregnant patients was 73.8 per cent and in 108 non-pregnant patients, 85.2 per cent, a difference, which although highly suggestive, is not statistically significant.

These findings were confirmed by analysis of the results in 101 pregnant and 101 non-pregnant patients individually matched for age, parity and marital status. The findings suggest that the incidence of chronic cervical inflammatory reaction, while appreciably lower in pregnant than in non-pregnant women, shows no significant difference between the two groups.

The distribution of cervical chronic inflammatory reaction in the 34 pregnant and 20 non-pregnant patients showing benign hyperplasia of the endocervical columnar epithelium was similar to that in the total series of pregnant and non-pregnant women, the difference in incidence between the pregnant and non-pregnant patients being not statistically significant. Closely similar results were obtained in the study of associated chronic inflammatory changes in the 36 pregnant and 37 non-pregnant patients showing squamous metaplasia of the cervical canal, and no significant difference in incidence of chronic inflammatory reaction was observed between the two groups.

These correlated findings suggest that chronic inflammatory reaction in the cervix does not influence the distribution of either benign hyperplasia or squamous metaplasia in the endocervices of pregnant or non-pregnant women.

COMPARISON OF THE HISTOLOGICAL CHARACTERISTICS OF BENIGN CERVICAL EPITHELIAL LESIONS IN PREGNANT AND NON-PREGNANT PATIENTS

ECTOCERVIX

Conflicting views have been expressed in the literature regarding the occurrence and significance of increase in the total thickness of the stratified squamous epithelium covering the ectocervix during the course of pregnancy. Some authors, including Levey (1934) reported no change, but the majority of writers reported increased thickness of the epithelial layer in a variable proportion of pregnant patients, either in association with increase in the thickness of the outer layers of the squamous epithelium (Murphy and Herbut, 1950), or with increase in the thickness of all layers in the stratified zone (Carrow and Greene, 1951). Similar findings were noted in non-pregnant patients (Carrow and Greene, 1951).

The results of the present histological study suggest that increase in the total thickness of the epithelial layer covering the ectocervix occurs in an appreciable number of pregnant patients particularly during the third trimester, but similar changes may be seen in non-pregnant women. Little pathological significance is attached to this finding as in the majority of instances, no corresponding increase in thickness of basal cell layers was observed in the thickened stratified squamous epithelium.

The results of the present investigation suggest that the histological features of basal cell hyperplasia are similar both in pregnant and in non-pregnant women. There is, therefore, no significant evidence of increased proliferative activity of the basal cells of the ectocervical stratified squamous epithelium during pregnancy.

ENDOCERVIX

Histological observations of normal columnar epithelium lining the cervical canal and glands suggest that the cellular features are similar in pregnant women during the first and second trimesters when compared with those in non-pregnant patients. Minor differences are seen during the third trimester when increase in length of individual columnar cells and increased secretory function reflect the general hypertrophic change occurring in the cervix subjected to intense hormonal stimulation.

It was observed that a similar effect was exerted, during the third trimester of pregnancy, on the individual cells of benign hyperplastic lesions of the endocervical columnar epithelium. This gave rise to more extreme histological features of benign hyperplasia than those observed in non-pregnant patients. The cellular pattern of individual lesions, however, presented benign histological characteristics in all such lesions observed in pregnant patients,

and the basic cellular features of benign hyperplasia were similar in the pregnant and non-pregnant women. In benign hyperplastic lesions, the columnar epithelium of the cervical glands was most frequently the site of proliferative changes in both pregnant and non-pregnant patients, but, although the hyperplastic reaction was less frequently observed in the surface epithelium of the cervical canal in both groups, the latter was involved in a larger proportion of pregnant than of non-pregnant women.

Comparison of the histological features of squamous metaplastic lesions in pregnant and non-pregnant patients suggests no significant difference in the anatomical distribution of the lesion in the cervical canal. The present findings support the observations of Carmichael and Jeaffreson (1941) that squamous metaplasia is limited anatomically to the surface epithelium of the canal and to the superificial cervical glands. The frequency of occurrence and the histological characteristics of tenuous squamous epithelium and compact forms of squamous metaplasia were similar in the pregnant and non-pregnant group of patients. The squamo-columnar type of lesion was observed in six of the pregnant patients and in 16 of the non-pregnant patients. The individual cellular characteristics of squamo-columnar metaplastic foci were similar in pregnant and non-pregnant women, but the gross histological features of this lesion were more striking in specimens obtained during pregnancy due to the highly vacuolated appearances resulting from

increased secretory activity of the columnar elements. Fluhmann (1961) considered that this type of squamous metaplastic lesion was especially prone to occur under the influence of progesterone, a phenomenon which he demonstrated experimentally in rodents.

SPECIFIC PREGNANCY CHANGES

Study of the histological characteristics of benign epithelial lesions in the present series of pregnant and non-pregnant patients supports the contention of most recent writers that specific epithelial lesions do not develop in the human cervix during pregnancy. The basic microscopic features of all proliferative epithelial lesions observed in the pregnant cervix were identified in similar lesions occurring in the non-pregnant cervix. Differences in the degree of proliferative change were observed principally in the columnar epithelium of the endocervix in pregnant women, but even the most pronounced features of hyperplasia of the endocervical mucosa showed no specific histological criteria attributable to the state of pregnancy.

The sole specific histological feature observed in the cervices of pregnant patients was decidual reaction in the cervical stroma. Similarly, cervical polypi from pregnant patients showed

no characteristic epithelial changes distinct from those in non-pregnant patients, but decidual reaction occurred in the stroma of one polyp during pregnancy. Despite the small number of cases involved, the present results suggest that the overall incidence of decidual reaction in the cervical stroma in pregnancy is relative to the frequency of the change occurring during each trimester, the maximum incidence of the lesion being found in the third trimester. Murphy and Herbut (1950) reported an overall incidence of 22 per cent in 50 pregnant patients, and Epperson et al. (1951) reported 10.4 per cent in 286 pregnant patients investigated, but in neither series was reference made to the trimester distribution of decidual reaction.

ATYPICAL EPITHELIAL LESIONS

No atypical lesions were observed in the sections of cervical tissue obtained from patients included in the Pregnancy Series. Histological changes observed in the ectocervical stratified squamous epithelium and in foci of endocervical squamous metaplasia in the pregnant patients did not present any pattern of epithelial change which might be confused with dysplasia or carcinoma in situ. Pronounced squamo-columnar metaplastic lesions with extensive vacuolation and trabeculation were considered more likely to be confused, on cursory examination, with malignant adenomatous

changes, although detailed scrutiny of individual cellular features should establish the benign characteristics of the lesion in the majority of cases.

Among the non-pregnant women included in the Control Series, cervical dysplasia was diagnosed in one patient. The microscopic features of this atypical lesion occurring in areas of extensive squamous metaplasia in the cervical canal did not fulfil the histological criteria necessary for a diagnosis of carcinoma in situ, but the atypical characteristics of the cells in the basal layers of the epithelium were recognizably different from the benign proliferative squamous epithelial lesions observed in other non-pregnant and pregnant patients.

That the frequency of occurrence of cervical dysplastic lesions can be determined only by screening of large portions of the female population is suggested by the results of recent workers in this field. Such large scale surveys necessarily require the use of cytological screening techniques which were not available in Northern Ireland until the completion of the present investigation in 1962. Using cytological screening methods, Lapid and Goldberger (1951) and Reagan et al. (1955) reported the prevalence of cervical dysplasia as 6 to 8 per 1,000 in the overall population, both surveys covering 2,000 and 10,553 women respectively, in the general population. Reagan et al. (1961) consider that the reaction is more prevalent during pregnancy and increases in frequency with relation to parity.

In the light of these recent observations, it is not possible to draw any conclusions from the results obtained in the present relatively small number of patients investigated, regarding the comparative incidence of cervical dysplasia in pregnant and non-pregnant women. Further extensive study of pregnant and non-pregnant women in comparable age and parity groups will be required in order to obtain the necessary material on which to base a comparative study of this subject.

C O N C L U S I O N S

1. From the study of a group of 110 pregnant patients, individually matched for age, parity and marital status with each member of a group of 110 non-pregnant patients, it is possible to achieve valid statistical comparison of the incidence of benign cervical epithelial lesions occurring in each group, and to assess the influence of pregnancy on the occurrence and histological characteristics of the various lesions.

2. No significant increase in the incidence of basal cell hyperplasia of the ectocervical stratified squamous epithelium is found in 79 pregnant patients when the results are compared with those in a comparable group of 78 non-pregnant women.

3. The incidence of keratinization of the ectocervical stratified squamous epithelium is significantly higher in non-pregnant than in pregnant women.

4. Pregnant women who have had three or less previous pregnancies show a significantly higher incidence of benign hyperplasia of the endocervical columnar epithelium than non-pregnant women of the same parity.

5. The incidence of endocervical squamous metaplasia in pregnant women does not differ significantly from that in non-pregnant women of similar age, parity and marital status.

6. In non-pregnant women, the incidence of squamous metaplasia of the endocervix is significantly higher in those who have had more than three previous pregnancies than in those who have had less than three previous pregnancies.

7. The incidence of microscopic chronic inflammatory reaction in the endocervical epithelium and stroma of pregnant patients does not differ significantly from that in non-pregnant patients.

8. The histological appearances of benign epithelial lesions in the ectocervix of pregnant women are similar to those in non-pregnant women.

9. The histological features of benign epithelial lesions of the endocervix in pregnant women differ only in the degree of proliferative activity and not in the basic cellular characteristics from those in non-pregnant women.

10. No evidence is found to support the contention of previous writers that specific changes occur in the cervical epithelia during pregnancy.

11. In the group of 110 pregnant patients studied, no atypical lesion in the ectocervical or endocervical epithelium leading to suspicion of neoplastic change was observed.

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